Harold Chen

Atlas of Genetic Diagnosis and Counseling

Second Edition

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With 2427 Figures and 1 Table

Springer

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I would like to dedicate this Atlas to Children's Hospital, Louisiana State University Health Sciences Center in Shreveport, Louisiana.

Preface to the Second Edition

It has been 5 years since the publication of the first edition of this atlas in 2006. Since then, significant progress has been made in the field of genetic diagnosis and counseling. The first edition of the atlas covered 203 chapters which were revised with current literature and addition of many illustrations, mostly in color. Fifty two new chapters have been added to this edition. Selected references have also been added to the text for the sources of the information.

As with the previous edition, a detailed outline of each disorder is provided, describing the genetics, basic defects, clinical features, diagnostic investigations, and genetic counseling, including recurrence risk, prenatal diagnosis, and management. Relevant references are added in the second edition. The cases are supplemented by case history and diagnostic confirmations by imaging, cytogenetic, biochemical, and/or molecular studies.

I am grateful to the following individuals for their contribution and support of this edition: Dr. Susonne Ursin, my genetic colleague and Chief of Perinatal Genetics, for case studies (Joubert syndrome, Mowatt-Wilson syndrome, otopalatodigital syndrome, rigid spine syndrome, Saethre-Chotzen syndrome, Silver-Russell syndrome); Dr. RMS Riel-Romero for megalencephalic leukoencephalopathy with subcortical cysts; Dr. Amal Anga for Duncan syndrome; Drs. Richard McCall, Phillip Gates, and Anne Hollister, Shreveport Shriners Hospital for Children; Dr. Ghali Ghali, Chairman of Oral and Maxillofacial Surgery; and Dr. Renata Pilatova, Pinecrest Development Center, for providing patients for studies and inclusion into this edition; Dr. Leonard Prouty, Ms. Rhonda Lee Young, and Mr. Jozo Ivancic, LSU Cytogenetics Laboratory for part of the karyotypes used in this edition; Mrs. Lynn Martin, Beverely Gildon, and Diane Dunki-Jacobs-Nolten for nursing care; and Ms. Ashli Daigle and Mrs. Barbara McHenry for their excellent clerical and secretarial help. My apologies in the event that I failed to mention others who have contributed to this edition. Without the patience and encouragement of my dear wife, Cheryl, this edition of the atlas would not have been possible. I would like to express my sincere appreciation to Dr. Joseph Bocchini, Chairman of the Department of Pediatrics, for his encouragement and support. I would like to dedicate this edition of the atlas to the Children's Hospital, Louisiana State University Health Sciences Center in Shreveport, for its excellence in pediatric care and education.

As previously, I would welcome comments, corrections, and criticism from readers.

Harold Chen, Shreveport, LA, USA
October 2011

Preface to the First Edition

This book, *Atlas of Genetic Diagnosis and Counseling*, reflects my experience in 38 years of clinical genetics practice. During this time, I have cared for many patients and their families and taught innumerable medical students, residents, and practicing physicians. As an academic physician, I have found that a picture is truly "worth a thousand words," especially in the field of dysmorphology. Over the years, I have compiled photographs of my patients, which are incorporated into this book to illustrate selected genetic disorders, malformations, and malformation syndromes. A detailed outline of each disorder is provided, describing the genetics, basic defects, clinical features, diagnostic investigations, and genetic counseling, including recurrence risk, prenatal diagnosis, and management. Color photographs are used to illustrate the clinical features of patients of different ages and ethnicities. Photographs of prenatal ultrasounds, imaging, cytogenetics, and postmortem findings are included to help illustrate diagnostic strategies. The cases are supplemented by case history and diagnostic confirmation by cytogenetic, biochemical, and molecular studies, if available. An extensive literature review was done to ensure up-to-date information and to provide a relevant bibliography for each disorder.

This book was written in the hope that it will help physicians improve their recognition and understanding of these conditions and their care of affected individuals and their families. It is also my intention to bring the basic science and clinical medicine together for the readers. *Atlas of Genetic Diagnosis and Counseling* is designed for physicians involved in the evaluation and counseling of patients with genetic diseases, malformations, and malformation syndromes, including medical geneticists, genetic counselors, pediatricians, neonatologists, developmental pediatricians, perinatologists, obstetricians, neurologists, pathologists, and any physicians and health care professionals caring for handicapped children such as craniofacial surgeons, plastic surgeons, otolaryngologists, and orthopedics.

I am grateful to many individuals for their invaluable help in reading and providing cases for illustration. The acknowledgments are provided on a separate page. Without the patience and encouragement of my dear wife, Cheryl, this atlas would not have been possible. I would like to dedicate this book to the Children's Hospital, Louisiana State University Health Sciences Center in Shreveport, for its continued excellence in pediatric care and education.

I would welcome comments, corrections, and criticism from readers.

Harold Chen, M.D., FAAP, FACMG

Biography

Harold Chen, M.D., M.S., FAAP, FACMG

Dr. Chen was born in I-Lan, Taiwan, and was a graduate from the National Taiwan University School of Medicine (M.D. degree) in Taipei, Taiwan. He received M.S. degree in Human Genetics from the University of Michigan Graduate School in Ann Arbor, Michigan. He finished pediatric residency and fellowship training from Wayne State University School of Medicine in Detroit, Michigan. He had been faculty at Wayne State University (Detroit), Wright State University (Dayton, Ohio), and University of South Alabama (Mobile, Alabama). Currently, he is professor of Pediatrics, Obstetrics and Gynecology, and Pathology at the Louisiana State University Health Sciences Center and Chief of Genetic Laboratory Services in Shreveport, Louisiana. Dr. Chen is board-certified in American Board of Pediatrics and American Board of Medical Genetics in Clinical Genetics and Clinical Cytogenetics.

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Acardia

Acardia is a bizarre fetal malformation occurring only in twins or triplets. It is also called acardius acephalus, acardiac twinning, or twin reversed arterial perfusion (TRAP) syndrome or sequence. This condition is very rare and occurs in 1 in 34,600 births or 1 in 100 monozygotic twins (Gillim and Hendricks 1953) and 1 in 30 monozygotic triplets (Van Allen et al. 1983; Napolitani and Schreiber 1960; Moore et al. 1990; Sanjaghsaz et al. 1998; Blenc et al. 1999), and even in quintuplets. Almost all cases reported are monozygotic twins. However, there are reports of dichorionic monozygotic twin gestations with TRAP sequence (French et al. 1998; Gewolb et al. 1983).

Arcadia requires the presence of arterial–arterial anastomosis in the placenta, with retrograde perfusion of poorly oxygenated blood from the normal twin (also called donor or pump twin) to the acardiac twin, venous–venous anastomosis carrying blood back from the acardiac to the donor twin, and circulatory failure of the acardiac twin (Steffensen et al. 2008).

Synonyms and Related Disorders

Acardius acephalus; Acardiac twinning; Twin reversed arterial perfusion sequence

Genetics/Basic Defects

1. Etiology
   a. Rare complication of monochorionic twinning, presumably resulting from the fused placentation of monochorionic twins.
   b. Represents manifestation of abnormal embryonic and fetal blood flow rather than a primary defect of cardiac formation.
   c. Heterogeneous chromosomal abnormalities are present in nearly 50% of the cases, although chromosome errors are not underlying pathogenesis of the acardiac anomaly. Rather, the placental vascular anastomoses are the principal pathogenetic event (Benirschke and des Roches Harper 1977).
      i. 45,XX,t(4;21)del(4p)
      ii. 46,X,i(Xp)
      iii. 47,XX,+2 (Blaicher et al. 2000)
      iv. 47,XX,+11
      v. 47,XY,+G
      vi. 47,XXY
      vii. 69,XXX
      viii. 70,XXX,+15
      ix. 94,XXXXYY
2. Pathogenesis: reversal of fetal arterial perfusion
   a. First hypothesis
      i. A primary defect in the development of the heart
      ii. Survival of the acardiac twin as a result of the compensatory anastomoses that develop
   b. Second hypothesis
      i. The acardiac twin begins life as a normal fetus
      ii. The reversal of the arterial blood flow results in atrophy of the heart and the tributary organs
3. Classification of TRAP sequence (syndrome)
   a. Classification according to the status of the heart of the acardiac twin
      i. Hemiacardius (with incompletely formed heart)
      ii. Holoacardius (with completely absent heart)

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b. Morphologic classification of the acardiac twin (Gillim and Hendricks 1953; Napolitani and Schreiber 1960; Nicolaidis et al. 1990; Alderman 1973; Thelmo et al. 2007; Obladen 2010)
   i. Acardius amorphous
      a) The least differentiated form
      b) Little more than a lump of connective tissue, covered by edematous skin
      c) No resemblance to classical human form
      d) Anatomical features: presence of only bones, cartilage, muscles, fat, blood vessels, and stroma
   ii. Acardius myelacephalus
      a) Resembles the amorphous type except presence of rudimentary limb formation
      b) Presence of rudimentary nerve tissue in addition to anatomical features in acardius amorphous
   iii. Acardius acephalus
      a) The most common type
      b) Missing head, part of the thorax, and upper extremities
      c) May have additional malformations in the remaining organs
   iv. Acardius anceps
      a) The least atrophied form
      b) Presence of a partially developed fetal head, a thorax, abdominal organs, and extremities
      c) Lacks even a rudimentary heart
   v. Acardius acormus
      a) The rarest type
      b) Presence of a rudimentary head only
      c) Lacks thorax
      d) The umbilical cord inserts in the head and connects directly to the placenta

4. The acardia
   a. Characterized by absence of a normally functioning heart
   b. Acardia as a recipient of twin transfusion sequence
      i. Reversal of blood flow in all various types of acardia, hence the term "twin reversed arterial perfusion (TRAP) sequence" has been proposed.
      ii. Receiving the deoxygenated blood from an umbilical artery of its co-twin through the single umbilical artery of the acardiac twin and returns to its umbilical vein. Therefore, the circulation is entirely opposite to the normal direction.
   c. Usually the severe reduction anomalies occur in the upper part of the body
   d. May develop various structural malformations
      i. Growth retardation
      ii. Anencephaly
      iii. Holoprosencephaly
      iv. Facial defects
      v. Absent or malformed limbs
      vi. Gastrointestinal atresias
      vii. Other abnormalities of abdominal organs
5. The co-twin
   a. Also known as the "pump twin or donor twin."
   b. The donor "pump" twin perfuses itself and its recipient acardiac twin through abnormal arterial anastomosis in the fused placenta.
   c. Increased cardiac workload often leading to cardiac failure and causing further poor perfusion and oxygenation of the acardiac co-twin.
   d. May develop various malformations (about 10%).

Clinical Features

1. Perinatal problems associated with acardiac twinning
   a. Pump-twin congestive heart failure
   b. In utero fetal death of the pump fetus
   c. Maternal polyhydramnios
   d. Premature rupture of membrane
   e. Preterm delivery
   f. Spontaneous abortions
   g. Soft tissue dystocia
   h. Uterine rupture
   i. Postpartum hemorrhage
   j. Increased rate of cesarean section, up to 50%
2. Majority of acardiac twins and their normal twin counterparts are females
3. Nonviable
4. Gross features
   a. Severe reduction anomalies, particularly of the upper body
   b. Characteristic subcutaneous edema
   c. Internal organs: invariably missing

   d. Absent or rudimentary cardiac development: the key diagnostic feature
      i. Pseudoacardia (rudimentary heart tissue)
      ii. Holoacardia (completely lacking a heart)
5. Growth abnormality
6. Cranial vault
   a. Absent
   b. Partial
   c. Intact
7. Brain
   a. Absent
   b. Necrotic
   c. Open cranial vault
   d. Holoprosencephaly
8. Facial features
   a. Absent facial features
   b. Rudimentary facial features
   c. Present with defects
   d. Anophthalmia/microphthalmia
   e. Cleft lip/palate
9. Upper limbs
   a. Absent
   b. Rudimentary
   c. Radial aplasia
   d. Syndactyly/oligodactyly
10. Lower limbs
   a. Absent
   b. Rudimentary/reduced
   c. Syndactyly/oligodactyly
   d. Talipes equinovarus
11. Thorax
   a. Absent
   b. Reduced
   c. Diaphragmatic defect
12. Lungs
   a. Absent
   b. Necrotic or rudimentary
   c. Single midline lobe
13. Cardiac
   a. Absent heart tissue
   b. Unfolded heart tube
   c. Folded heart with common chamber
14. Gastrointestinal
   a. Esophageal atresia
   b. Short intestine
   c. Interrupted intestine
   d. Omphalocele
   e. Incomplete rotation of the gut
   f. Imperforated anus
   g. Ascites
15. Liver
   a. Absent
   b. Reduced
16. Kidney
   a. Absent (bilateral)
   b. Hypoplastic and/or lobulated
17. Other viscera
   a. Absent gallbladder
   b. Absent spleen
   c. Absent to reduced pancreas
   d. Absent adrenal
   e. Absent to hypoplastic gonads
   f. Exstrophy of the cloaca
   g. Skin with myxedematous thickening
18. Umbilical cord vessels
   a. Two vessels
   b. Three vessels
19. Severe obstetrical complications
   a. Maternal polyhydramnios
   b. Preterm labor
   c. Cord accidents
   d. Dystocia
   e. Uterine rupture
20. Severe neonatal complications
   a. Hydrops
   b. Intrauterine demise
   c. Prematurity
   d. Heart failure
   e. Anemia
   f. Twin-to-twin transfusion syndrome
21. Outcome for the normal sib in an acardiac twin pregnancy (Healey 1994).
   a. Unsatisfactory
      i. Adapting to the increasing circulatory load, resulting in the following situations:
         a) Intrauterine growth retardation
         b) Hydrops
         c) Ascites
         d) Pleural effusion
         e) Hypertrophy of the right ventricle
         f) Hepatosplenomegaly
         g) Severe heart failure resulting in pericardial effusion and/or tricuspid insufficiency
      ii. Stillbirth

iii. Prematurity
iv. Neonatal death

b. Mortality for the normal twin reported as high as 50% without intervention (Aggarwal et al. 2002)

Diagnostic Investigations

1. Radiography
   a. Absent or rudimentary skull
   b. Absent or rudimentary thorax
   c. Absent or rudimentary heart
   d. Vertebral anomalies
   e. Rib anomalies
   f. Limb defects, especially upper limbs
2. Pathology
   a. Microcephaly
   b. Severely rudimentary brain
   c. Developmental arrest of brain at the prosencephalic stage (holoprosencephaly)
   d. Hypoxic damage to the holospheric brain mantle with cystic change (hydranencephaly)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: overall recurrence risk of about 1 in 10,000 (The recurrence risk is for monoamniotic twinning (1% for couples who have had one set of monozygotic twins) times the frequency of the occurrence of TRAP sequence with near-term survival (about 1% of monozygotic twin sets))
   b. Patient's offspring: not applicable (a lethal condition)
2. Prenatal ultrasonography (Sherer et al. 1989; Stiller et al. 1989; Langlotz et al. 1991; Donnenfeld et al. 1991; Shalev et al. 1992; Zucchini et al. 1993; Coulam 1996; Schwarzler et al. 1999; Bonilla-Musoles et al. 2001)
   a. Monochorionic placenta with a single umbilical artery in two-thirds of cases
   b. Acardiac fetus
      i. Unrecognizable head or upper trunk.
      ii. Without a recognizable heart or a partially formed heart.
      iii. A variety of other malformations.
      iv. Reversal of blood flow in the umbilical artery with flow going from the placenta toward the acardiac fetus (reversed arterial perfusion). Such a reversal of the blood flow in the recipient twin can be demonstrated in utero by transvaginal Doppler ultrasound as early as 12 weeks of gestation.
      v. Early diagnosis by transvaginal sonography on the following signs:
         a) Monozygotic twin gestation (absence of the lambda sign)
         b) Biometric discordance between the twins
         c) Diffuse subcutaneous edema or morphologic anomalies of one of the twins or both
         d) Detection of reversed umbilical cord flow; cardiac activity likely to disappear as the pregnancy progresses
         e) Absence of cardiac activity, although hemicardia or pseudocardia may be present
   c. The donor fetus
      i. Hydrops
      ii. Cardiac failure (cardiomegaly, pericardial effusion, tricuspid regurgitation)
3. Amniocentesis to diagnose associated chromosome abnormalities (about 10% of pump twins)
4. Management of pregnancies complicated by an acardiac fetus (Donnenfeld et al. 1991; Hanafy and Peterson 1997; Søggard et al. 1999)
   a. Conservative treatment
      i. Monitor pregnancy by serial ultrasonography
      ii. Conservative approach as long as there is no evidence of cardiac circulatory decompensation in the donor twin
   b. Termination of pregnancies
   c. Treatment and prevention of preterm labor by tocolytics
      i. Magnesium sulfate
      ii. Beta sympathomimetics
      iii. Indomethacin
   d. Treatment of pump fetus heart failure involving maternal digitalization
   e. Treatment of polyhydramnios by therapeutic repeated amniocentesis
   f. Selective termination of the acardiac twin
      i. To occlude the umbilical artery of the acardiac twin in order to stop umbilical flow through the anastomosis

a) Intrafunicular injection and mechanical occlusion of the umbilical artery
b) Embolization by steel or platinum coil, alcohol-soaked suture material, or ethanol
c) Hysterotomy and delivery of acardiac twin
d) Ligation of the umbilical cord
e) Hysterotomy and umbilical cord ligation

ii. Fetal surgery: best available treatment for acardiac twinning (Arias et al. 1998)
a) Endoscopic laser coagulation of the umbilical vessels at or before 24 weeks of gestation
b) Endoscopic- or sonographic-guided umbilical cord ligation at 24 weeks of gestation

iii. Summary of acardiac twins treated with invasive procedures reported in the literature
a) Mortality of the pump twin (13.6%)
b) Preterm delivery (50.3%)
c) Delivery before 30 weeks gestation (27.2%)
d) Perinatal mortality if untreated is at least 50%

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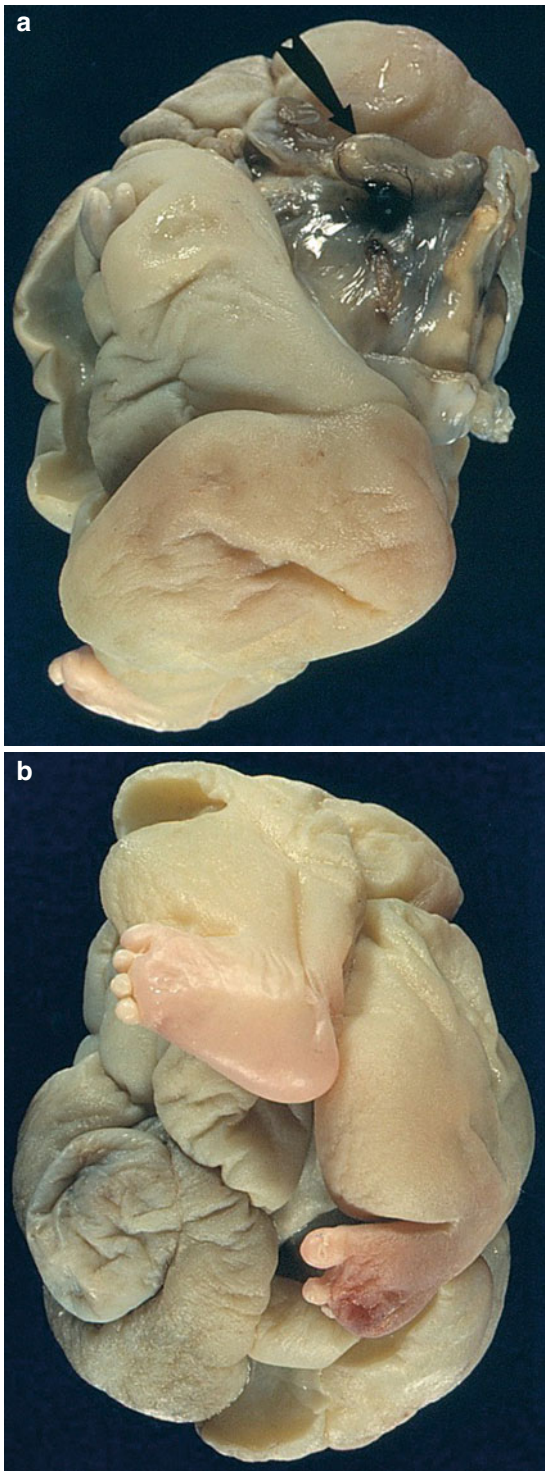

Fig. 1 (**a, b**) Ventral view of an acardiac acephalus fetus (*upper photo*) shows a large abdominal defect, gastroschisis (*arrow*), through which small rudiments of gastrointestinal tract are seen. Dorsal view (*lower photo*) shows a very underdeveloped cephalic end and relatively well-developed lower limbs. The co-twin had major malformations consisting of a large omphalocele, ectopia cordis, and absent pericardium, incompatible with life (Chen et al. 1983)

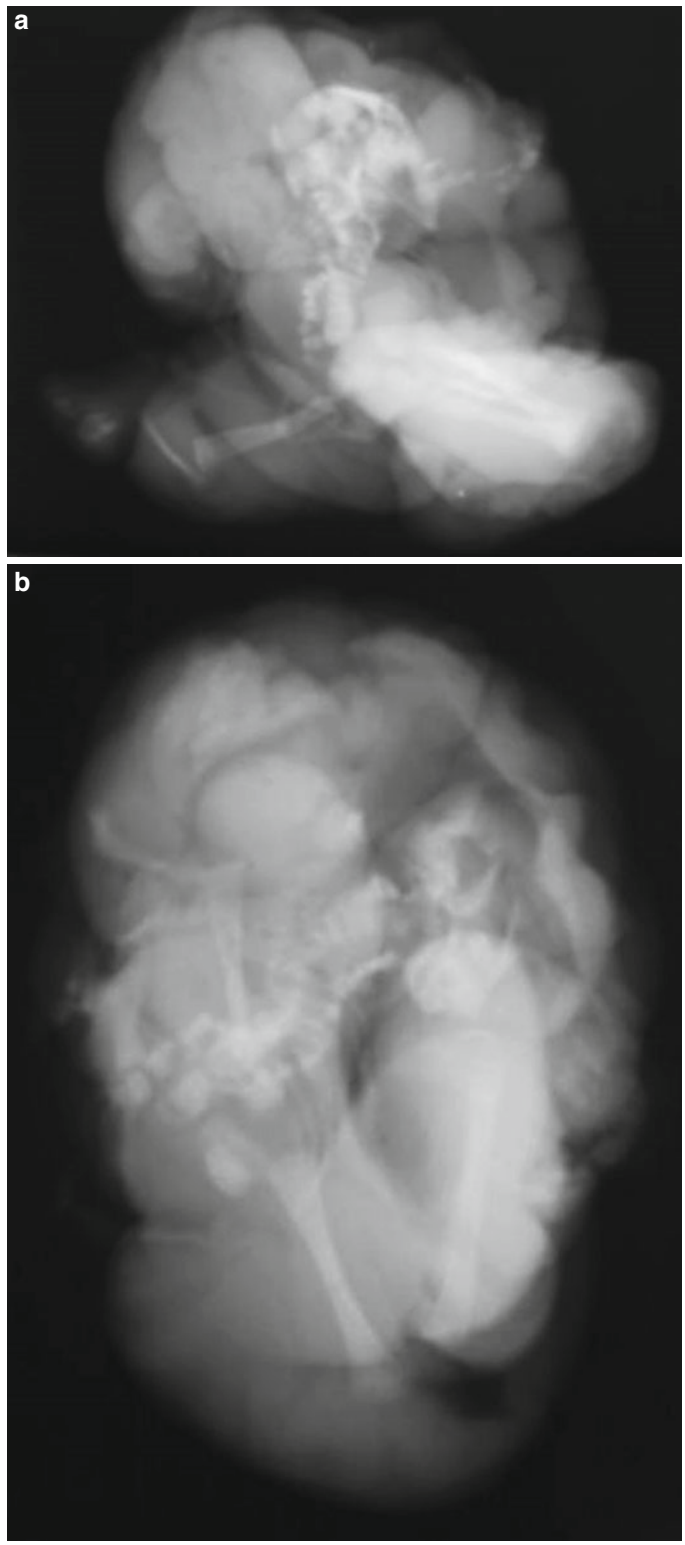

Fig. 2 (**a, b**) Radiographs of the above acardiac fetus showing a missing head, cervical vertebrae and part of upper thoracic vertebrae, rudimental lower ribs, malformed lower thoracic and lumbar vertebrae, and relatively well-formed lower limbs

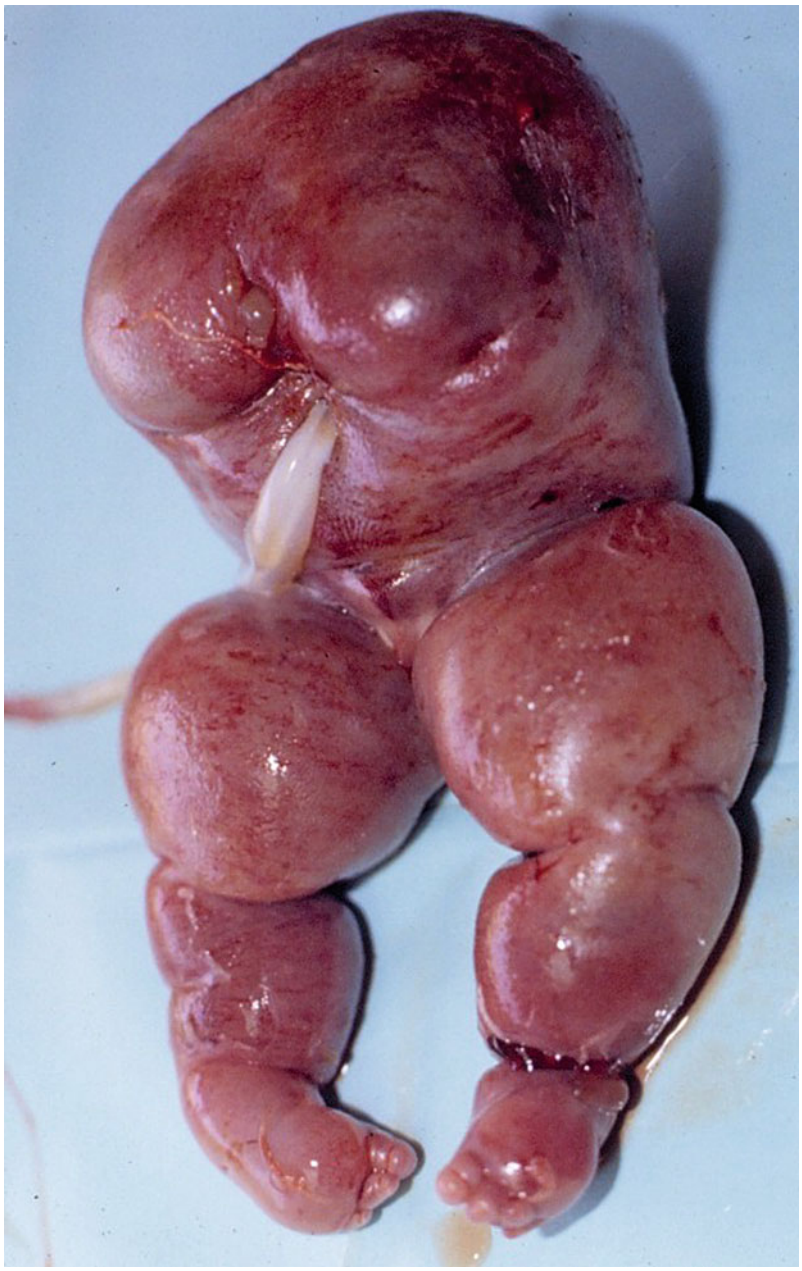

Fig. 3 The head and part of the thorax of this acardiac fetus are completely missing with relatively well-formed lower limbs

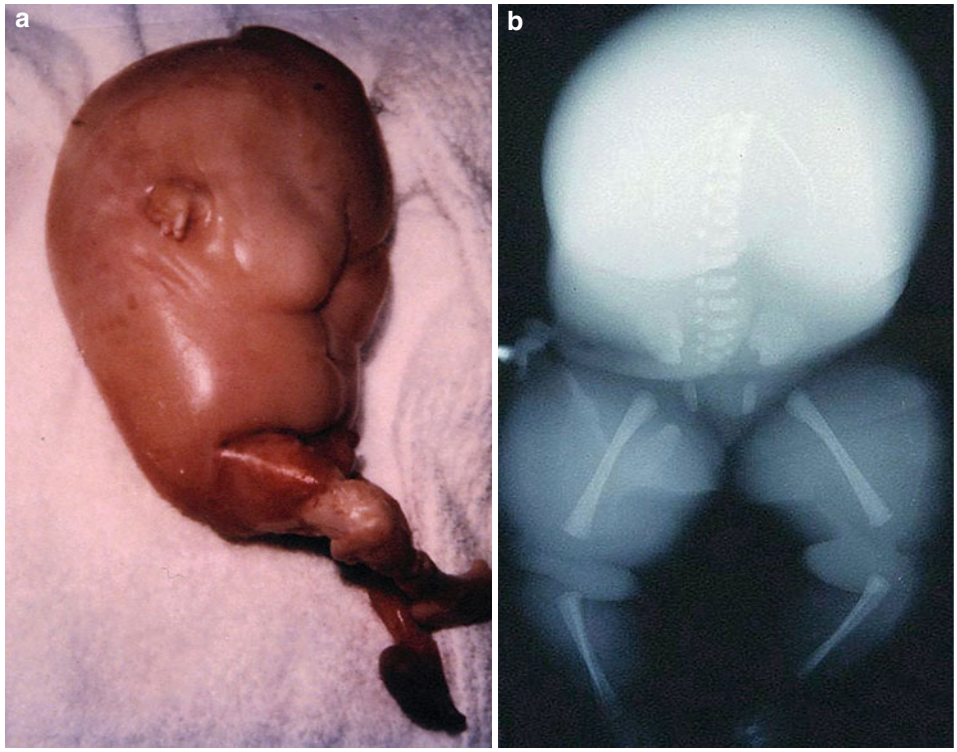

Fig. 4 (**a, b**) Another acardiac fetus with a missing head and part of the upper thorax. Radiograph shows missing head, cervical and part of thoracic vertebrae, and ribs. Pelvis and lower limbs are well formed

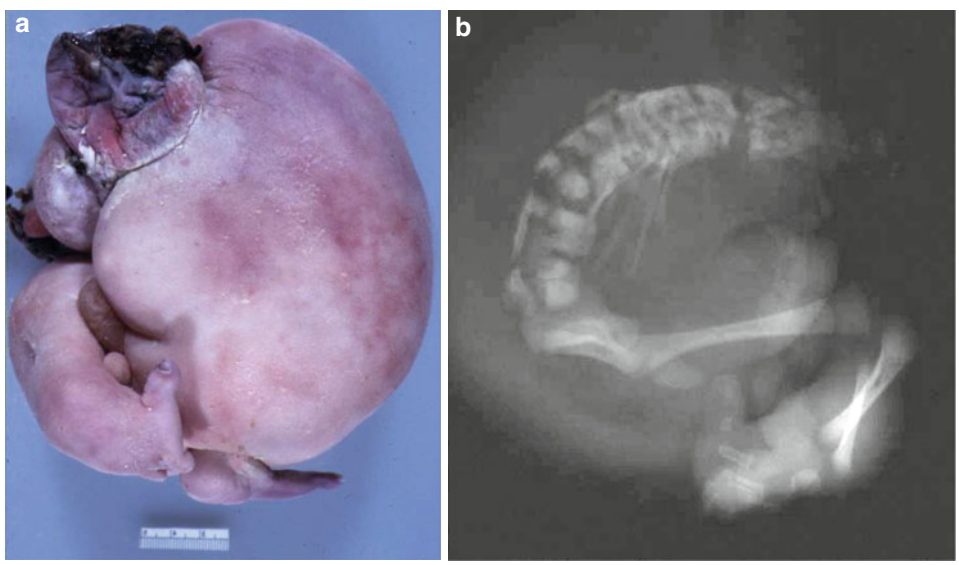

Fig. 5 (**a, b**) Acardius (second twin, 36 weeks gestation) showing spherical body with a small amorphous mass of leptomeningeal and glial tissue at the cephalic end. There were one deformed lower extremity and a small arm appendage. Small intestinal loops, nodules of adrenal glands, and testicles were present in the body. There was no heart or lungs. The placenta was nonoamniotic monochorionic with velamentous insertion of the umbilical cord. The other identical twin was free of birth defects. Radiograph of acardius twin shows a short segment of the spine, a femur, a tibia, and a fibula

Achondrogenesis

Marco Fraccaro first described achondrogenesis in 1952 (Fraccaro 1952). He used the term to describe a stillborn female with severe micromelia and marked histological cartilage changes. The term was later used to characterize the most severe forms of chondrodysplasia in humans, which were invariably lethal before or shortly after birth. By the 1970s, researchers concluded that achondrogenesis was a heterogeneous group of chondrodysplasias lethal to neonates; achondrogenesis type I (Fraccaro-Houston-Harris type) and type II (Langer-Saldino type) were distinguished on the basis of radiological and histological criteria.

Achondrogenesis type I was further subdivided, on the basis of convincing histological criteria, into type IA, which has apparently normal cartilage matrix but inclusions in chondrocytes, and type IB, which has an abnormal cartilage matrix. Classification of type IB as a separate group has been confirmed recently by the discovery of its association with mutations in the diastrophic dysplasia sulfate transporter (*DTDST*) gene, making it allelic with diastrophic dysplasia.

Synonyms and Related Disorders

Achondrogenesis type IA (Houston-Harris type); Achondrogenesis type IB (Fraccaro type); Achondrogenesis type II (Langer-Saldino type)

Genetics/Basic Defects

1. Type IA: an autosomal recessive disorder: caused by mutation in the thyroid hormone recepter interacter 11 (TRIP 11) gene which is mapped on 14q32.12) (Smits et al. 2010)
2. Type IB
   a. An autosomal recessive disorder
   b. Resulting from mutations of the *DTDST* gene, which encodes the SLC26A2 sulfate transporter, is located at 5q32–q33 (Superti-Furga et al. 1996)
3. Type II
   a. Autosomal dominant type II collagenopathy
   b. Resulting from mutations in the *COL2A1* gene, which is located at 12q13.1–q13.3
   c. Report of a familial case of achondrogenesis type II caused by a dominant *COL2A1* mutation and "patchy" expression in the mosaic father (Forzano et al. 2007) suggests that somatic mosaicism can lead to a milder but generalized clinical phenotype.
4. Mutations within the *COL2A1* gene also cause the following skeletal dysplasias (Forzano et al. 2007):
   a. Hypochondrogenesis
   b. Spondyloepiphyseal dysplasia (SED) congenita
   c. SED Namaqualand type
   d. Mild SED with precocious osteoarthritis
   e. Spondyloepimetaphyseal dysplasia, Strudwick type
   f. Kniest dysplasia
   g. Multiple epiphyseal dysplasia with myopia and conductive deafness
   h. Spondyloperipheral dysplasia
   i. Stickler dysplasia type I

Clinical Features

1. Prenatal/perinatal history
   a. Polyhydramnios
   b. Hydrops

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c. Breech presentation
d. Perinatal death
2. Achondrogenesis type I
   a. Growth
      i. Lethal neonatal dwarfism
      ii. Mean birth weight of 1,200 g
   b. Craniofacial features
      i. Disproportionately large head
      ii. Soft skull
      iii. Sloping forehead
      iv. Convex facial plane
      v. Flat nasal bridge, occasionally associated with a deep horizontal groove
      vi. Small nose, often with anteverted nostrils
      vii. Long philtrum
      viii. Retrognathia
      ix. Increased distance between lower lip and lower edge of chin
      x. Double chin appearance
   c. Extremely short neck
   d. Thorax
      i. Short and barrel-shaped thorax
      ii. Lung hypoplasia
   e. Heart
      i. Patent ductus arteriosus
      ii. Atrial septal defect
      iii. Ventricular septal defect
   f. Protuberant abdomen
   g. Limbs
      i. Extremely short (micromelia), shorter than type II
      ii. Flipper-like appendages
3. Achondrogenesis type II (Langer-Saldino type)
   a. Growth
      i. Lethal neonatal dwarfism
      ii. Mean birth weight of 2,100 g
   b. Craniofacial features
      i. Disproportionately large head
      ii. Large and prominent forehead
      iii. Midfacial hypoplasia
         a) Flat facial plane
         b) Flat nasal bridge
         c) Small nose with severely anteverted nostrils
      iv. Normal philtrum
      v. Micrognathia
      vi. Cleft palate
   c. Extremely short neck
   d. Thorax
      i. Short and flared thorax
      ii. Bell-shaped cage
      iii. Lung hypoplasia
   e. Protuberant abdomen
   f. Extremely short limbs (micromelia)

Diagnostic Investigations

1. Radiological features
   a. Variable features
   b. No single obligatory feature
   c. Distinction between type IA and type IB on radiographs not always possible
   d. Degree of ossification: age dependent, and caution is needed when comparing radiographs at different gestational ages
   e. Achondrogenesis type I
      i. Skull: Varying degree of deficient cranial ossification consisting of small islands of bone in membranous calvaria
      ii. Thorax and ribs
         a) Short and barrel-shaped thorax
         b) Thin ribs with marked expansion at costochondral junction, frequently with multiple fractures
      iii. Spine and pelvis
         a) Poorly ossified spine, ischium, and pubis
         b) Poorly ossified iliac bones with short medial margins
      iv. Limbs and tubular bones
         a) Extreme micromelia, with limbs much shorter than in type II
         b) Prominent spike-like metaphyseal spurs
         c) Femur and tibia frequently presenting as short bone segments
      v. Subtype IA (Houston-Harris type)
         a) Poorly ossified skull
         b) Thin ribs with multiple fractures
         c) Unossified vertebral pedicles
         d) Arched ilium
         e) Hypoplastic but ossified ischium
         f) Wedged femur with metaphyseal spikes
         g) Short tibia and fibula with metaphyseal flare

vi. Subtype IB (Fraccaro type)
  a) Adequately ossified skull
  b) Absence of rib fractures
  c) Total lack of ossification or only rudimentary calcification of the center of the vertebral bodies
  d) Ossified vertebral pedicles
  e) Iliac bones with ossification only in their upper part, giving a crescent-shaped, "paraglider-like" appearance on X-ray
  f) Unossified ischium
  g) Shortened tubular bones without recognized axis
  h) Metaphyseal spurring giving the appearance of a "thorn apple" or "acanthocyte" (a descriptive term in hematology)
  i) Trapezoid femur
  j) Stellate tibia
  k) Unossified fibula
  l) Poorly ossified phalanges

f. Achondrogenesis type II
  i. Skull
    a) Normal cranial ossification
    b) Relatively large calvaria
  ii. Thorax and ribs
    a) Short and flared thorax
    b) Bell-shaped cage
    c) Shorter ribs without fractures
  iii. Spine and pelvis: relatively well-ossified iliac bones with long, crescent-shaped medial and inferior margins
  iv. Limbs and tubular bones
    a) Short, broad bones, usually with some diaphyseal constriction and flared, cupped metaphyseal ends
    b) Metaphyseal spurs, usually smaller than type I

2. Histologic features
  a. Achondrogenesis type IA
    i. Normal cartilage matrix
    ii. Absent collagen rings around the chondrocytes
    iii. Vacuolated chondrocytes
    iv. Presence of intrachondrocytic inclusion bodies (periodic acid-Schiff [PAS] stain positive, diastase resistant)
    v. Extraskeletal cartilage involvement
    vi. Enlarged lacunas
    vii. Woven bone
  b. Achondrogenesis type IB
    i. Abnormal cartilage matrix: presence of "demasked" coarsened collagen fibers, particularly dense around the chondrocytes, forming collagen rings
    ii. Abnormal staining properties of cartilage
      a) Reduced staining with cationic dyes, such as toluidine blue or Alcian blue, probably because of a deficiency in sulfated proteoglycans
      b) This distinguishes type IB from type IA, in which the matrix is close to normal and inclusions can be seen in chondrocytes, and from achondrogenesis type II, in which cationic dyes give a normal staining pattern.
  c. Achondrogenesis type II
    i. Cartilage
      a) Slightly larger than normal
      b) Grossly distorted (lobulated and mushroomed)
    ii. Markedly deficient cartilaginous matrix
    iii. Severe disturbance in endochondral ossification
    iv. Hypercellular and hypervascular reserve cartilage with large, primitive mesenchymal (ballooned) chondrocytes with abundant clear cytoplasm (vacuoles) ("Swiss cheese-like")
    v. Overgrowth of membranous bones resulting in cupping of the epiphyseal cartilages
    vi. Decreased amount and altered structure of proteoglycans
    vii. Relatively lower content of chondroitin 4-sulfate
    viii. Lower molecular weight and decreased total chondroitin sulfation
    ix. Absence of type II collagen
    x. Increased amounts of type I and type III collagen

3. Biochemical testing
  a. Lack of sulfate incorporation: cumbersome and not used for diagnostic purposes
  b. Sulfate incorporation assay in cultured skin fibroblasts or chondrocytes: recommended in

the rare instances in which the diagnosis of achondrogenesis type IB is strongly suspected but molecular genetic testing fails to detect *SLC26A2* (*DTDST*) mutations

4. Molecular genetic studies
   a. Mutation analysis of the *DTDST* gene, reported in:
      i. Achondrogenesis type IB (the most severe form)
      ii. Atelosteogenesis type II (an intermediate form)
      iii. Diastophic dysplasia (the mildest form)
      iv. Recessive multiple epiphyseal dysplasia
   b. Achondrogenesis type IB
      i. Mutation analysis: testing of the following four most common *SLC26A2* (*DTDST*) gene mutations (mutation detection rate about 60%)
         a) R279W
         b) IVS1 + 2 > C ("Finnish" mutation)
         c) delV340
         d) R178X
      ii. Sequence analysis of the *SLC26A2* (*DTDST*) coding region (mutation detection rate over 90%)
         a) Private mutations
         b) Common mutations
   c. Achondrogenesis type II: mutation analysis of the *COL2A1* gene

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Achondrogenesis type IA and type IB (autosomal recessive disorders)
         a) Recurrence risk: 25%
         b) Unaffected sibs of a proband: two third chance of being heterozygotes
      ii. Achondrogenesis type II
         a) Usually caused by a new dominant mutation, in which case recurrence risk is not significantly increased
         b) Asymptomatic carrier parent (germline mutation for a dominant mutation) may be present in the families of affected patients, in which case recurrence risk can be up to 50%.
   b. Patient's offspring: lethal entities not surviving to reproduction
2. Prenatal diagnosis
   a. Ultrasonography
      i. Polyhydramnios
      ii. Fetal hydrops
      iii. Disproportionally big head
      iv. Nuchal edema
      v. Cystic hygroma
      vi. A narrow thorax
      vii. Short limbs
      viii. Poor ossification of vertebral bodies and limb tubular bones (leading to difficulties in determining their length)
      ix. Suspect achondrogenesis type I
         a) An extremely echo-poor appearance of the skeleton
         b) A poorly mineralized skull
         c) Short limbs
         d) Rib fractures
   b. Molecular genetic studies
      i. Prenatal diagnosis of achondrogenesis type IB and type II by mutation analysis of chorionic villus DNA or amniocyte DNA in the first or second trimester
      ii. Achondrogenesis type IB
         a) Characterize both alleles of *DTDST* beforehand
         b) Identify the source parent of each allele
         c) Theoretically, analysis of sulfate incorporation in chorionic villi might be used for prenatal diagnosis, but experience is lacking.
      iii. Achondrogenesis type II
         a) The affected fetus usually with a new dominant mutation of the *COL2A1* gene
         b) Possible presence of asymptomatic carriers in families of an affected patient
         c) Prenatal diagnosis possible if the mutation has been characterized in the affected family
3. Management
   a. Supportive care
   b. No treatment available for the underlying lethal disorder

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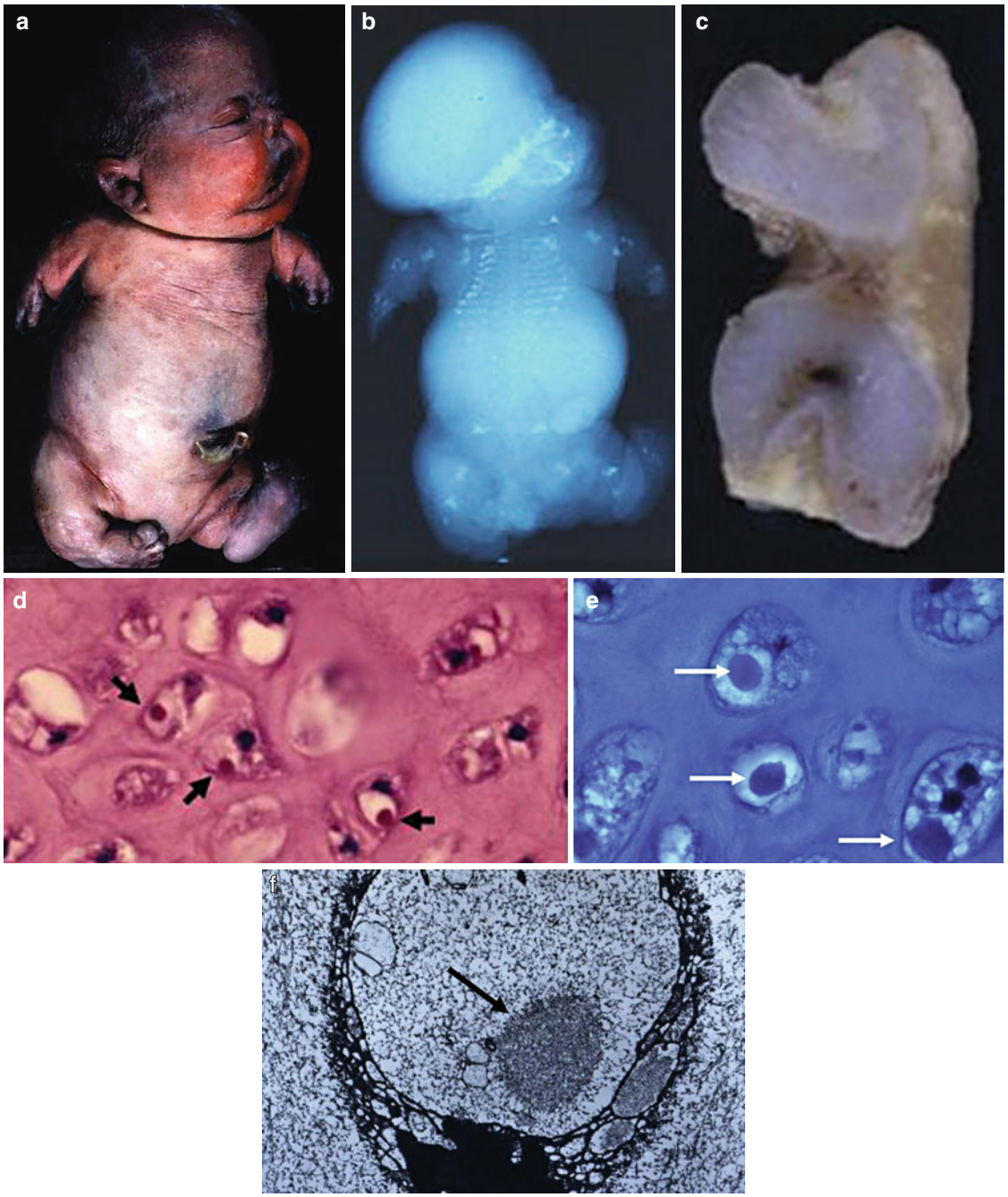

Fig. 1 (**a**–**f**) A neonate with achondrogenesis type I showing large head, short trunk, and extreme micromelia. Radiograph shows unossified calvarium, vertebral bodies, and some pelvic bones. The remaining bones are extremely small. There are multiple rib fractures. The sagittal section of the femora and the humeri are similar. An extremely small ossified shaft is capped by a relatively large epiphyseal cartilage at both ends. Photomicrographs of resting cartilage with high magnification show many chondrocytes that contain large cytoplasmic inclusions which are within clear vacuoles (Diastase PAS stain). Electron micrograph shows inclusion as a globular mass of electron dense material. It is within a distended cistern of rough endoplasmic reticulum

Fig. 2 (**a**–**e**) Achondrogenesis type II. As in type I, this neonate shows large head, short trunk, and micromelia (Potter's pathology of Fetus and Infant, by Gilbert-Barness). Sagittal section of the femur shows much better ossification of the shaft than type I. The cartilage lacks glistering appearance due to cartilage matrix deficiency. Photomicrograph of the entire cartilage shows severe deficiency of cartilage matrix. The cartilage canals are large, fibrotic, and stellate in shape. Physeal growth zone is severely retarded

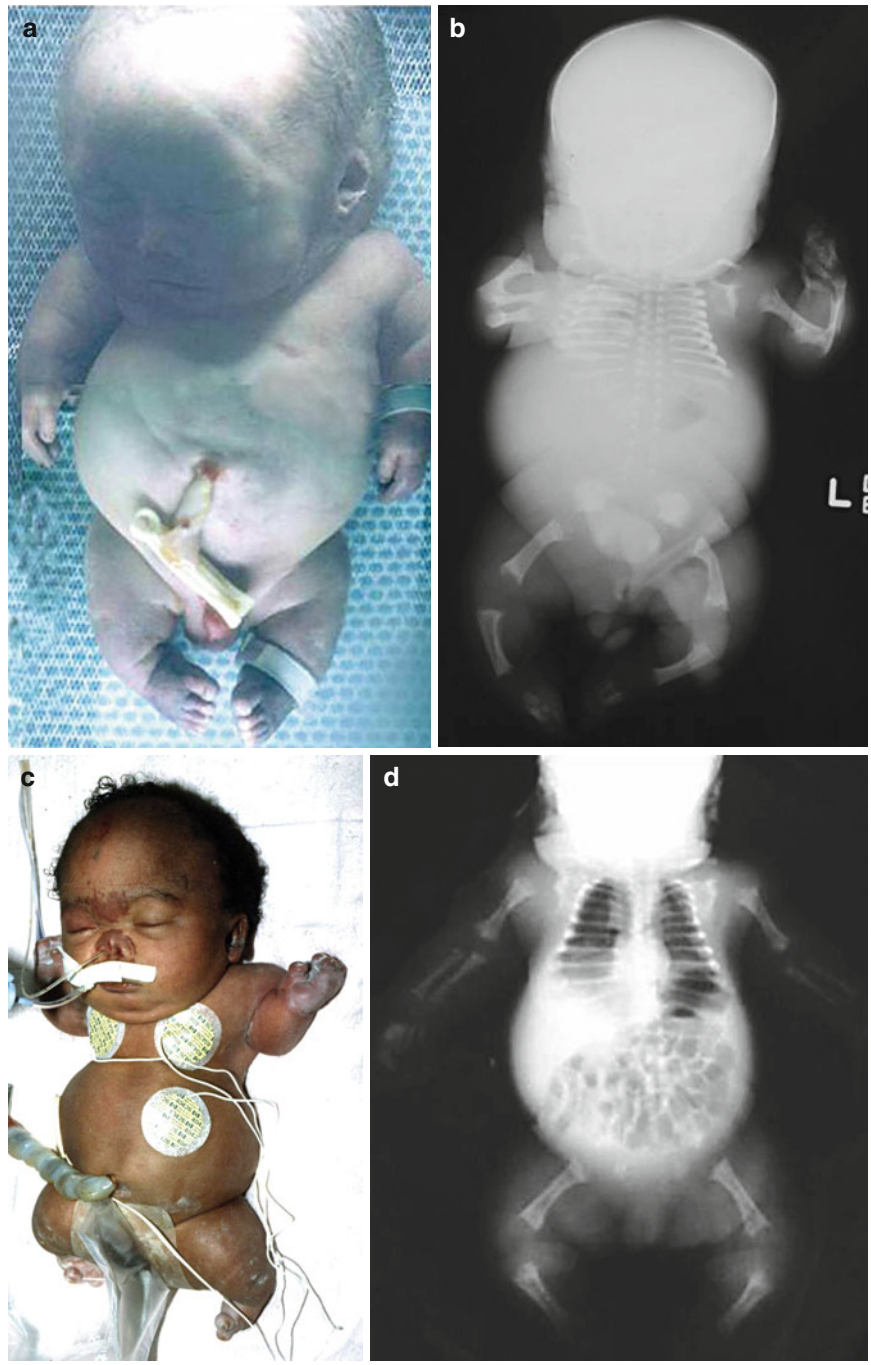

Fig. 3 (**a**–**d**) Two infants with achondrogenesis type II showing milder spectrum of manifestations, bordering the type II and spondyloepiphyseal congenita

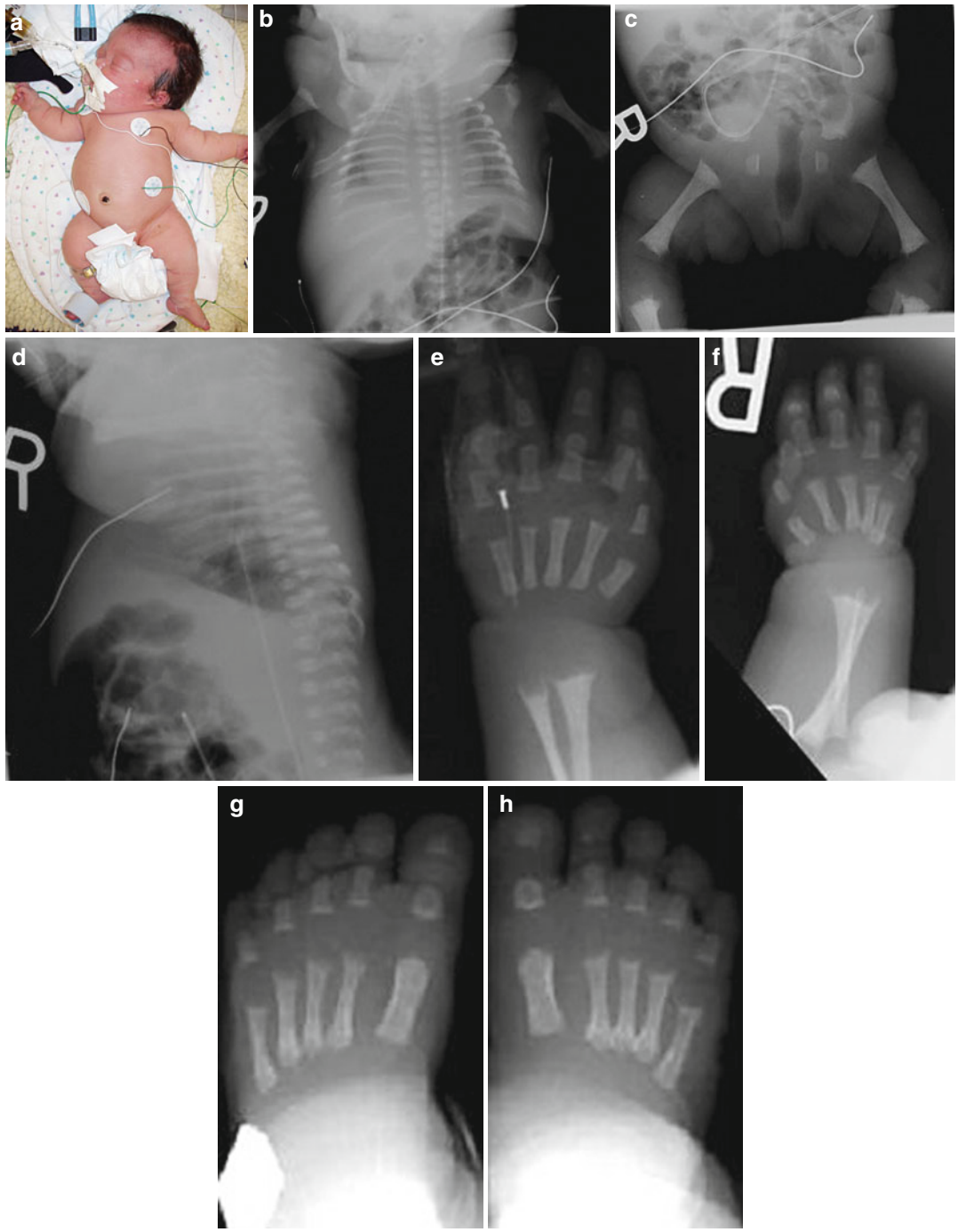

Fig. 4 (**a**–**h**) A newborn girl with achondrogenesis type II showing large head, midfacial hypoplasia, short neck, small chest, and short limbs. The radiographs shows generalized shortening of the long bones of the upper and lower extremities with marked cupping (metaphyseal spurs) at the metaphyseal ends of the bones. This is most evident at the distal ends of the tibia, fibular, radius and ulna, and distal ends of the digits. Radiographs also shows short ribs without fractures and hemivertebrae involving thoracic vertebrae as well as the sacrum. Conformation sensitive gel electrophoresis analysis indicated a sequence variation in the fragment containing exon 19 and the flanking sequences of the *COL2A1* gene (Gly244Asp). Similar mutations in this area have been seen in patients diagnosed with hypochondroplasia and achondrogenesis type II

Achondroplasia

Achondroplasia is the most common form of short-limbed dwarfism. Gene frequency is estimated to be 1/16,000 and 1/35,000. There are about 5,000 achondroplasts in the U.S.A. and 65,000 on Earth. The incidence for achondroplasia is between 0.5 and 1.5 in 10,000 births. The mutation rate is high and is estimated to be between 1.72 and 5.57×10^{-5} per gamete per generation. Most infants with achondroplasia are born unexpectedly to parents of average stature.

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant disorder with complete penetrance
   b. Sporadic in about 80% of the cases, the result of a de novo mutation
   c. Presence of paternal age effect (advanced paternal age in sporadic cases)
   d. Gonadal mosaicism (two or more children with classic achondroplasia born to normal parents)
2. Caused by mutations in the gene of the fibroblast growth factor receptor 3 (*FGFR3*) on chromosome 4p16.3
   a. About 98% of achondroplasia with G-to-A transition and about 1% G-to-C transversion at nucleotide 1138. Both mutations resulted in the substitution of an arginine residue for a glycine at position 380 (G380A) of the mature protein in the transmembrane domain of *FGFR3*.
   b. A rare mutation causing substitution of a nearby glycine 375 with a cysteine (G375C)
   c. Another rare mutation causing substitution of glycine346 with glutamic acid (G346E)
   d. The specific mechanisms by which *FGFR3* mutations disrupt skeletal development in achondroplasia remain elusive
3. Different mutations in *FGFR3* can cause the following spectrum of disorders (Lemyre et al. 1999; Superti-Furga and Unger 2007)
   a. Hypochondroplasia
   b. Severe achondroplasia with developmental delay and acanthosis nigricans
   c. Thanatophoric dysplasia
4. *FGFR3* mutations affect the cartilaginous growth plate in the growing skeleton, therefore disturbing cartilage function during linear bone growth (Richette et al. 2008)
5. Basic defect: zone of chondroblast proliferation in the physeal growth plates
   a. Abnormally retarded endochondral ossification with resultant shortening of tubular bones and flat vertebral bodies, while membranous ossification (skull, facial bones) is not affected
   b. Physeal growth zones show normal columnization, hypertrophy, degeneration, calcification, and ossification. However, the growth is quantitatively reduced significantly.
   c. Achondroplasia as the result of a quantitative loss of endochondral ossification rather than the formation of abnormal tissue
   d. Normal diameter of the bones secondary to normal subperiosteal membranous ossification of tubular bones; the results being production of short, thick tubular bones, leading to short stature with disproportionately shortened limbs

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Clinical Features

1. Major clinical symptoms
   a. Delayed motor milestones during infancy and early childhood
   b. Sleep disturbances secondary to both neurological and respiratory complications
   c. Breathing disorders
      i. A high prevalence (75%) of breathing disorders during sleep
      ii. Obstructive apnea caused by upper airway obstruction
      iii. The majority of respiratory complaints due to restrictive lung disease secondary to diminished chest size or upper airway obstruction and rarely due to spinal cord compression
   d. Symptomatic spinal stenosis in more than 50% of patients as a consequence of a congenitally small spinal canal
      i. Back pain
      ii. Lower extremity sensory changes
      iii. Incontinence
      iv. Paraplegia
      v. Onset of symptoms: usually after 20 s or 30 s
   e. Neurologic symptoms classified based on neurologic severity and presentation of spinal stenosis (Lutter and Langer 1977)
      i. Type I (back pain with sensory and motor change of an insidious nature)
      ii. Type II (intermittent claudication limiting ambulation)
      iii. Type III (nerve root compression)
      iv. Type IV (acute onset paraplegia)
   f. Symptoms secondary to foramen magnum stenosis
      i. Respiratory difficulty
      ii. Feeding problems
      iii. Cyanosis, quadriparesis
      iv. Poor head control
   g. Symptoms secondary to cervicomedullary compression
      i. Pain
      ii. Ataxia
      iii. Incontinence
      iv. Apnea
      v. Progressive quadriparesis
      vi. Respiratory arrest
2. Major clinical signs
   a. Disproportionate short stature (dwarfism)
   b. Hypotonia during infancy and early childhood
   c. Relative stenosis of the foramen magnum in all patients, documented by CT
   d. Foramen magnum stenosis considered as the cause of increased incidence of:
      i. Hypotonia
      ii. Sleep apnea
      iii. Sudden infant death syndrome
   e. Symptomatic hydrocephalus in infancy and early childhood rarely due to narrowing of the foramen magnum
   f. Characteristic craniofacial appearance
      i. Disproportionately large head
      ii. Frontal bossing
      iii. Depressed nasal bridge
      iv. Midfacial hypoplasia
      v. Narrow nasal passages
      vi. Prognathism
      vii. Dental malocclusion
   g. A normal trunk length
   h. A thoracolumbar kyphosis or gibbus usually present at birth or early infancy
   i. Exaggerated lumbar lordosis when the child begins to ambulate
   j. Prominent buttocks and protuberant abdomen secondary to increased pelvic tilt in children and adults
   k. Generalized joint hypermobility, especially the knees
   l. Rhizomelic micromelia (relatively shorter proximal segment of the limbs compared to the middle and the distal segments)
   m. Limited elbow and hip extension
   n. Trident hands (inability to approximate the third and fourth fingers in extension produces a “trident” configuration of the hand)
   o. Short fingers (brachydactyly)
   p. Bowing of the legs (genu varum) due to lax knee ligaments
   q. Excess skin folds about thighs
3. Complications/risks
   a. Recurrent otitis media during infancy and childhood
      i. Conductive hearing loss
      ii. Delayed language development
   b. Thoraco-lumbar gibbus
   c. Osteoarthropathy of the knee joints

d. Neurological complications
   i. Small foramen magnum
   ii. Cervicomedullary junction compression causing sudden unexpected death in infants with achondroplasia
   iii. Apnea
   iv. Communicating hydrocephalus
   v. Spinal stenosis
   vi. Paraparesis
   vii. Quadriparesis
   viii. Infantile hypotonia
e. Obesity
   i. Aggravating the morbidity associated with lumbar stenosis
   ii. Contributing to the nonspecific joint problems and to the possible early cardiovascular mortality in this condition
f. Obstetric complications
   i. Large head of the affected infant
   ii. An increased risk of intracranial bleeding during delivery
   iii. Marked obstetrical difficulties secondary to very narrow pelvis of achondroplastic women

4. Prognosis
   a. Normal intelligence and healthy, independent, and productive lives in vast majority of patients. Rarely, intelligence may be affected because of hydrocephalus or other CNS complications.
   b. Mean adult height
      i. Approximately 131 cm ± 5.6 for males
      ii. Approximately 124 cm ± 5.9 for females
   c. Psychosocial problems related to body image because of severe disproportionate short stature
   d. Life span for heterozygous achondroplasia
      i. Usually normal unless there are serious complications
      ii. Mean life expectancy approximately 10 years less than the general population
   e. Homozygous achondroplasia
      i. A lethal condition with severe respiratory distress caused by rib-cage deformity and upper cervical cord damage caused by small foramen magnum. The patients die soon after birth.
      ii. Radiographic changes much more severe than the heterozygous achondroplasia
   f. Normal fertility in achondroplasia
      i. Pregnancy at high risk for achondroplastic women
      ii. Respiratory compromise common during the third trimester
      iii. Advise baseline pulmonary function studies before pregnancy to aid in evaluation and management
      iv. A small pelvic outlet usually requiring Cesarean section under general anesthesia since the spinal or epidural approach is contraindicated because of spinal stenosis
   g. Anticipatory guidance: Patients and their families can benefit greatly from anticipatory guidance published by American Academy of Pediatrics Committee on Genetics (1995) and Clinical Report (2005).
   h. Adaptations of patients to the environment to foster independence
      i. Lowering faucets and light switches
      ii. Using a step stool to keep feet from dangling when sitting
      iii. An extended wand for toileting
      iv. Adaptations of toys for short limbs
   i. Support groups: Many families find it beneficial to interact with other families and children with achondroplasia through local and national support groups.

Diagnostic Investigations

1. Diagnosis of achondroplasia made by clinical findings, radiographic features, and/or *FGFR3* mutation analysis
2. Radiologic Features
   a. Skull
      i. Relatively large calvarium
      ii. Prominent forehead
      iii. Depressed nasal bridge
      iv. Small skull base
      v. Small foramen magnum
      vi. Dental malocclusion
   b. Spine
      i. Caudal narrowing of interpedicular distances in the lower lumbar spine
      ii. Short vertebral pedicles
      iii. Wide disc spaces

iv. Dorsal scalloping of the vertebral bodies in the newborn
v. Concave posterior aspect of the vertebral bodies in childhood and adulthood
vi. Different degree of anterior wedging of the vertebral bodies causing gibbus

c. Pelvis
i. Lack of iliac flaring
ii. Narrow sacroiliac notch
iii. Horizontal acetabular portions of the iliac bones

d. Limbs
i. Rhizomelic micromelia
ii. Square or oval radiolucent areas in the proximal humerus and femur during infancy
iii. Tubular bones with widened diaphyses and flared metaphyses during childhood and adulthood
iv. Markedly shortened humeri
v. Short femoral neck
vi. Disproportionately long fibulae in relation to tibiae

3. Craniocervical MRI
a. Narrowing of the foramen magnum
b. Effacement of the subarachnoid spaces at the cervicomedullary junction
c. Abnormal intrinsic cord signal intensity
d. Mild to moderate ventriculomegaly

4. Histology
a. Normal histologic appearance of epiphyseal and growth plate cartilages
b. Shorter than normal growth plate: The shortening is greater in homozygous than in heterozygous achondroplasia, suggesting a gene dosage effect.

5. Mutation analysis
a. G1138A substitution in *FGFR3* (about 98% of cases)
b. G1138C substitution in *FGFR3* (about 1% of cases)

Genetic Counseling

1. Recurrence risk
a. Patient's sib
i. Recurrence risk after the conception of an affected child has always been considered very low and less than 30 cases of recurrences among sibs have been reported so far (Natacci et al. 2008). It was possible to demonstrate somatic and germinal mosaicism in the mother (Henderson et al. 2000) and germinal mosaicism in the father (Natacci et al. 2008).
ii. Recurrence risk of achondroplasia in the sibs of achondroplastic children with unaffected parents: presumably higher than twice the mutation rate because of gonadal mosaicism. Currently, the risk is estimated as 1 in 443 (0.2%).
iii. Fifty percent affected if one of the parents is affected
iv. Twenty-five percent affected with homozygous achondroplasia (resulting in a much more severe phenotype that is usually lethal early in infancy) and 50% affected with heterozygous achondroplasia if both parents are affected with achondroplasia

b. Patient's offspring
i. Fifty percent affected (with heterozygous achondroplasia) if the spouse is normal
ii. Twenty-five percent affected with homozygous achondroplasia and 50% affected with heterozygous achondroplasia if the spouse is also affected with achondroplasia. There is still a 25% chance that the offspring will be normal.

2. Prenatal diagnosis
a. Prenatal ultrasonography
i. Suspect achondroplasia on routine ultrasound findings of a fall-off in limb growth (<3rd percentile), increased biparietal diameter (>95th percentile) and low nasal bridge (Cordone et al. 1993; Mesoraca et al. 1996), usually during the third trimester of pregnancy, in case of parents with normal heights. About one third of cases are suspected this way. However, one must be cautious because disproportionately short limbs are observed in a variety of conditions.
ii. Inability to make specific diagnosis of achondroplasia with certainty by ultrasonography unless by radiography late in gestation or after birth
iii. Request of prenatal ultrasonography by an affected parent, having 50% risk of having

a similarly affected child, to optimize obstetric management
iv. Follow pregnancy by a femoral growth curve in the second trimester by serial ultrasound scans to enable prenatal distinction between homozygous, heterozygous, and unaffected fetuses, in case of both affected parents

b. Prenatal radiography
i. Shortened long bones with wide metaphyses
ii. Slim and radiolucent area in the proximal femur
iii. Horizontal acetabular roof
iv. The above features not always detected

c. 3-Dimensional computed tomography scan (3D CT scan) may be used after 30 weeks of gestation (Krakow et al. 2003; Ruano et al. 2004).
i. Slightly flat vertebral bodies with medial spurs
ii. Pointed femora with proximal extremity
iii. Round and square ilia with an oval radiolucent area in the proximal femur

d. On computed tomography and postnatal X-ray, proximal femoral metaphysis appeared rounded, with poor, uneven ossification. Connection to diaphysis was abnormal, with relative overgrowth of the periosteum, creating a new diagnostic sign, called the "collar hoop" sign (Boulet et al. 2009).

e. Prenatal molecular testing
i. Molecular technology applied to prenatal diagnosis of a fetus suspected of or at risk for having achondroplasia
ii. Simple methodology requiring only one PCR and one restriction digest to detect a very limited number of mutations causing achondroplasia
iii. Preimplantation genetic diagnosis
a) Available at present (Moutou et al. 2003)
b) The initial practice raising questions on the feasibility of such a test, specially with affected female patients

3. Management
a. Adaptive environmental modifications
i. Appropriately placed stools
ii. Seating modification
iii. Other adaptive devices

b. Obesity control

c. Obstructive apnea
i. Adenoidectomy and tonsillectomy
ii. Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) for clinically significant persistent obstruction
iii. Extremely rare for requiring temporary tracheostomy

d. Experimental growth hormone therapy (Horton et al. 1992; Shohat et al. 1996; Seino et al. 2000)
i. Resulting in transient increases in growth velocity
ii. Long term result not conclusive

e. Hydrocephalus
i. Observation for benign ventriculomegaly
ii. May need surgical intervention for clinically significant hydrocephalus

f. Kyphosis
i. Adequate support for sitting in early infancy
ii. Bracing using a thoracolumbosacral orthosis for severe kyphosis in young children
iii. Surgical intervention for medically unresponsive cases

g. Surgical decompression for unequivocal evidence for cervical cord compression

h. Decompression laminectomy for severe and progressive lumbosacral spinal stenosis

i. Limb lengthening through osteotomy and stretching of the long bones (Aldegheri et al. 1988; Lavini et al. 1990; Ganel et al. 1979; Ganel and Horoszowski 1996)
i. Controversial
ii. Difficult to achieve the benefits of surgery
a) Need strong commitment on the part of the patients and their families for the time in the hospital and the number of operations
b) A high risk of infection
c) Occurrence of possible severe permanent sequelae (damage to joint and soft tissue)
d) May result in poorer quality of life

j. Potential anesthetic risks related to:
i. Obstructive apnea
ii. Cervical compression

k. Risks associated with pregnancy in women with achondroplasia: relatively infrequent
i. Worsening neurologic symptoms related to increasing hyperlordosis and maternal respiratory failure
ii. Anticipate a scheduled cesarean delivery due to cephalopelvic disproportion
iii. Preeclampsia
iv. Polyhydramnios

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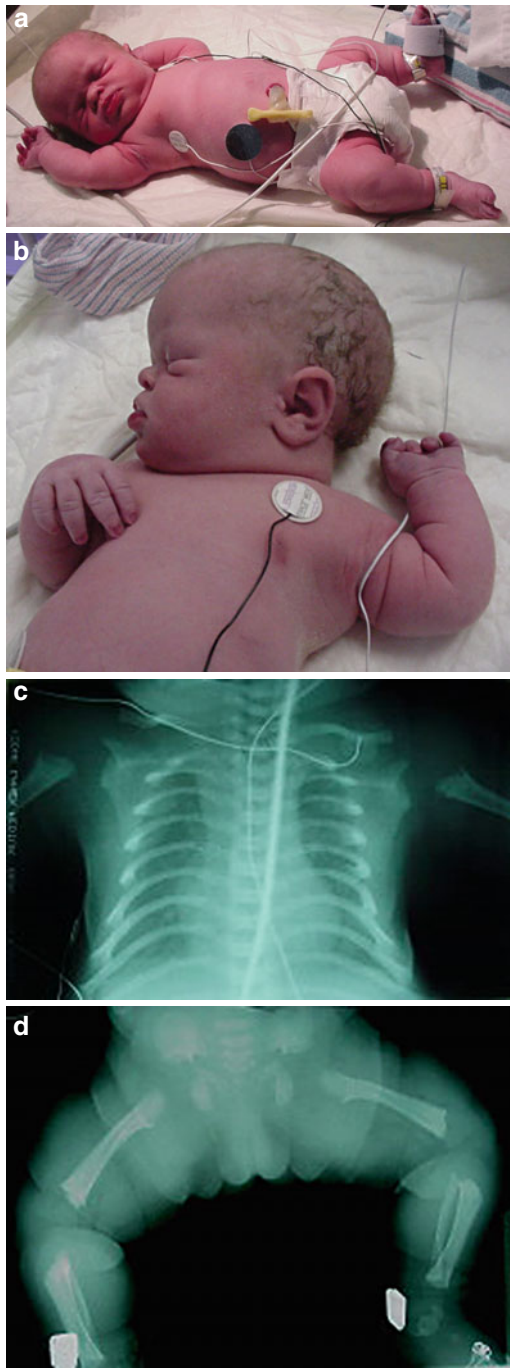

Fig. 1 (**a**–**d**) A newborn with achondroplasia showing large head, depressed nasal bridge, short neck, normal length of the trunk, narrow chest, rhizomelic micromelia, and trident hands. The radiographs showed narrow chest, characteristic pelvis, micromelia, and oval radiolucent proximal portion of the femurs. Molecular analysis showed 1138 G → C transversion mutation which has been observed in approximately 1.9% of achondroplasia chromosomes

Fig. 2 A 4-month-old boy with achondroplasia showing typical craniofacial features and rhizomelic shortening of limbs (confirmed by radiograms). Molecular study revealed 1138 G-to-A transition mutation which has been observed in approximately 98% of achondroplasia chromosomes

Fig. 3 (**a**–**c**) Another achondroplastic neonate with typical clinical features and radiographic findings. Note the abnormal vertebral column with wide intervertebral spaces and abnormal vertebral bodies

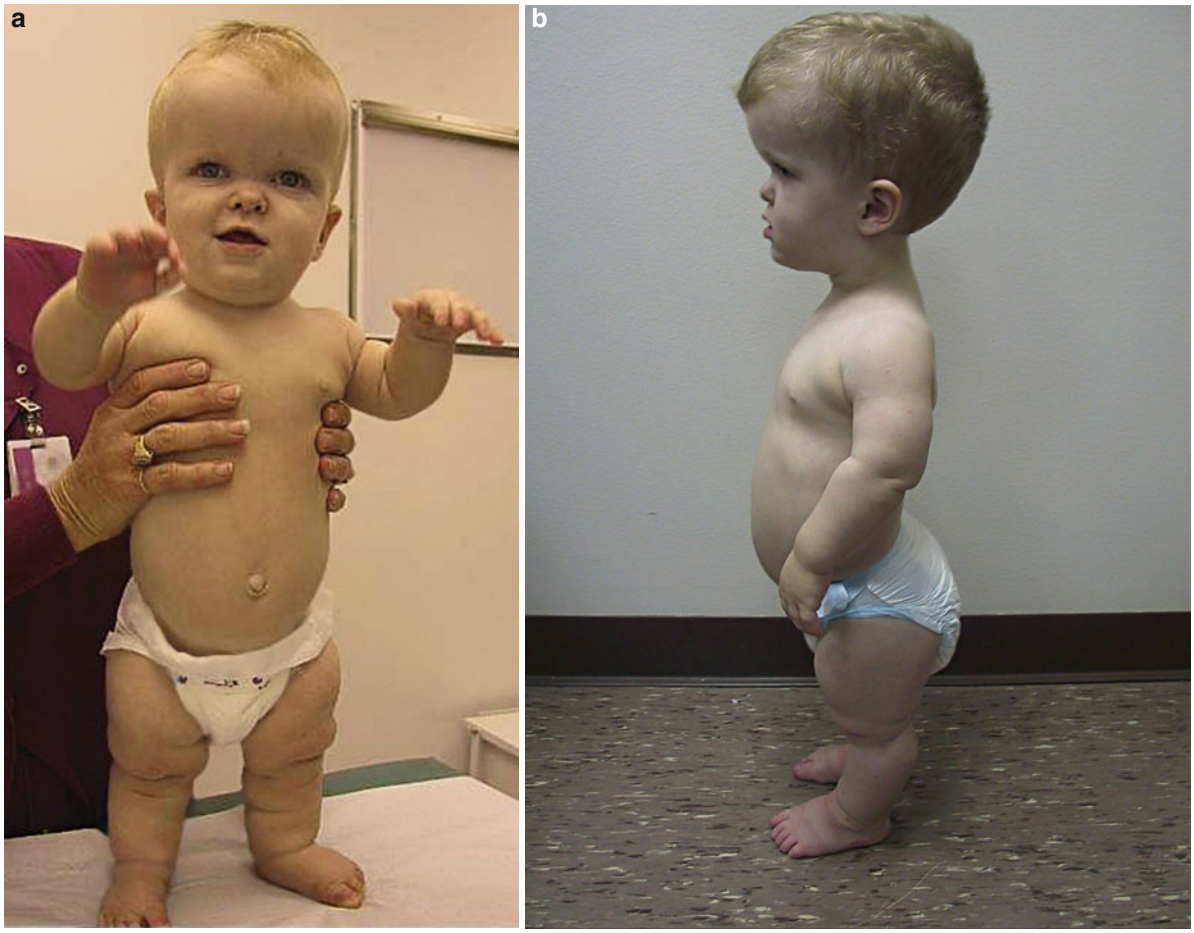

Fig. 4 (**a**, **b**) A boy (7 month and 2 year 7-month old) with achondroplasia showing a large head, small chest, normal size of the trunk, rhizomelic micromelia, and exaggerated lumbar lordosis

Fig. 5 (**a**–**c**) Two older children with achondroplasia showing rhizomelic micromelia, typical craniofacial features, exaggerated lumbar lordosis, and trident hands

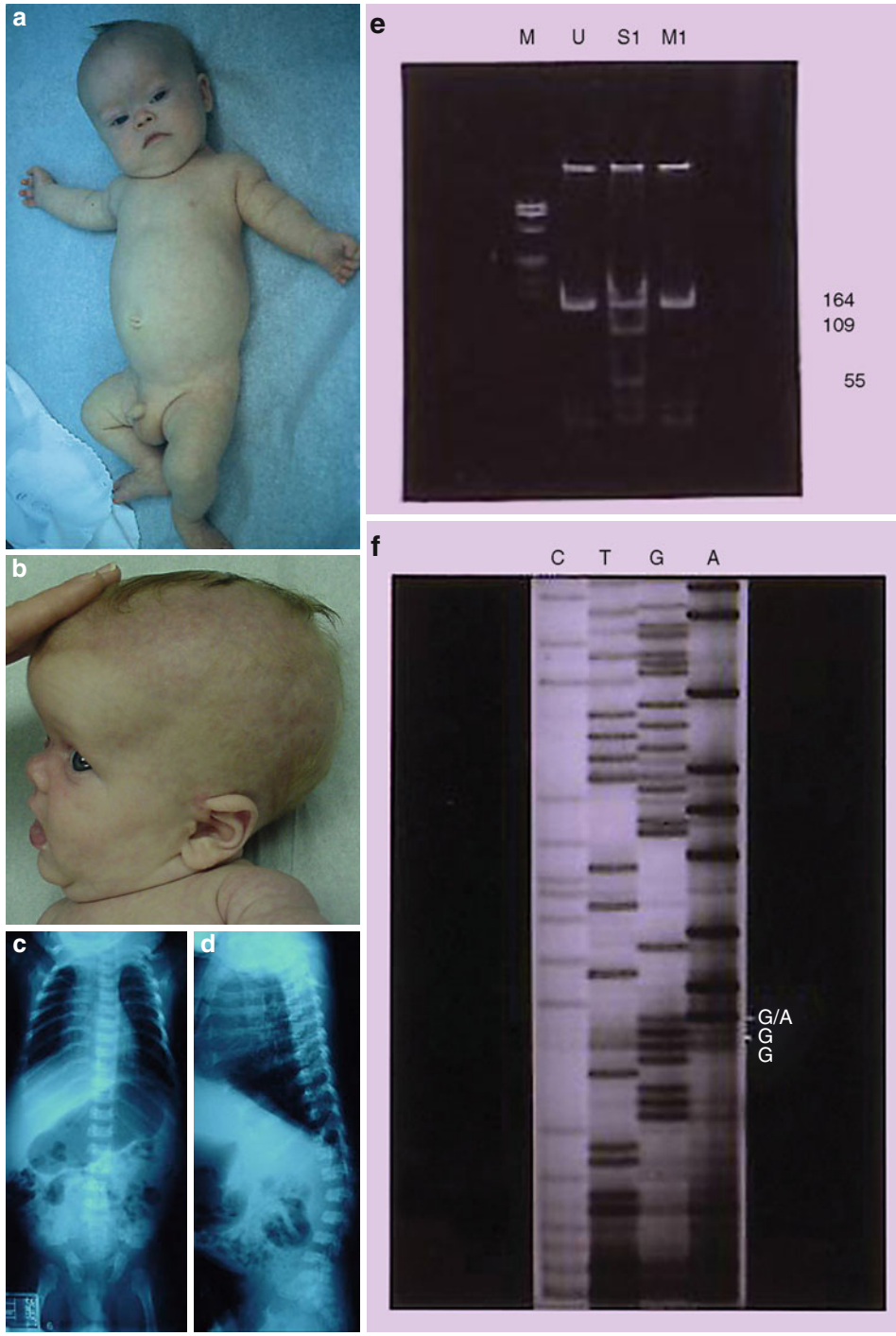

Fig. 6 (**a**–**f**) A boy with achondroplasia and i(21q) Down syndrome presented with diagnostic dilemma. Besides craniofacial features typical for Down syndrome, the skeletal findings of achondroplasia dominate the clinical picture. The diagnosis of Down syndrome was based on the clinical features and the cytogenetic finding of i(21q) trisomy 21. The diagnosis of achondroplasia was based on the presence of clinical and radiographic findings, and confirmed by the presence of a common FGFR3 gene mutation (Gly380Arg) detected by restriction enzyme analysis and sequencing of the PCR products

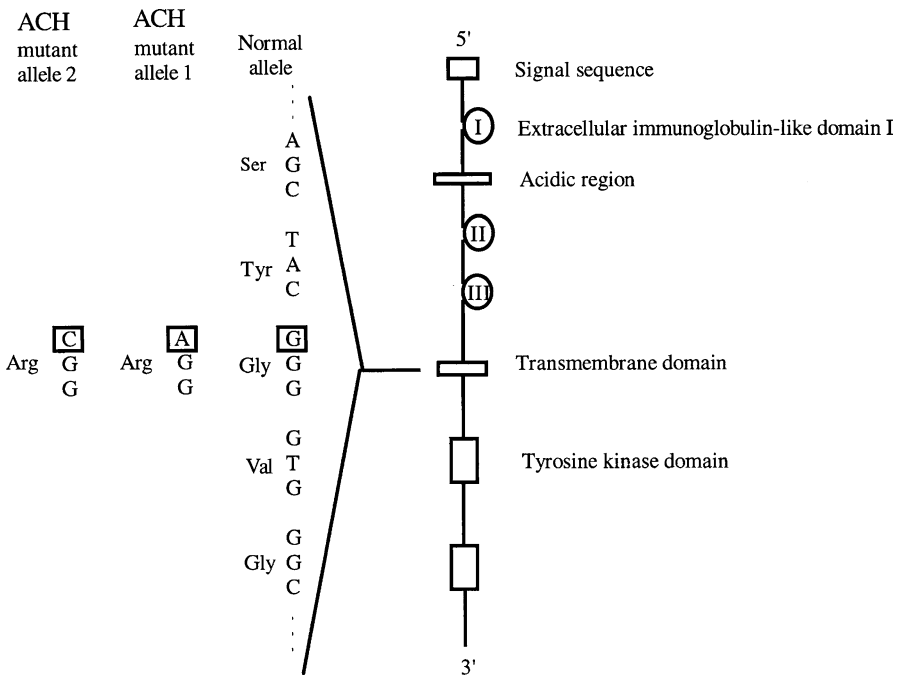

Fig. 7 Schematic of the FGFR3 gene and DNA sequence of normal allele and mutant FGFR3 achondroplasia allele (Modified from Shiang et al. 1994)

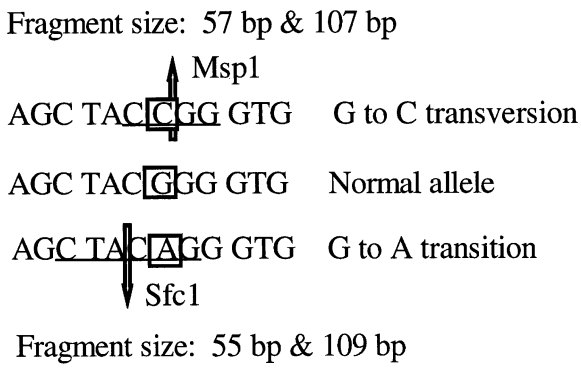

Fig. 8 Nucleotide change in the 1138 C allele creates a Msp1 site and nucleotide change in the 1138A allele creates a Sfc1. The base in the coding sequence that differs in the three alleles is boxed (Modified from Shiang et al. 1994)

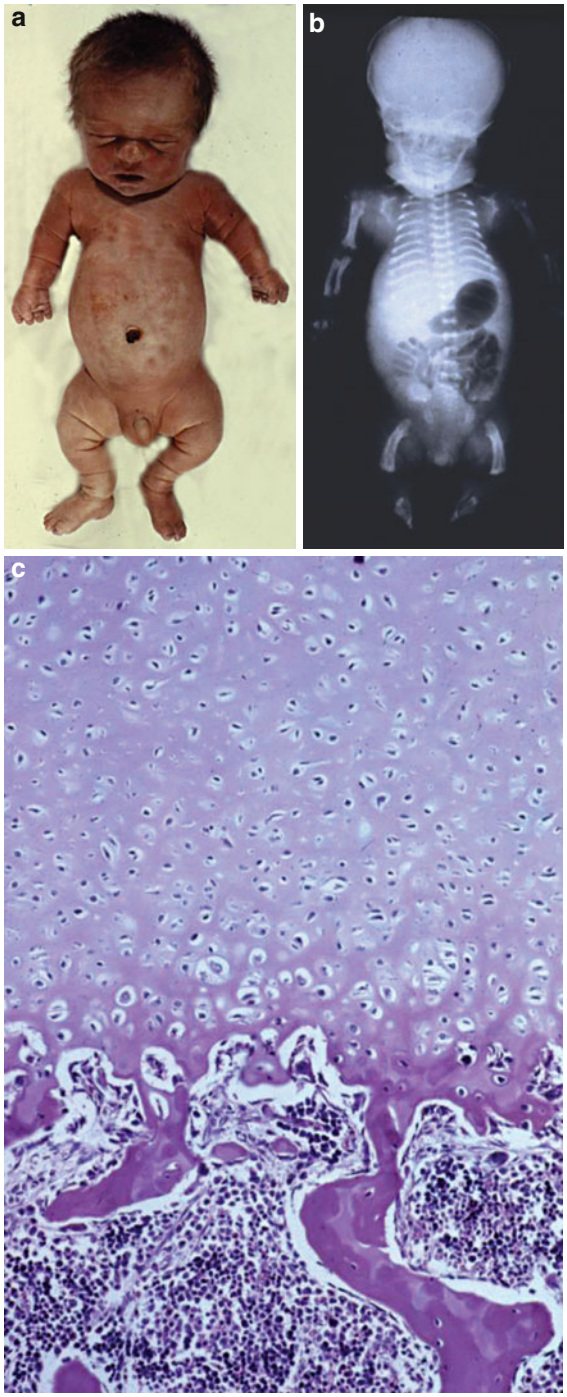

Fig. 9 (**a**–**c**) Homozygous achondroplasia. Both parents are achondroplastic. The large head, narrow chest and severe rhizomelic shortening of the limbs are similar to those of thanatophoric dysplasia. Radiograph shows severe platyspondyly, small ilia and short limb bones. Photomicrograph of the physeal growth zone shows severe retardation and disorganization, similar to that of thanatophoric dysplasia

Adams–Oliver Syndrome

In 1945, Adams and Oliver described congenital transverse limb defects associated with aplasia cutis congenita in a three-generation kindred with typical autosomal dominant inheritance and intrafamilial variable expressivity.

Synonyms and Related Disorders

Aplasia cutis congenita with terminal transverse limb defects

Genetics/Basic Defects

1. Genetic heterogeneity
   a. Autosomal dominant in most cases
      i. The family described by Adams and Oliver, and revisited by Whitley and Gorlin in 1991, illustrates vertical transmission, with multiple affected members spanning four generations and includes male-to-male transmission, consistent with autosomal dominant inheritance
      ii. Reports from over 20 further kindreds provide support for the role of a heterozygous autosomal gene mutation (Snape et al. 2009).
   b. Autosomal recessive in some cases
      i. The combination of aplasia cutis congenita and terminal transverse limb defects within sibships provides evidence for an autosomal recessive mode of inheritance
      ii. Further supported by the occurrence of affected siblings within inbred families
2. Pathogenesis
   a. Trauma
   b. Uterine compression
   c. Amniotic band sequelae
   d. Vascular disruption sequence
      i. Concomitant occurrence of Poland sequence
      ii. Both Poland sequence and Adams–Oliver syndrome: secondary to vascular disruption due to thrombosis of subclavian and vertebral arteries
   e. Massive thrombus from the placenta occluding the brachial artery
   f. Abnormalities in small vessel structures manifesting during embryogenesis
   g. A developmental disorder of morphogenesis
3. Molecular basis of the syndrome remains unknown, although the common occurrence of cardiac and vascular anomalies suggests a primary defect of vasculogenesis (Snape et al. 2009).

Clinical Features

1. Marked intrafamilial and interfamilial variability
2. Terminal transverse limb defects
   a. Most common manifestation (84%)
   b. Usually asymmetrical
   c. Tendency toward bilateral lower limb rather than upper limb involvement
   d. Mild spectrum of defects
      i. Nail hypoplasia
      ii. Cutaneous syndactyly
      iii. Bony syndactyly
      iv. Ectrodactyly
      v. Brachydactyly
   e. Severe spectrum of transverse defects
      i. Absence of the hand

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ii. Absence of the foot
iii. Absence of the limb

3. Aplasia cutis congenita
   a. Second most common defect (almost 75%)
   b. Associated with skull defect (64%): the most common site is the vertex, often with scalp defect extending to periosteum, skull, and dura
      i. Small lesion: 0.5 cm in diameter
      ii. Intermediate lesion: 8–10 cm involving the vertex
      iii. Severe lesion: involve most of the scalp with acrania
   c. Skull defect without scalp defect, often mistaken for an enlarged fontanelle
   d. May involve other areas of the body
   e. Severe end of the spectrum of scalp defects
      i. Encephalocele
      ii. Acrania
   f. Most severe manifestations can be associated with a mortality rate of 20–55% (Bjpai and Pal 2003)
      i. Associated with dilated and tortuous scalp veins with significant morbidity
      ii. Associated with hemorrhage or infection
4. Congenital cardiovascular malformations (13.4–20%)
   a. Mechanisms proposed to explain the pathogenesis of congenital cardiovascular malformations
      i. Alteration of mesenchymal cell migration resulting in conotruncal malformations, e.g., tetralogy of Fallot, double outlet right ventricle, and truncus arteriosus
      ii. Alteration of fetal cardiac hemodynamics resulting in different malformations such as coarctation of the aorta, aortic stenosis, perimembranous VSD, and hypoplastic left heart
      iii. Persistence of normal fetal vascular channels resulting in postnatal vascular abnormalities
   b. Diverse vascular and valvular abnormalities
      i. Bicuspid aortic valve
      ii. Pulmonary atresia
      iii. Parachute mitral valve
      iv. Pulmonary hypertension
5. Other associated anomalies
   a. Cutis marmorata telangiectasia congenita (12%)
   b. Dilated and tortuous scalp veins (11%)
   c. Poland anomaly
   d. Encephalocele
   e. Facial features
      i. Hemihypoplasia
      ii. Hypertelorism
      iii. Epicanthal folds
      iv. Microphthalmia
      v. Esotropia
      vi. High arch palate
      vii. Cleft palate
   f. Cryptorchidism
   g. Lymphatic abnormalities
      i. Lymphedema of the leg
      ii. Chylothorax
      iii. Dilated pulmonary lymphatics
      iv. Intestinal lymphangiectasia
      v. Marmorata telangiectasia congenita (a cutaneous vascular abnormality)
   h. CNS abnormalities: unusual manifestation
      i. Mental retardation
      ii. Learning disability
      iii. Epilepsy
   i. Short stature
   j. Renal malformations
   k. Spina bifida occulta
   l. Accessory nipples
6. Major and minor features of Adams–Oliver syndrome (Snape et al. 2009): The presence of two major features is considered sufficient for a diagnosis. The combination of one major and one minor feature should place Adams–Oliver syndrome high in the differential diagnosis of such individuals.
   a. Major features
      i. Terminal transverse limb defects
      ii. Aplasia cutis congenita
      iii. Family history of Adams–Oliver syndrome
   b. Minor features
      i. Cutis marmorata telangiectasia congenita
      ii. Congenital cardiac defect
      iii. Vascular anomaly
7. Differential diagnosis (Snape et al. 2009)
   a. Amniotic band sequence
   b. Moebius and Poland syndromes (McGuirk et al. 2001)
   c. Teratogenic agents such as phenytoin, misoprostol, and ergotamine
      i. Asymmetric bilateral transverse terminal limb defects
      ii. Tend to affect the upper limb more severely than the lower limb (Spranger et al. 1980; Holmes 2002)

d. Limb anomalies
   i. Caused by thalidomide: tends to be symmetrical and longitudinal (Smithells and Newman 1992)
   ii. Caused by chorionic villus sampling during pregnancy (Holmes 2002)
e. Isolated aplasia cutis congenita: substantial heterogeneity based on association with known abnormalities or exposure to teratogens such as methimazole (Frieden 1986)
f. Cutis marmorata telangiectasia congenita
   i. Common in kindreds with Adams–Oliver syndrome
   ii. Can be seen in combination with both terminal transverse limb defects (Maniscalco et al. 2005) and aplasia cutis congenita (Verdyck et al. 2003)
   iii. Can be an isolated finding in otherwise unaffected family members (Scribanu and Temtamy 1975; Toriello et al. 1988)
   iv. Can be associated with skin atrophy and ulcerations, capillary malformations, capillary and cavernous vascular malformations, under- or overgrowth of the affected extremity, macrocephaly and glaucoma, and in association with vascular syndromes including Sturge–Weber and Klippel–Trenaunay (Amitai et al. 2000)

Diagnostic Investigations

1. Radiography
   a. Transverse limb defects
   b. Ectrodactyly
   c. Brachydactyly
   d. Syndactyly
   e. Nail hypoplasia
   f. Skull defect
2. CT scan or MRI of the brain
   a. Polymicrogyria
   b. Ventriculomegaly
   c. Irregular cortical thickening
   d. Cerebral cortex dysplasia
   e. Microcephaly
   f. Arhinencephaly
   g. Periventricular and parenchymal calcium deposits

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal dominant: not increased unless a parent is affected in which case the risk is 50%
      ii. Autosomal recessive: 25%
   b. Patient's offspring
      i. Autosomal dominant: 50%
      ii. Autosomal recessive: not increased unless the spouse carries the gene or is affected
2. Prenatal diagnosis by ultrasonography
   a. Transverse limb defects
   b. Concomitant skull defect
3. Management
   a. Treat minor scalp lesions with daily cleansing of the involved areas with applications of antibiotic ointment
   b. Surgically close larger lesions and exposed dura with minor or major skin grafting procedure (split thickness or full thickness)
   c. Prevent sepsis and/or meningitis from an open scalp lesion which is highly vascular and rarely involves the sagittal sinus predisposing to episodes of spontaneous hemorrhage
   d. Urgent surgical intervention may be required with operative measures that include primary closure, skin grafting, local scalp flaps with or without tissue expansion, and cranial vault reconstruction using split rib grafts and free latissimus dorsi muscle flap (Bajpai and Pal 2003)
   e. Orthopedic care for various degree of limb defects

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Fig. 1 A 9-month-old boy with Adams–Oliver syndrome showing alopecia, absent eyebrows and eyelashes, scalp defect, tortuous scalp veins, and limb defects (brachydactyly, syndactyly, broad great toes, and nail hypoplasia). Radiography showed absent middle and distal phalanges of second to fifth toes and absent distal phalanges of the great toes

Agnathia

Agnathia is an extremely rare lethal neurocristopathy. The disorder has also been termed agnathia-holoprosencephaly spectrum, agnathia-otocephaly complex, agnathia-astomia-synotia, or cyclopia-otocephaly association. The incidence is estimated to be 1 in 70,000 infants (Schiffer et al. 2002).

The spectrum of agnathia ranges from isolated agnathia, or virtual absence of the mandible, to otocephaly, which refers to a broader malformation of mandibular hypoplasia or agnathia, downward displacement of the ears and/or synotia (approximation of the ears in the midline), with or without aglossia (no tongue), and microstomia (small mouth) (Petrikovsky 1999). Agnathia-otocephaly is a lethal malformation complex characterized by absence of the mandible, microstomia, aglossia, and positioning of the ears toward the midline (Pauli et al. 1981; Bixler et al. 1985). Although ear positioning is variable and the use of the term "otocephaly" does not seem always justified, otocephaly is commonly used to assemble all ear abnormalities with displacement toward the midline (Schiffer et al. 2002). Agnathia-otocephaly can occur alone or in combination with a variety of associated malformations, holoprosencephaly being the most commonly reported association.

Synonyms and Related Disorders

Agnathia-holoprosencephaly spectrum; Agnathia-otocephaly complex

Genetics/Basic Defects

1. Sporadic occurrence in majority of cases
2. Rare autosomal recessive inheritance: two siblings with isolated dysgnathia complex who survived infancy (Baker et al. 2004)
3. Possible autosomal dominant inheritance
   a. Supported by an observation of dysgnathia in mother and daughter (Erlich et al. 2000)
   b. Possibility of a defect in the *OTX2* gene as the basis of the disorder (Matsuo et al. 1995)
4. Teratogenic factors have been described in humans
   a. Salicylate (Benawra et al. 1980)
   b. Amidopyrine (Mollica et al. 1979)
   c. Theophylline (Ibba et al. 2000)
5. A prechordal mesoderm inductive defect affecting neural crest cells
   a. A developmental field defect
   b. Different etiologic agents (etiological heterogeneity) acting on the same developmental field producing a highly similar complex of malformations
6. Possible existence of a mild form of agnathia without brain malformation (holoprosencephaly)
   a. Situs inversus-congenital hypoglossia
   b. Severe micrognathia, aglossia, and choanal atresia
7. A well-recognized malformation complex in the mouse (Juriloff et al. 1985), guinea pig (Wright 1934), rabbit, sheep, and pig

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Clinical Features

1. Polyhydramnios due to persistence of oropharyngeal membrane or blind-ending mouth
2. Agnathia (absence of the mandible)
3. Microstomia or astomia (absence of the mouth)
4. Aglossia (absence of the tongue)
5. Blind mouth
6. Ear anomalies
   a. Otocephaly (variable ear positions)
   b. Synotia (external ears approaching one another in the midline)
   c. Dysplastic inner ear
   d. Atretic ear canal
7. Down-slanting palpebral fissures
8. Variable degree of holoprosencephaly: nearly 100 patients reported as having holoprosencephaly and features consistent with the spectrum of agnathia (Kauvar et al. 2010).
   a. Cyclopia
   b. Synophthalmia
   c. Arrhinencephaly
9. Other brain malformations
   a. Cerebellar hypoplasia
   b. Septum pellucidum cavum
   c. Absence of cranial nerves (I–IV)
   d. Absence of the corpus callosum
   e. Meningocele
10. Intrauterine growth retardation
11. Cleft lip/palate
12. Occular malformations
   a. Microphthalmos/anophthalmia
   b. Proptosis (protruding eyes)
   c. Absence of the eyelids
   d. Epibulbar dermoid
   e. Aphakia
   f. Retinal dysplasia
   g. Microcornea
   h. Anterior segment dysgenesis
   i. Uveal colobomas
13. Nasal anomalies
   a. Absence of the nasal cavity
   b. Cleft nose
   c. Blind nasal pharynx
14. Various visceral malformations
   a. Choanal atresia
   b. Tracheoesophageal fistula
   c. Absence of the thyroid gland
   d. Absence of the submandibular and parotid salivary glands
   e. Abnormal glottis and epiglottis
   f. Thyroglossal duct cyst
   g. Carotid artery anomalies
   h. Situs inversus
   i. Cardiac anomalies
   j. Unlobulated lungs
   k. Renogenital anomalies
      i. Unilateral renal agenesis
      ii. Renal Ectopia
      iii. Cystic kidneys
      iv. Horseshoe kidneys
      v. Solitary kidney
      vi. Mullerian duct agenesis
      vii. Cryptorchidism
15. Skeletal anomalies
   a. Vertebral anomalies
   b. Rib anomalies
   c. Tetramelia
16. Anatomical variations
   a. Ears
      i. Absence of the tragus
      ii. Synotia
   b. Mandible
      i. Rudimentary
      ii. Absent
      iii. Two small separate masses
   c. Mouth: microstomia with vertical orientation
   d. Buccopharyngeal membrane: absent to present
   e. Tongue
      i. Small to absent body
      ii. Present in (hypo)pharynx
   f. Absent submandibular glands
   g. Other skull bones: approximated maxillae, palatine, zygomatic, and temporal

Diagnostic Investigations

1. Radiography
   a. Reduced maxilla
   b. Absence of the zygomatic process
   c. Absence of the hyoid bone
   d. Vertebral anomalies
   e. Absence of the ribs
   f. Sprengel deformity
2. Cranial ultrasonography to define holoprosencephaly

3. Postnatal reconstructed CT for detailed 3-D structure of the cranium in agnathia-otocephaly
4. Chromosome analysis
   a. Normal in majority of cases
   b. Unbalanced der(18),t(6;18)(pter → p24.1; p11.21 → qter) in two female sibs with agnathia-holoprosencephaly
5. Autopsy to define postmortem findings

Genetic Counseling

1. Recurrence risks
   a. Risk to patient's sib: not increased unless in a rare autosomal recessive inheritance
   b. Risk to patient's offspring
      i. Not applicable to lethal cases since the patients do not survive to reproductive age
      ii. Autosomal dominant (some case may survive to reproductive age): 50%
2. Prenatal diagnosis by 3-D ultrasonography (Ducarme et al. 2007; Tantbirojn et al. 2008). 3-D imaging by helical computed tomography (CT), and/or MRI imaging (Chen et al. 2003, 2007)
   a. Polyhydramnios: secondary to an atretic, constricted, or obstructed oropharynx that prevents the fetus from swallowing amniotic fluid efficiently or at all
   b. Intrauterine growth retardation
   c. Mandibular absence (agnathia) or major hypoplasia
   d. Holoprosencephaly
   e. Cyclopia, marked hypotelorism or frontal proboscis
3. Management
   a. Although a lethal entity, several survivals beyond infancy have been reported (Brecht and Johnson 1985; Kamiji et al. 1991; Walker et al. 1995; Shermak and Dufresne 1996; Baker et al. 2004). Our third case with agnathia is still surviving with normal neurological development at 20 years of age.
   b. All survivors required tracheotomy immediately soon after delivery since no laryngeal opening is most likely present for endotracheal tube insertion
   c. EXIT (*ex utero* intrapartum treatment) procedure, a technique for safely managing airway obstruction at birth, in which placental support is maintained until the airway can be evaluated and secured (Umekawa et al. 2007)

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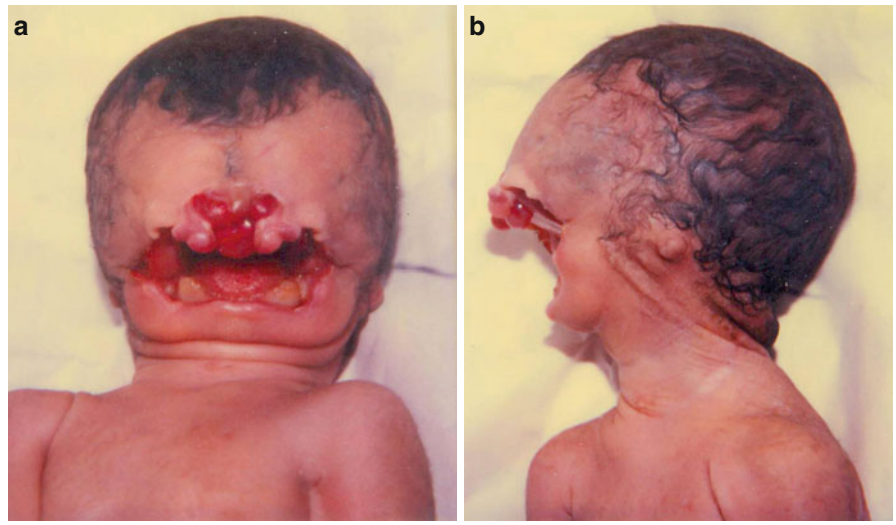

Fig. 1 (**a**, **b**) A neonate (28 week gestation) with agnathia-holoprosencephaly complex showing a large defect involving entire midface area with almost total absence of jaw, absence of eyes and nose, and severe microtia. Absence of olfactory bulbs and grooves (arrhinencephaly) were demonstrated by necropsy. Additional anomalies included 13 pairs of ribs, atresia of left ureter with resultant hydronephrosis, and left renal cortical cysts. Maternal hydramnios was present

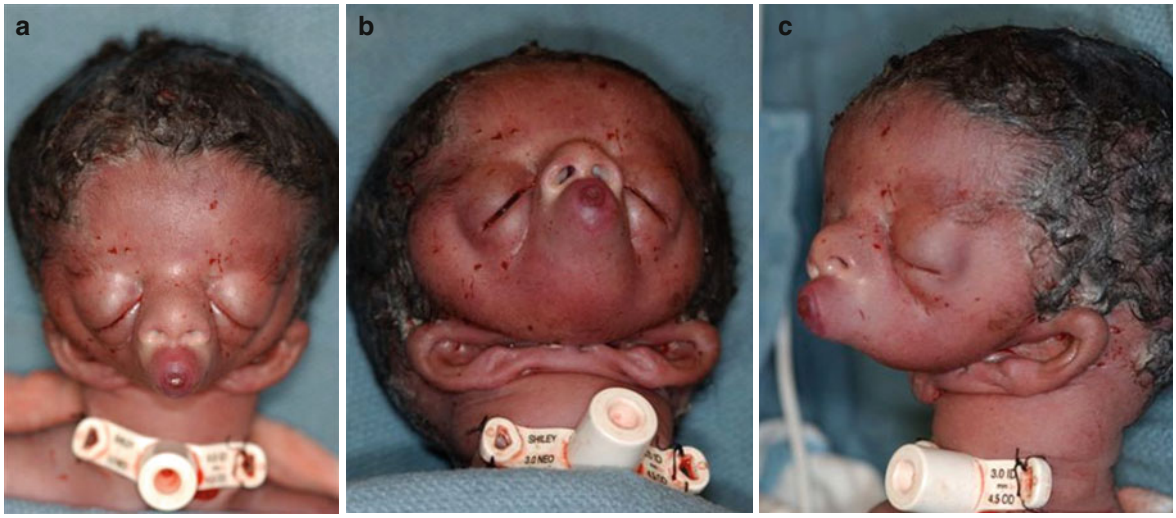

Fig. 2 (**a**–**c**) The female infant was born via elective caesarian section with Apgar scores of 1, 1, 1 at 1, 5 and 10 min respectively. After a failed attempt at nasotracheal intubation, an emergent tracheostomy was performed. However, the infant expired shortly after placement. Postmortem examination of the baby revealed congenital absence of the mandible (agnathia), microstomia with a slit-like oral opening, posterior choanal atresia, proptosis, and external ears placed ventrally with posterior rotation approaching each other in the midline. Amniocentesis revealed normal chromosomes

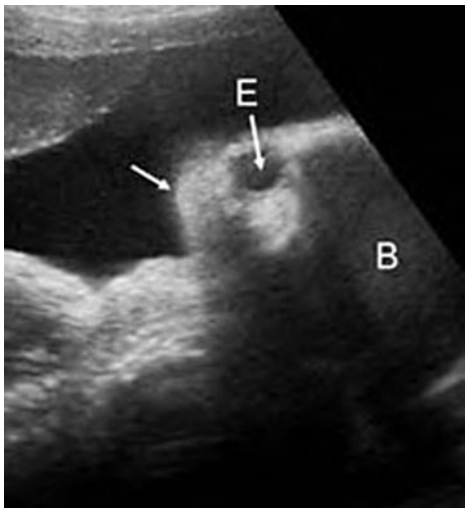

Fig. 3 Prenatal ultrasound showed absence of fetal jaw (*arrow*) (*E* fetal eye, *B* fetal brain)

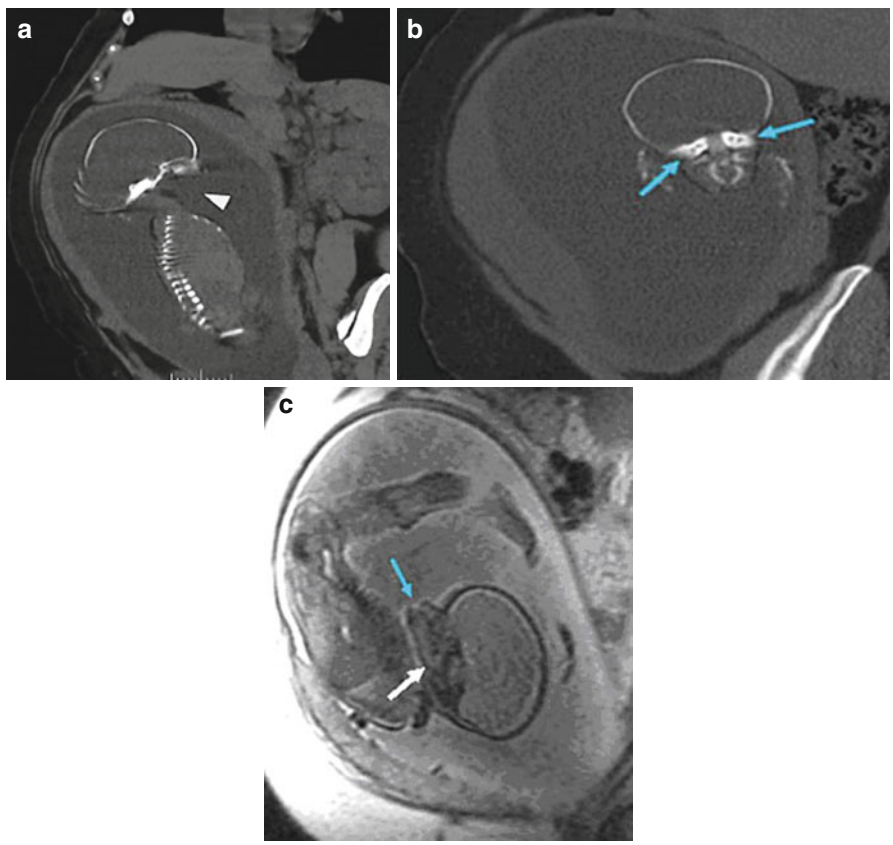

Fig. 4 (**a**–**c**) Maternal abdominal T2 MRI showed agnathia (*blue arrow*) and the lower end of the large horizontal ear meeting at the jaw area (*white arrow*)

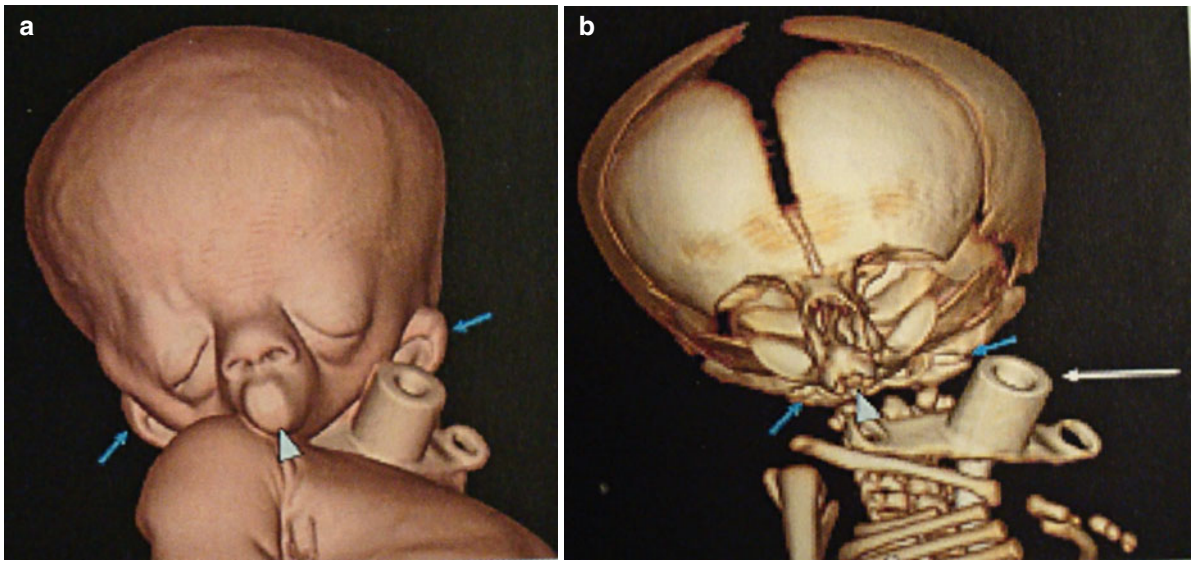

Fig. 5 (**a**, **b**) Postmortem CT scan demonstrated mandibular agnathia with synotia (posterior rotation with ventromedial displacement of the external ear structures approaching fusion near the midline), hypoplasia of the superior maxillary bone and persistece of the inner ears in their initial fetal position

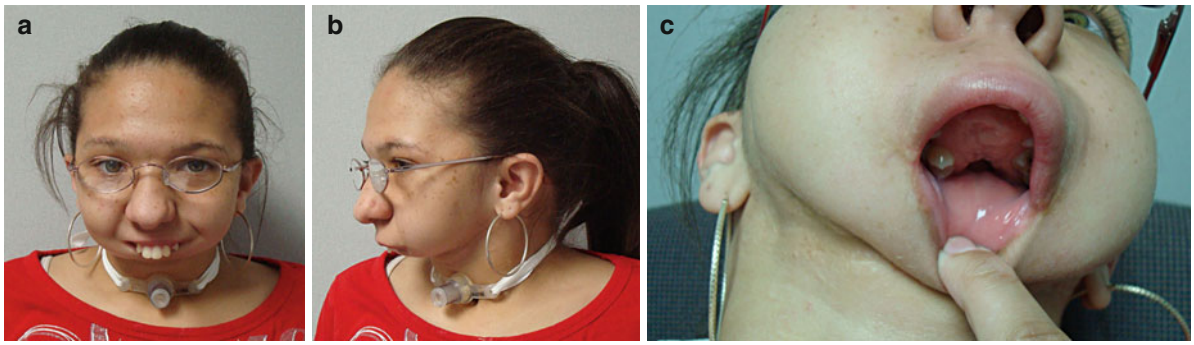

Fig. 6 (**a**–**c**) A 20-year-old female with agnathia with tracheotomy. She has severe microretrognathia due to absence of mandible, cleft palate, Arnold-Chiari malformation, severe bilateral hearing loss, Klippel-Feil syndrome, and scoliosis

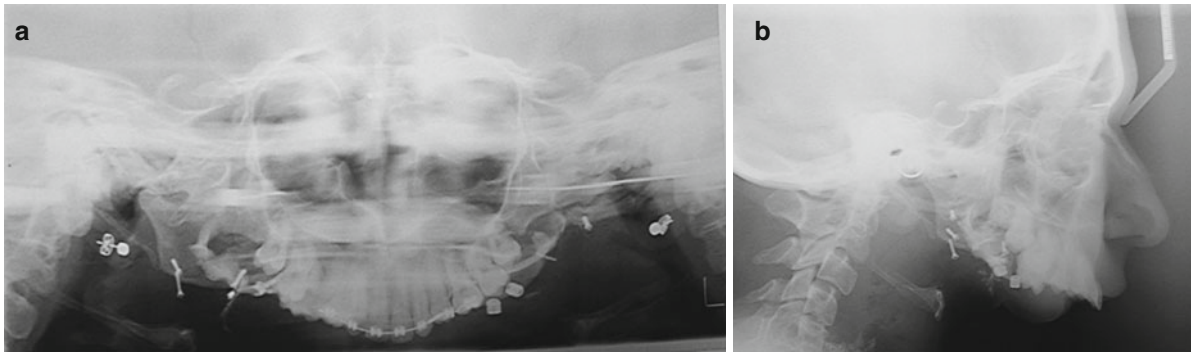

Fig. 7 (**a**, **b**) Radiographs of orofacial structures showed absence of mandible

Aicardi Syndrome

In 1965, Aicardi et al. reported a new syndrome consisting of spasms in flexion, callosal agenesis, and ocular abnormalities. Actual frequency of the condition is not known, but about 1–4% of cases of infantile spasms from tertiary referral centers may be due to Aicardi syndrome.

Synonyms and Related Disorders

Agenesis of corpus callosum with chrioretinal abnormality

Genetics/Basic Defects

1. Inheritance (Aicardi 2005)
   a. An X-linked dominant, lethal in males (Aicardi 1999)
   b. Almost exclusively affects females with two X chromosomes (heterozygous for a particular mutant X-chromosome gene to manifest)
   c. Exceptions
      i. Boys with XXY chromosome constitution (Hopkins et al. 1979; Aicardi 2005; Chen et al. 2009) allowing heterozygous expression of the gene as in the female
      ii. Two phenotypic boys with 46,XY males (Curatolo et al. 1980; Aggarwal et al. 2000): Aicardi has disputed the observations that are too atypical for classification as Aicardi syndrome due to the presence of lissencephaly or chorioretinal lesions not reminiscent of lacunae (Aicardi 1980).
      iii. 5-year-old male was reported to have clinical triad of Aicardi syndrome (Chappelow et al. 2008): Routine cytogenetic analysis showed 46, XY. A chromosome microarray analysis failed to detect any known microdeletion or microduplication. The possibility of low mosaic for 47,XXY Klinefelter cannot be ruled out.
   d. Not known to be a familial condition, except an isolated familial instance involving two sisters (Molina et al. 1989)
   e. The mutation
      i. Seems to arise de novo, accounting for the almost complete absence of familial cases
      ii. Could occur as a postzygotic event in early embryonic development as suggested by the observation of a monozygotic twin in a pair in which only one twin had Aicardi syndrome, the other being unaffected (Costa et al. 1997)
2. A gene responsible for Aicardi syndrome has not been identified
3. Gene map postulated on chromosome Xp22.3 from an observation in an affected girl with t(X;3)(p22;q12)

Clinical Features

1. Classic triad
   a. Pathognomonic chorioretinal lacunae
      i. Multiple, rounded, unpigmented, and yellow-white lesions
      ii. Occasionally unilateral
      iii. May be absent in rare cases
   b. Infantile spasms: the most characteristic type of seizure

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i. Frequently asymmetric or even unilateral (Bour et al. 1986)
ii. Often preceded or precipitated by a focal clonic or tonic seizure limited to the side in which the spasms predominate
c. Agenesis of the corpus callosum
2. Other CNS abnormalities
a. Ependymal cysts
b. Choroid plexus papillomas
c. Cortical migration abnormalities
d. Optic disc coloboma
e. Hydrocephaly
f. Porencephaly
g. Cerebellar agenesis
h. Heterotopias
3. Variable neurologic abnormalities
a. Hemiparesis or hemiplegia
i. The most frequent abnormality
ii. Often on the side where the spasms predominate
b. Quadriplegia
c. Hypotonia
d. Hypertonia
e. Development of microcephaly, though head circumference is normal at birth
4. Microphthalmia
5. Extra-CNS tumors
a. Soft palatal benign teratoma
b. Hepatoblastoma
c. Parapharyngeal embryonal cell carcinoma
d. Limb angiosarcoma
e. Scalp lipoma
f. Multiple gastrointestinal polyps
6. Scoliosis or costovertebral anomalies
7. Severe cognitive and physical handicaps
a. Global developmental delay
b. Moderate to severe mental retardation in most patients
c. Unable to ambulate in most children
d. Limited visual ability
8. New diagnostic criteria (Aicardi 1999, 2005)
a. Classic triad
i. Infantile spasms
ii. Chorioretinal lacunae
iii. Agenesis/dysgenesis of the corpus callosum
b. New major features (present in most patients studied by MRI)
i. Cortical malformations, mostly microgyria (probably constant but may not be possible to evidence)
ii. Periventricular and subcortical heterotopia
iii. Cysts around the third ventricle and/or choroid plexuses
iv. Papillomas of choroid plexuses
v. Optic disc/nerve coloboma
c. Supporting features (present in some cases)
i. Vertebral and costal abnormalities
ii. Microphthalmia and/or other eye abnormalities
iii. "Split-brain" EEG (associated suppression-burst tracing)
iv. Gross hemispheric asymmetry
9. Estimated survival rate
a. 76% at 6 years of age
b. 40% at 15 years of age

Diagnostic Investigations

1. Ophthalmological examination
a. Choroid retinal lacunae
b. Optic disc coloboma
2. Electroencephalograms
a. "Split-brain" EEG
b. Asymmetry or asynchrony
c. Quasiperiodicity
d. Hypsarrhythmia
3. CT or MRI of the brain
a. Agenesis or partial agenesis of the corpus callosum
b. Choroid plexus papillomas
c. Cerebellar dysgenesis
d. Cortical heterotopias
e. Porencephaly
f. Agenesis or hypoplasias of the cerebellar vermis
4. Radiography for skeletal malformations
5. Chromosome analysis in case of Klinefelter syndrome
6. Not caused by copy number variants detectable with currently used high-resolution array platform (Wang et al. 2009)
7. Histopathology
a. Multiple brain malformations
i. Complete or partial agenesis of the corpus callosum
ii. Cortical heterotopias

iii. Gyral malformation
iv. Intraventricular cysts
v. Microscopic evaluation of the parenchyma
a) Disordered cellular organization
b) Disruption of the normal layered appearance of the cortex

b. Chorioretinal lacunae
i. Well-circumscribed, punched-out lesions in the retinal pigment epithelium and choroid
ii. Severely disrupted retinal architecture
a) All layers are thinned.
b) Decreased choroidal vessel number and caliber are decreased
c) Presence of pigmentary ectopia and pigmentary epithelial hyperplasia

Genetic Counseling

1. Recurrence risk
   a. Patient's sibs: recurrence not likely (exception with one report of two affected sibs, likely due to gonadal mosaicism in one of the parent).
   b. Patient's offspring: 50% of offspring of affected females are expected to carry the abnormal X chromosome but affected individuals are not expected to survive to reproduce.
2. Prenatal diagnosis: not available currently. The prenatal ultrasonographic findings include:
   a. Arachnoid cysts
   b. Agenesis of the corpus callosum (development of the corpus callosum may not be complete until 22 weeks of gestation)
   c. Ventriculomegaly
3. Management
   a. Anticonvulsants for control of seizures
   b. Specific therapy for infantile spasm
      i. Adrenocorticotropic hormone (ACTH): effective for some patients
      ii. Vigabatrin, a more recently introduced therapy for infantile spasm
         a) An enzyme that breaks down GABA, the major inhibitory neurotransmitter in the brain
         b) Effective for infantile spasm without the serious life-threatening adverse effects of ACTH
         c) Possible ophthalmologic sequelae of constriction of the visual fields
         d) Not currently approved for use in the USA
   c. A multidisciplinary team approach to developmental handicaps
   d. Orthopedic surveillance and treatment of scoliosis
   e. Vigorous treatment of any infection as pulmonary problems are the commonest cause of death

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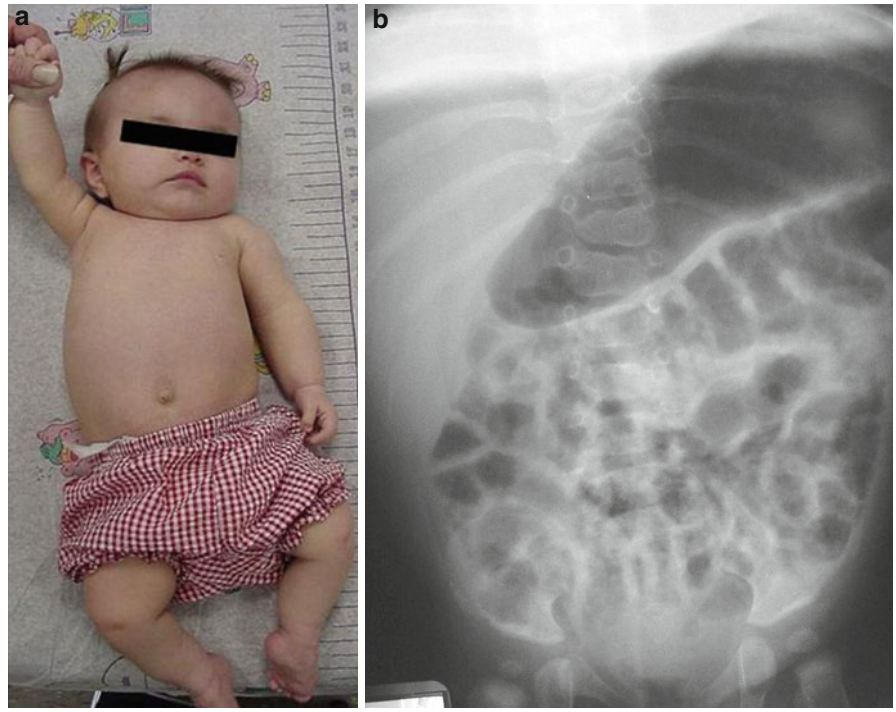

Fig. 1 (**a**, **b**) A 8 month old girl with Aicardi syndrome characterized by infantile spasms, chrioretinopathy, brain malformation, and costovertebral anomalies

Alagille Syndrome

In 1969, Alagille et al. described a syndrome characterized by chronic cholestasis resulting from paucity of interlobular bile ducts, peripheral pulmonary stenosis, butterfly-like vertebral arch defect, posterior embryotoxon, and peculiar facies. The syndrome is also known as arteriohepatic dysplasia.

Alagille syndrome occurs in approximately 1 in 60,000 live births based on the presence of neonatal cholestasis (Danks et al. 1977). This may be an underestimate as molecular testing has demonstrated that many individuals with a disease-causing mutation do not have neonatal liver disease (Kamath and Poccoli 2003).

Synonyms and Related Disorders

Arteriohepatic dysplasia; *JAG1*-related Alagille syndrome; NOTCH2-related Alagille syndrome

Genetics/Basic Defects

1. Inheritance:
   a. Sporadic in 45–50% of cases
   b. Autosomal dominant
      i. Reduced penetrance
      ii. Variable expressivity
   c. Alagille syndrome gene mapped to 20p12 (Li et al. 1996)
2. Molecular defect
   a. Caused by mutations or deletions of Jagged-1 gene (*JAG1*), encoding a ligand for the NOTCH transmembrane receptor, implicated in cell differentiation (Li et al. 1997)
   b. More than 120 described intragenic mutations of the *JAG1* gene
   c. No clear genotype–phenotype correlation in Alagille syndrome
   d. NOTCH2 mutations were identified in 2/11 individuals with classic Alagelle syndrome who do not have an identifiable *JAG1* mutation (McDaniel et al. 2006)

Clinical Features

1. High variability of phenotypic findings
2. Major features
   a. Neonatal chronic cholestasis
      i. Episodes of jaundice separated by periods of remission
      ii. Pruritus
      iii. Hepatomegaly
      iv. Splenomegaly: may be associated with portal hypertension
      v. Xanthoma: progressive and observed in:
         a) Extensor surface of the fingers
         b) Palmar creases
         c) Nape of the neck
         d) Anal folds
         e) Popliteal fossa
         f) Inguinal areas
   b. Facial features
      i. Broad prominent forehead
      ii. Deep-set, widely spaced eyes
      iii. Long, straight nose
      iv. Underdeveloped mandible

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   c. Complex congenital cardiovascular anomalies
      i. Pulmonary artery stenosis (67%)
      ii. Ventricular septal defects
      iii. Patent ductus arteriosus
      iv. Pulmonary valve atresia
      v. Tetralogy of Fallot (7–16%)
      vi. Tricuspid regurgitation
      vii. Right ventricular hypertrophy
   d. Vertebral arch anomalies (butterfly-like vertebrae)
   e. Posterior embryotoxon (prominent Schwalbe's ring)
3. Less frequently associated features
   a. Growth retardation
   b. Neurologic complications from vitamin E deficiency
   c. Mental retardation (2–30%)
   d. Systemic vascular malformations
      i. Coarctation of the aorta
      ii. Middle aortic syndrome
      iii. Arterial hypoplasia (hepatic, renal, carotid, celiac)
      iv. Artery stenosis (renal, subclavian)
      v. Moyamoya disease
      vi. Carotid artery aneurysm
      vii. Intracranial hemorrhage
      viii. Hypoplastic portal vein branch
   e. Renal abnormalities
      i. Interstitial nephritis
      ii. Glomerular intramembranous and mesangial lipidosis
      iii. Tubular dysfunction
      iv. Renal hypoplasia
      v. Renal agenesis
      vi. Horseshoe kidney
      vii. Cystic disease
   f. Small bowel atresia or stenosis
   g. Pancreas
      i. Diabetes
      ii. Exocrine pancreatic insufficiency
   h. Lung: tracheal and bronchial stenosis
   i. Larynx: high-pitched voice
   j. Eye abnormalities
      i. Posterior embryotoxon
      ii. Optic disc drusen
      iii. Angulated retinal vessels
      iv. Pigmentary retinopathy
      v. Iris strands
      vi. Cataract
      vii. Myopia
      viii. Strabismus
      ix. Glaucoma
      x. Fundus hypopigmentation
   k. Skeletal abnormalities
      i. Lack of normal progression of interpedicular distance in the lumbar spine
      ii. Spina bifida
      iii. Shortening of distal phalanges and metacarpal bones
      iv. Clinodactyly
   l. Hepatocellular carcinoma: a rare complication of Alagille syndrome (Bhadri et al. 2005)
4. Prognosis
   a. Characterized by recurrent episodes of cholestasis
   b. Often associated with common respiratory tract infections, especially during the first year of life
   c. Good long survival but mortality rate may be up to 25%

Diagnostic Investigations

1. Biochemical studies (Alagille et al. 1987)
   a. Hypercholesterolemia: Cholesterol levels ranging from 220–1,600 mg% in all children with xanthomas (Garcia et al. 2005)
   b. Hyperphospholipidemia
   c. Hypertriglyceridemia
   d. Prominent increase in the pre-β-lipoprotein and apolipoprotein B levels
   e. Very high total bile acids, gammaglutamyl transferase, and alkaline phosphatase blood levels
2. Ophthalmologic assessment for posterior embryotoxon and other ocular anomalies
3. Abdominal ultrasonography
   a. Evaluation of the hepatobiliary tree and hepatic parenchyma
   b. Evaluation of renal anomalies
4. Radiography for vertebral anomalies
5. Other imagings
   a. Dimethyl iminodiacetic acid scanning
   b. Magnetic resonance cholangiopancreatography
   c. Endoscopic retrograde cholangiopancreatography
   d. Intraoperative cholangiography
6. Echocardiography for cardiovascular malformations
7. Histology (liver biopsy)
   a. Paucity of interlobular bile ducts
   b. Cholestasis in hepatocytes and canaliculi

8. Molecular genetic analysis
   a. Sequence analysis of the *JAG1* gene detects mutations in approximately 70% of individuals who meet clinical diagnostic criteria.
   b. FISH detects a microdeletion of 20p12, including the entire *JAG1* gene, in approximately 5–7% of cases.
   c. Mutations in NOTCH2 gene have been observed in fewer than 1% of individuals with Alagille syndrome (McDaniell et al. 2006)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. A low but slightly increased risk due to parental germline mosaicism in clinically normal appearing parents
      ii. A 50% risk if a parent is affected
   b. Patient's offspring: a 50% risk of having an offspring with Alagille syndrome
2. Prenatal diagnosis
   a. Prenatal ultrasonography
      i. Severe pulmonary artery stenosis
      ii. Progressive severe intrauterine growth retardation
   b. Prenatal molecular diagnosis on fetal DNA obtained from amniocentesis or CVS is available if a disease-causing mutation (demonstrated by molecular genetic testing) or a deletion (detected by FISH) is identified in an affected family member
   c. Preimplantation genetic diagnosis (Renbaum et al. 2007)
      i. A polar body (PB)-based multiplex fluorescent PCR reaction for a female affected with Alagille syndrome
      ii. The protocol included analysis of the Jagged 1 (*JAG1*) familial mutation and five closely linked highly polymorphic markers (D20S162, D20S901, D20S894, and D20S186)
      iii. A reliable diagnosis was possible in all developing embryos
3. Management
   a. Medical care (Alagille et al. 1987)
      i. Low-fat diets with medium-chain triglyceride supplementation
      ii. Hypercaloric diets to severely malnourished patients
      iii. Vitamin supplements
      iv. Pruritus
         a) Antihistamine agents
         b) Cholestyramine or rifampin in management of bile acid-induced pruritus
   b. Surgical care for patients with refractory disease
      i. Biliary diversion
      ii. Eventual orthotopic liver transplantation (Englert et al. 2006; Arnon et al. 2010)
         a) Indications: Progressive hepatic dysfunction, severe portal hypertension, failure to thrive, intractable pruritus, and osteodystrophy
         b) Associated with good long-term graft survival, although it is lower than that in biliary atresia
         c) Death from graft failure, neurological, and cardiac complications was significantly higher than in patients with biliary atresia
         d) The higher rate of mortality and graft failure may be related to the multisystem involvement of Alagille syndrome
      iii. Cardiac surgery for complex congenital heart defects

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Fig. 1 An infant with Alagille syndrome showing neonatal jaundice, broad forehead, and underdeveloped mandible. This infant had peripheral pulmonary artery stenosis and paucity of interlobular bile ducts

Fig. 2 A 2-month-old boy with Alagille syndrome showing neonatal jaundice (conjugated hyperbilirubinemia). Liver biopsy showed paucity of the bile ducts. He was put on Mephyton 2.5 mg qd

Albinism

Albinism, derived from the Latin *albus*, is a group of inherited disorders in which melanin biosynthesis is reduced or absent. It involves the skin, hair, and eyes (oculocutaneous albinism) or may be limited primarily to the eyes (ocular albinism). Current classification of albinism is determined by the affected gene, making the previously used terms "partial or complete" and "tyrosinase-positive or tyrosinase-negative" obsolete (King et al. 2007; Summers et al. 1996). The prevalence of all forms of albinism varies considerably worldwide, estimated at approximately 1/17,000 and about 1 in 70 people carry a gene for oculocutaneous albinism (OCA) (Grønskov et al. 2007).

Synonyms and Related Disorders

Chediak–Higashi syndrome; Griscelli syndrome; Hermansky–Pudlak syndrome; Oculocutaneous albinism (OCA) type 1 (tyrosinase-negative OCA, tyrosinase-related OCA); OCA type 2 (tyrosinase-positive OCA); OCA type 3 (Brown albinism); OCA, X-linked

Genetics/Basic Defects

1. Classification of albinism (genetic heterogeneity)
   a. OCA: a common phenotype for a group of recessive genetic disorders of melanin synthesis. Mutations in at least 12 genes are responsible for this phenotype. Mutations in OCA-related genes result in reduction of melanin synthesis by the melanocytes:
      i. Common types of OCA with cutaneous and ocular hypopigmentation without significant involvement of other tissue
         a) Oculocutaneous albinism 1 (OCA1): subdivided into OCA1A, OCA1B, OCA1ts
         b) Oculocutaneous albinism 2 (OCA2)
         c) Oculocutaneous albinism 3 (OCA3)
      ii. Less common types of OCA with more complex manifestations
         a) Hermansky–Pudlak syndrome
         b) Chediak–Higashi syndrome
   b. Ocular albinism:
      i. Ocular albinism 1 (OA1): X-linked recessive
      ii. Autosomal recessive ocular albinism (AROA)
2. Molecular defects causing four known types of OCA (Grønskov et al. 2007)
   a. OCA1 (tyrosinase-related albinism)
      i. Inherited in an autosomal recessive manner
      ii. Caused by mutations of tyrosinase gene (*TYR*) located at 11q14.3.
      iii. Several different types of mutations to the tyrosinase gene (missense, nonsense, and frameshift) are responsible for producing OCA1A and OCA1B.
      iv. OCA1A ("tyrosinase negative" albinism with inactive enzyme) produced by null mutations of the *Tyr* gene:
         a) 0% tyrosinase enzyme activity
         b) Over 100 mutations spanning all parts of the gene reported

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c) Compound heterozygotes with different maternal and paternal alleles in majority of patients

v. OCA1B (tyrosinase-related albinism with partially active enzyme) produced by leaky mutations of the *Tyr* gene:
a) "Yellow" form of albinism with 5–10% activity of tyrosinase
b) A base substitution within the gene may result in reduced rather than completely abolished enzyme activity

vi. OCA1ts (tyrosinase-related albinism with thermolabile enzyme):
a) A temperature-sensitive tyrosinase is only partly functional.
b) The first reported cases had a missense substitution within the tyrosinase gene.

b. OCA2 ("tyrosinase-positive" albinism): brown OCA in Africans
i. *OCA2* gene: the pink-eye dilution gene (*p*) located at 15q11.2-q12
ii. Caused by mutations of the P gene on the chromosome 15, homologous to the mouse pinked-eye dilution, or p gene
iii. Inherited in an autosomal recessive manner
iv. The mutated region is also deleted in Prader–Willi syndrome (PWS) and Angelman syndrome (AS), accounting for close linkage of OCA2 to PWS and AS

c. OCA3 (Brown albinism)
i. *OCA3* gene: tyrosinase-related protein-1 gene (*TRP1*) located at 9p23
ii. The gene homologous to the mouse "brown" gene
iii. Mutation of the gene possibly synergistic with a polymorphism or partially active mutation in OCA1 or OCA2
iv. 1 in 8,500 in Africans
v. Rare in white Europeans and Asians

d. OCA4
i. Resulting from mutation in the *SLC45A2* gene, formerly called membrane-associated transporter protein gene (*MATP*), located at 5p13.3
ii. 1 in 85,000 in Japanese
iii. Rare in white Europeans

3. Molecular defects causing other types of albinism
a. XLOA (X-linked ocular albinism, OA1)
i. *GPR143*, located at Xp22.3-22.2, is the only gene known to be associated with XLOA
ii. Intragenic deletions, frameshift mutations, and point mutations identified
iii. Affects males because of X-linked recessive inheritance
iv. 85–90% of obligate carriers show pigmentary mosaicism in the fundi, representing the lionization effect (X-inactivation), although there are no functional sequelae

b. OAR (autosomal recessive ocular albinism)
i. Gene mapping: 6q13-q15
ii. May not be a clinical entity
iii. Tyrosinase in some cases
iv. P protein in some cases

c. Hermansky–Pudlak syndrome (HPS): a bleeding disorder due to absence of dense bodies in platelets
i. Hermansky–Pudlak syndrome 1 is caused by mutations of the *HPS1* gene which is localized to 10q23.
ii. *HPS2* gene was localized to 5q13. Hermansky–Pudlak syndrome 2 is caused by mutation of the *APB1* gene, which is localized to 5q13, resulting in a defect in adapter complex 3 AP-3, β3A subunit.

d. Chediak–Higashi syndrome
i. Immunodeficiency associated with neurologic problems
ii. Defect in *CHS1* gene (lysosomal trafficking regular gene) located at 1q42-44

e. Griscelli syndrome: resulting from mutations in the *RAB27A* gene located or *MYO5A* gene, both located at 15q21

4. Pathophysiology
a. Melanin in the skin
i. Melanin, a photoprotective pigment in the skin, absorbs UV light from the sun, thus preventing skin damage.
ii. Normal skin tans upon sun exposure due to increased melanin pigment in the skin.
iii. Patient with albinism develop sunburn because of the lack of melanin.

b. Consequence of the absence of melanin during the development of the eye
i. Hypoplasia of fovea
ii. Alteration of neural connections between the retina and the brain

c. Melanin pathway
i. Consisting of a series of reactions that converts tyrosine into two types of melanin,

black-brown eumelanin and red-blond pheomelanin
   ii. Tyrosinase: a major enzyme in a series of conversions to melanin from tyrosine and it is also responsible for converting tyrosine to DOPA and then to dopaquinone, which subsequently converts to either eumelanin or pheomelanin
   iii. Two other enzymes involved in the formation of eumelanin: tyrosinase-related protein 1 (TRP1, DHICA oxidase) and tyrosinase-related protein 2 (TRP2, dopachrome tautomerase). Mutation of the TRP1 results in OCA3; mutation of the TRP2 does not cause albinism.
   iv. P protein, a melanosomal membrane protein, believed to be involved in the transport of tyrosine prior to melanin synthesis. Mutation of this *P* gene causes OCA2.
5. Pathogenesis of the ocular features
   a. Development of the optic system highly dependent on the presence of melanin
   b. Ocular features appear if melanin is reduced or absent
   c. Mechanisms
      i. Misrouting of the retinogeniculate projections resulting in abnormal decussation of optic nerve fibers
      ii. Sensation of photophobia and decreased visual acuity caused by light scattering within the eye
      iii. Light-induced retinal damage postulated as a contributing mechanism to decreased visual acuity
      iv. Foveal hypoplasia: the most significant factor causing decreased visual acuity

Clinical Features

1. General clinical features of albinism
   a. Skin, hair, and eye discoloration caused by abnormalities of melanin metabolism (might not be obvious in ocular albinism)
   b. Reduced visual acuity due to foveal hypoplasia (common to all types of albinism, even though a rudimentary annular reflex has been described in a few patients with better visual acuity) (Summers 2009)
   c. Translucent iris due to reduction in iris pigment
   d. Visible choroid vessels due to reduction in retinal pigment
   e. Photophobia due to iris pigmentary abnormalities
   f. Anomalous visual pathway projections due to misrouting of the optic nerves at the chiasm
   g. Nystagmus (Summers 2009)
      i. Due to abnormal decussation of optic nerve fibers
      ii. Typically pendular in nature
      iii. More noticeable with fatigue and illness
      iv. Amplitude of nystagmus diminishes as child matures
   h. Alternating strabismus
   i. Hyperopia, myopia, and astigmatism
2. Oculocutaneous albinism 1 (OCA1)
   a. Incidence: approximately 1 in 40,000 individuals
   b. Oculocutaneous albinism 1A (OCA1A)
      i. Classic "tyrosinase-negative" OCA: complete lack of melanin production throughout life
      ii. Most severe form of OCA
      iii. White hair and white skin that does not tan
      iv. Blue and translucent irides that do not darken with age
      v. Foveal hypoplasia
      vi. No tanning potential
      vii. At risk for sun burning and skin cancer
      viii. Diminished visual acuity as low as 20/400
      ix. Photophobia and nystagmus worst in this subtype
   c. Oculocutaneous albinism 1B (OCA1B)
      i. Yellow mutant type OCA, referred to as Amish albinism, or xanthous albinism
      ii. Variable pigmentation ranging from very little cutaneous pigmentation to nearly normal skin pigmentation
      iii. Increased skin, hair, and eye pigment with age and tan with sun exposure
      iv. Yellow hair pigment develops in the first few years of life and continuously accumulates pigment, principally yellow-red pheomelanin, in the hair, eyes, and skin in the later life
      v. Decreased visual acuity improving with age
   d. Temperature-sensitive albinism (OCA1ts)
      i. A subtype of OCA1B
      ii. Mutation of the tyrosinase gene that produces a temperature-sensitive tyrosinase enzyme

iii. The heat-sensitive tyrosinase enzyme activity is approximately 25% of the normal tyrosinase activity at 37°C. The activity improves at lower temperatures.
iv. Dark hair pigment in the arms and legs (cooler areas of the body) while axillary and scalp hair remains white
v. Pigment is absent in the fetus because of high fetal temperature.

3. Oculocutaneous albinism 2 (OCA2)
   a. "Tyrosinase-positive" OCA
   b. Incidence: approximately 1 in 15,000 individuals
   c. Most prevalent type of albinism in all races and especially frequent among African-American population (1 in 10,000)
   d. Phenotypic variability
      i. Ranging from absence of pigmentation to almost normal pigmentation
      ii. Absence of black pigment (eumelanin) in the skin, hair, or eyes at birth
      iii. Gradual development of pigmentation with age
      iv. Increased pigmentation resulting in improved vision
4. Oculocutaneous albinism 3 (OCA3)
   a. Previously known as red/rufous OCA
   b. Incidence of the disease unknown
   c. Phenotype in African patients
      i. Light brown skin and hair
      ii. Blue-brown irides
      iii. Ocular features not fully consistent with diagnosis of OCA (no iris translucency, nystagmus, strabismus, or foveal hypoplasia)
   d. Phenotype in Caucasians and Asians: not known
5. Oculocutaneous albinism 4 (OCA4)
   a. Cannot be distinguished from OCA2 on clinical findings
   b. Hypopigmentation of the skin and hair
   c. Characteristic ocular changes found in all other types of albinism
      i. Nystagmus
      ii. Reduced iris pigment with iris translucency
      iii. Reduced retinal pigment with visualization of the choroidal blood vessels on ophthalmoscopic examination
      iv. Foveal hypoplasia associated with reduction in visual acuity
      v. Misrouting of the optic nerves at the chiasm associated with alternating strabismus
      vi. Reduced stereoscopic vision
      vii. An altered visual-evoked potential (VEP)
6. Ocular albinism 1 (OA1) (Lewis 2011)
   a. X-linked recessive OA (XLOA)
   b. Incidence of the disease approximately 1 in 50,000 individuals
   c. Extreme variability in clinical expression
   d. Involving eyes only
      i. Decreased visual acuity
      ii. Refractive errors: typical findings
         a) Hypermetropia
         b) Astigmatism
      iii. Hypopigmentation of the fundus and the iris
      iv. Absent foveal reflex (foveal hypoplasia)
      v. Congenital nystagmus
      vi. Photophobia
      vii. Strabismus
      viii. Iris translucency
      ix. Posterior embryotoxon
      x. Loss of stereoscopic vision due to misrouting of the optic tracts
   e. Normal skin
   f. Male manifesting complete phenotype
   g. Carrier females
      i. Normal vision
      ii. Hypopigmented streaks (characteristic patchy hypopigmentation as a result of mosaic inactivation of the affected X chromosomes) in the periphery
      iii. Marked iris translucency
   h. Severity depending on ethnic background: less severe in races exhibiting very dark constitutive skin pigmentation than those more lightly pigmented
7. Autosomal recessive ocular albinism (OAR)
   a. Children with ocular features of albinism and normal cutaneous pigmentation born to normally pigmented parents
   b. Classified as autosomal recessive because both males and females are affected
   c. Not considered a clinical entity
8. Hermansky–Pudlak syndrome
   a. A group of related disorders
      i. Common oculocutaneous albinism

   ii. A platelet storage disorder
   iii. Ceroid-lipofuscin lysosomal storage disease
  b. An autosomal recessive disorder with very variable expression
  c. Incidence of the disease: rare, except in Puerto Rico where its frequency is 1 in 1,800 individuals (Witkop et al. 1990)
  d. Bleeding diathesis resulting from a platelet storage pool deficiency
  e. Patients exhibit severe immunologic deficiency with neutropenia and lack of killer cells (DePinho and Kaplan 1985)
  f. Ceroid storage disease
   i. Accumulation of a Ceroid-lipofuscin material in various organ systems
   ii. Interstitial pulmonary fibrosis
   iii. Granulomatous colitis and gingivitis
   iv. Kidney failure
   v. Cardiomyopathy
9. Chediak–Higashi syndrome (Russell-Eggitt 2001)
  a. An autosomal recessive disorder with variable expression
  b. Consisting of a very rare group of conditions
  c. Severe immune disorder
   i. Abnormal intracellular granules in most cells, especially white cells
   ii. Susceptible to bacterial infections
   iii. Defective neutrophils function
   iv. Episodes of macrophage activation known as accelerated phases:
    a) Fever
    b) Anemia
    c) Neutropenia
    d) Occasionally thrombocytopenia
    e) Hepatosplenomegaly
    f) Lymphadenopathy
    g) Jaundice
  d. Hypopigmentation of skin, hair, irides, and ocular fundi
  e. Bleeding diathesis
   i. Easy bruising
   ii. Mucosal bleeding
   iii. Epistaxis
   iv. Petechiae
  f. Eye symptoms
   i. Photophobia
   ii. Nystagmus
   iii. Reduced stereoacuity
   iv. Strabismus
  g. Often succumb during childhood to severe viral and bacterial infections, bleeding or development of the accelerated phase
  h. May develop a peripheral and cranial neuropathy in survivors
   i. Autonomic dysfunction
   ii. Weakness and sensory deficits
   iii. Loss of deep tendon reflexes
   iv. Clumsiness with a wide-based gait
   v. Seizures
   vi. Abnormal EEG
   vii. Abnormal EMG with decreased motor nerve conduction velocities
10. Griscelli syndrome (Mancini et al. 1998)
  a. A rare disorder
  b. Immune impairment
  c. Neurological deficit
  d. Hypopigmentation of skin and hair
  e. Presence of large clumps of pigment in hair shafts
11. Waardenburg syndrome: a syndrome of sensory deafness and partial albinism, referred to as the albinism-deafness syndrome (Waardenburg 1951)

Diagnostic Investigations

1. Ophthalmologic examination for detection of reduced retinal pigment with visualization of the choroidal blood vessels (OCA1) and foveal hypoplasia
2. Visual acuity reduction
3. Hair bulb incubation assay for tyrosinase activity
  a. OCA1A: no tyrosinase activity
  b. OCA1B: greatly reduced activity of tyrosinase but still present
4. Visual-evoked potential (VEP): an accurate diagnostic test for albinism by demonstrating an asymmetry of VEP between the two eyes secondary to misrouting of optic pathways
5. Electron microscopy of skin and hair bulb: not routinely performed but probably the best diagnostic method for albinism.

c. Chediak–Higashi syndrome
   i. Treat infections
   ii. Bone marrow transplantation: improves immunological status but no effect on ocular and cutaneous albinism

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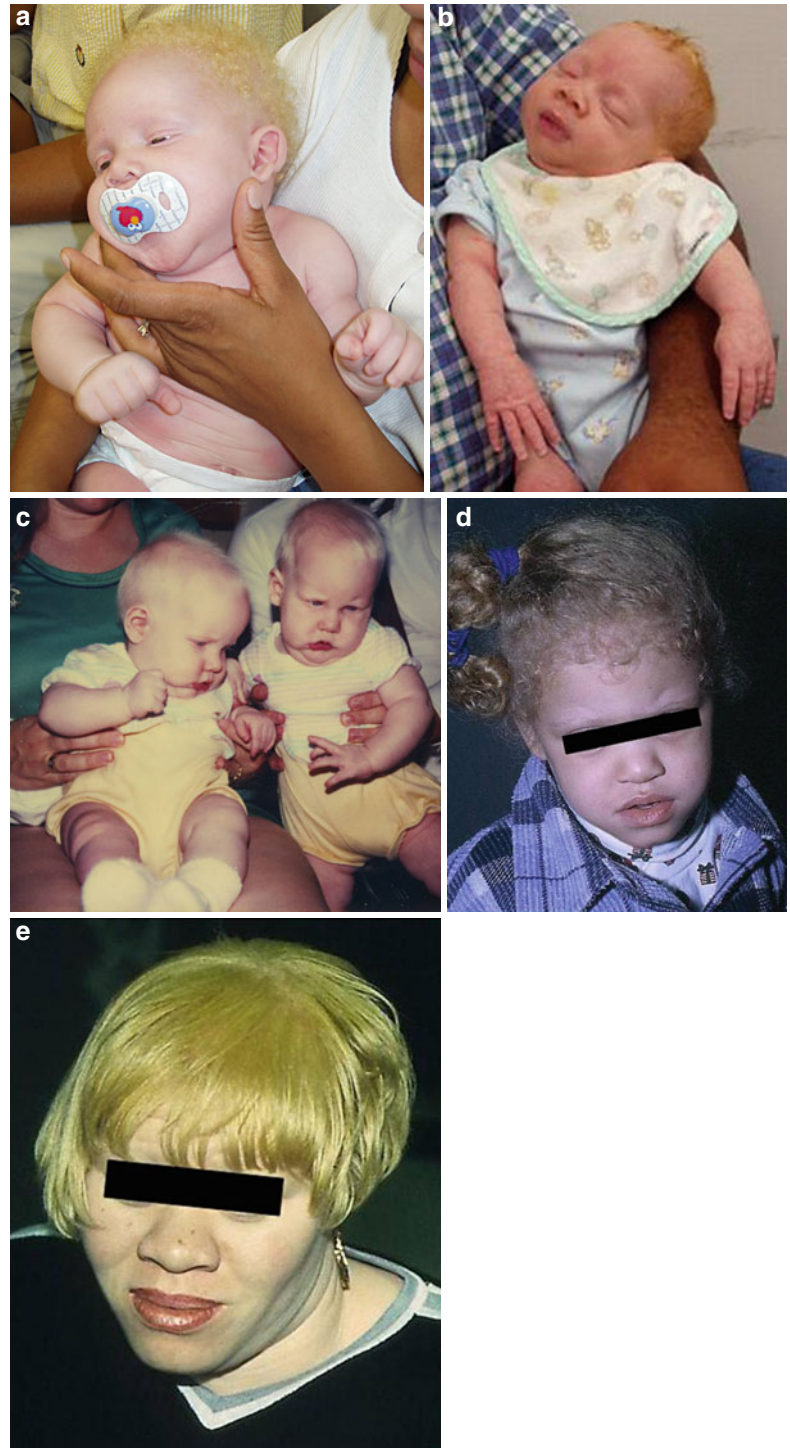

Fig. 1 (**a–e**) Oculocutaneous albinism in different age groups including one set of identical twins

Fig. 2 A 7-month-old infant boy with light skin color, *silverish white* scalp hair, eyebrows, and eyelashes, and absence of nystagmus or strabismus. The infant possesses one detectable mutation in the *OCA2* gene encoding the P protein, namely, V433I: c.1327G > A. This mutation has been reported in the literature and is a known cause of OCA2. The second variation, IVS12-44C > T was noted. A homozygous sequence change (IVS7-17insA) was observed in the *OCA3* gene. The intronic sequence changes in the *OCA2* and *OCA3* genes have not been reported in the literature and therefore clinical significance is unknown. No mutations were observed in the *OCA1* gene, the *OCA4* gene, or the *OA1* gene

Alpha-Thalassemia X-linked Mental Retardation Syndrome

Alpha-thalassemia X-linked mental retardation (ATRX) syndrome, one form of X-linked mental retardation, is characterized by severe mental retardation, typical dysmorphic facies, genital abnormalities, and an unusually mild form of hemoglobin H disease (Gibbons et al. 1995a).

Synonyms and Related Disorders

ATRX syndrome; X-linked mental retardation-hypotonic face syndrome

Genetics/Basic Defects

1. An X-linked recessive disorder
2. The gene involved in the disease, *ATRX*, is mapped to Xq13.3
3. The function of the ATRX protein: unknown but may play a role in gene expression based on the fact that alpha globin expression is perturbed in the patients
4. Genetically related (allelic) disorders
   a. Several X-linked mental retardation (XLMR) syndromes: These disorders should be considered to be in the phenotypic spectrum of ATRX syndromes and there are no compelling reasons to maintain the syndromic names.
      i. Carpenter–Waziri syndrome
      ii. Holmes–Gang syndrome
      iii. Chudley–Lowry syndrome
      iv. XLMR with spastic paraplegia
      v. XLMR with epilepsy
      vi. Nonsyndromic XLMR
   b. ATRX mutations are identified in the following two syndromes but not in the original reported families and therefore the relationship between ATRX syndrome and these two syndromes is unclear.
      i. Juberg–Marsidi syndrome
      ii. Smith–Fineman–Myers syndrome

Clinical Features

1. Central nervous system features
   a. Global developmental delay
      i. Limited expressive language
      ii. Delayed walking until late childhood or unable to ambulate
   b. Generalized hypotonia, a hallmark of the condition, in early childhood, contributing to facial manifestations, drooling, and developmental retardation
   c. Seizures (1/3 of cases)
2. Characteristic craniofacial features
   a. Microcephaly
   b. Upsweep of the frontal hair
   c. Telecanthus or ocular hypertelorism
   d. Small triangular nose with retracted columella
   e. Tented upper lip
   f. Prominent or everted lower lip
   g. Open mouth
   h. Other features
      i. Irregular anatomy of the pinnae
      ii. Wide spacing of the teeth

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iii. Tongue protrusion
iv. Coarse facial appearance particularly after the first few years of life

3. Abnormal external genitalia: broad spectrum of possible genital anomalies but the type of genital anomaly appears to be consistent within a family
   a. Often minor anomalies
      i. First-degree hypospadias
      ii. Undescended testes
      iii. Underdevelopment of the scrotum
   b. More severe defects
      i. Second- and third-degree hypospadias
      ii. Micropenis
      iii. Ambiguous genitalia
   c. Occasional gonadal dysgenesis resulting in inadequate testosterone production and ambiguous genitalia or normally appearing female external genitalia
4. Skeletal anomalies
   a. Short stature
   b. Digital anomalies
      i. Brachydactyly
      ii. Clinodactyly
      iii. Tapered digits
   c. Joint contractures
   d. Spine anomalies
      i. Pectus carinatum
      ii. Kyphosis
      iii. Scoliosis
      iv. Dimples over the lower spine
   e. Foot anomalies
      i. Varus and valgus foot deformation
      ii. Pes planus
5. Gastrointestinal features
   a. Gastroesophageal reflux (2/3 of cases): may cause aspiration with a fatal complication in some
   b. Chronic constipation (1/3 of cases)
   c. Report of pseudo-obstruction (gastric pseudovolvulus) resulting from abnormal suspension of the stomach and constipation from colon hypoganglionosis
6. Major malformations: uncommon
   a. Ocular coloboma
   b. Cleft palate
   c. Cardiac defects
   d. Inguinal hernia
   e. Heterotaxy
   f. Asplenia

Diagnostic Investigations

1. Diagnosis is suspected on the basis of characteristic craniofacial, genital, skeletal, other somatic features, and hematological findings and should be confirmed by molecular genetic testing
2. Hematologic studies: demonstration of evidence of alpha-thalassemia
   a. Hb H inclusions (β-globin tetramers) ranging from 0.01% to 30% in erythrocytes demonstrated in most individuals with *ATRX* mutations
   b. Hemoglobin electrophoresis: demonstration of Hb H (not highly sensitive)
   c. Red blood cell indices: microcytic hypochromic anemia in some affected individuals
3. Molecular genetic testing
   a. Sequence analysis and mutation scanning of select exons
   b. Sequence analysis and mutation scanning of all exons and splice junctions
   c. Deletion/duplication analysis
   d. X-chromosome inactivation studies: The finding of nonrandom X-chromosome inactivation is not unique to ATRX syndrome and is therefore not diagnostic
4. Carrier testing in at-risk females possible when the disease-causing mutation in the family is known

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Carrier mother
         a) A 50% chance of transmitting the *ATRX* mutation
         b) Offspring with a 46,XY karyotype who inherit the *ATRX* mutation will be affected
         c) Offspring with a 46,XX karyotype who inherit the mutation are unaffected female carriers
      ii. Sibs of proband with de novo gene mutation: at increased risk of inheriting the disease-causing mutation because of possible germline mosaicism in the mother
   b. Patient's offspring: Affected individual do not reproduce

2. Prenatal diagnosis and preimplantation genetic diagnosis: possible for pregnancies at increased risk for ATRX syndrome when the disease-causing mutation in the family is known
3. Management
   a. Multidisciplinary interventions
      i. Infant stimulation
      ii. Early intervention
      iii. Special education
   b. Management of feeding and gastrointestinal problems
      i. Gavage feeding for difficulty in sucking
      ii. Fundoplication and feeding gastrostomy may be required for gastroesophageal reflux
      iii. Surgical correction of pseudovolvulus
      iv. Prevention of constipation
      v. Consider biopsy to rule out Hirschsprung's disease and colonic hypoganglionosis
      vi. Control of severe drooling
         a) Anticholinergics
         b) Botulinum toxin type A injection of the salivary glands
         c) Surgical redirecting of the submandibular ducts
   c. Seizure control
   d. Genitourinary problems
      i. Orchidopexy for cryptorchidism
      ii. Treat recurrent urinary tract infections
   e. Orthopedic management for musculoskeletal anomalies
   f. Hearing loss management
   g. Alpha-thalassemia
      i. No treatment required for the mild anemia
      ii. Iron not required unless iron stores are shown to be low

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Fig. 1 (**a, b**) A 7-year-old boy with global developmental delay and the characteristic facial appearance of ATRX syndrome: upswept frontal hair line, ocular hypertelorism, epicanthal folds, a small triangular upturned nose, open mouth, tented upper lip, prominent everted lower lip, and hypotonic appearing face. He has mild microcytic, hypochromic anemia (mean cell volume 74.8 FL (76–90), MCH 23.6 pg (27–31), MCHC 31.5 g/dl (32–36)). Sequence analysis showed a C > T change at nucleotide 736 in the *XNP* gene (c.736C > T). This change results in the substitution of a cysteine for an arginine at amino acid 246 (R246C). This change is consistent with the diagnosis of ATRX syndrome. His mother has the same *XNP* gene mutation

Fig. 2 A maternal uncle was similarly affected with recurrent pneumonias, anemia, and mental retardation

Ambiguous Genitalia

Most cases of ambiguous genitalia are discovered at birth, occurring approximately once in every 1,000 live births. Genital ambiguity usually is due to virilization of genetic females or undervirilization of genetic males who have normal gonads. Less common are disorders of sexual differentiation that involve gonadal dysgenesis (Chi et al. 2008).

In females, congenital adrenal hyperplasia (CAH), specifically 21-hydroxylase deficiency, is the most common condition leading to inappropriate virilization. In males, defects in testosterone production, metabolism, or peripheral action can lead to ambiguous genitalia. Later presentations of ambiguous genitalia often include previously unrecognized genital ambiguity, inguinal hernia in a girl (e.g., complete androgen insensitivity), delayed or incomplete puberty, primary amenorrhea or virilization in a girl, breast development in a boy, and gross or cyclic hematuria in a boy (unrecognized virilized 46,XX with CAH) (Lee et al. 2006).

Synonyms and Related Disorders

Genetic disorders of sexual differentiation (gonadal dysgenesis, true hermaphroditism, sex reversal); Undervirilization of male infant; Virilization of female infant

Genetics/Basic Defects

1. Normal development of the human reproductive system (Chi et al. 2008)
   a. Sexual differentiation of the fetus begins at 6–7 weeks of gestation
   b. During embryogenesis, the fetus contains both female (müllerian) and male (wolffian) genital ducts
      i. Müllerian ducts: develop into fallopian tubes, uterus, and the upper one third of the vagina
      ii. Wolffian ducts: develop into the vas deferens, epididymis, and seminal vesicles
   c. "Default" pathway of the bipotential gonad and internal structures: female
   d. Presence of the sex-determining region Y gene (SRY) in males: activates a cascade of events that culminates in differentiation of the gonad as a testis which produces the following two key hormones
      i. Testosterone
         a) Function: stimulates wolffian duct differentiation
         b) Production: initially driven by placental human chorionic gonadotrophin (hCG) which subsequently replaced by fetal pituitary gonadotrophins after the first trimester, both acting through the luteinizing hormone (LH) receptor
         c) Local conversion of testosterone to dihydrotestosterone (DHT) by the enzyme 5-α reductase leads to fusion of the labioscrotal folds and formation of the scrotum and penis, both critical events occurring in the first trimester
      ii. Müllerian inhibiting substance (MIS) or anti-müllerian hormone (AMH): stimulates müllerian duct regression
   e. Absence of testosterone and MIS in females leads to:
      i. Involution of the wolffian ducts.

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ii. Differentiation of the müllerian ducts into female internal genitalia
iii. Needs both X chromosomes to develop normally differentiated and functional ovaries; females with X chromosome deletion (Turner syndrome) have abnormal gonadal differentiation and oocytes loss, leading to streak gonads.

2. Broad categories of ambiguous genitalia
   a. XX baby with virilization
      i. In the virilized XX baby, the gonads are ovaries and the internal genitalia are female.
      ii. The external genitalia are masculinized by circulating androgens to a variable degree, ranging from subtle clitoromegaly to complete labial fusion with urethral tubularization to the tip of the enlarged phallus.
      iii. If exposure occurred late, clitoromegaly without labial fusion is seen. The gonads are not palpable.
      iv. The commonest cause of virilization in the XX "female" is congenital adrenal hyperplasia. This autosomal recessive condition results from an enzymatic defect in adrenal steroidogenesis, leading to accumulation of steroids proximal to the block, which are converted to androgens. The commonest of these is 21-hydroxylase deficiency, followed by 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase deficiency. The serum and urinary steroid profile will help to confirm the diagnosis. Other possible causes include exposure to exogenous androgens, such as from maternal androgens or progestin ingestion, or rarely, maternal androgen-producing tumors.
      v. The majority of true hermaphrodites also have a 46 XX chromosomal makeup, but these form a distinct group.
   b. The XY baby with undervirilization
      i. The undervirilized XY baby presents with a small phallus with severe chordee, posterior hypospadias, poorly formed, bifid scrotum with or without testicular maldescent. Inadequate testosterone production, either as a result of testicular dysgenesis or autosomal recessive enzymatic defects, is rare.
      ii. The commonest cause is a group of disorders known as androgen insensitivity syndrome (AIS), previously also known as testicular feminization syndrome. This is an X-linked disorder resulting from peripheral resistance to androgen action, either from mutations in the androgen receptor gene, or elsewhere in the molecular pathway.
      iii. Whether AIS may, in fact, be due to a defect in the conversion of dihydrotestosterone to 5-α-androstanediol remains to be seen.
      iv. 5-α-reductase deficiency, an autosomal recessive defect resulting in deficient dihydrotestosterone necessary in the virilization of the external genitalia in early embryogenesis, is another cause of undervirilization.
   c. True hermaphroditism
      i. In the true hermaphrodite, both testicular and ovarian tissues coexist.
      ii. The gonads are usually ovary-testis, or ovary-ovotestis.
      iii. The genotype is usually 46 XX, although 46 XY or mosaicism can occur.
      iv. Asymmetry of the gonads, internal and external genitalia is a feature in true hermaphroditism. The right side is more commonly the "masculine" side while the left side is often more "feminine."
   d. Mixed gonadal dysgenesis
      i. In mixed gonadal dysgenesis, there is a testis on one side (more commonly the right side) and a streak gonad on the other.
      ii. The testis may be dysgenetic or initially normal, and the streak gonad histologically is composed of whorls of ovarian stroma without oocytes.
      iii. The karyotype is most commonly 45,X/46,XY, but other mosaic patterns have been described.
      iv. As with true hermaphrodites, asymmetry is a feature in mixed gonadal dysgenesis.
3. XX true hermaphroditism
   a. Mechanisms
      i. Hidden mosaicism with a Y-bearing cell line
      ii. Translocation of Y-material including SRY from paternal Y-to-X chromosome
      iii. An autosomal or X-linked mutation that permits testis differentiation in the absence of SRY
   b. An unusual cause of ambiguous genitalia
      i. Both ovarian and testicular tissue present either in the same or in a contralateral gonad
      ii. Predominantly 46,XX karyotype

c. Several familial forms reported although the great majority of cases are sporadic
   i. Occurring with a higher frequency in South African blacks suggesting a genetic origin
   ii. Several families in which 46,XX males coexist with 46,XX true hermaphrodites strongly suggest that both disorders are alternative manifestations of the same genetic defect
d. SRY-negative true hermaphroditism could be the result of genetic defects at an unknown X-linked or autosomal sex-determining locus
e. Mutations in SRY originated ovotestes development described in 46,XY patients
f. Absence of SRY in gonadal tissue reported in cases of 46,XX true hermaphroditism
g. Possible underestimate of gonadal hidden mosaicism for SRY in XX true hermaphrodites suggesting that true hermaphroditism is a genetically heterogeneous condition

4. Causes of ambiguous genitalia (Chi et al. 2008)
   a. Virilization of female infant
      i. Excessive androgen production: congenital adrenal hyperplasia
         a) 21-α hydroxylase deficiency
         b) 11-β hydroxylase deficiency
         c) 3-β hydroxysteroid dehydrogenase deficiency
      ii. Defects in androgen metabolism: placental aromatase deficiency
      iii. Maternal hyperandrogenism
         a) Maternal androgen production (luteoma of pregnancy, adrenal tumor, untreated CAH)
         b) Progestational agents
   b. Undervirilization of male infant
      i. Defects in testosterone production
         a) Leydig cell hypoplasia/agenesis
         b) Defects in testicular and adrenal steroidogenesis (steroid acute regulatory (StAR) protein deficiency, 3-β hydroxysteroid dehydrogenase deficiency, 17-α hydroxylase/17,20 lyase deficiency, 17-α hydroxysteroid dehydrogenase (ketosteroid reductase) deficiency
      ii. Defects in testosterone metabolism: 5-α reductase deficiency
      iii. Defects in testosterone action: androgen insensitivity syndrome
      iv. Exogenous estrogen/progestin exposure
   c. Genetic disorders of sexual differentiation
      i. Gonadal dysgenesis
         a) 45,X (streak ovaries)
         b) 46,XX gonadal dysgenesis
         c) 46,XY complete and partial gonadal dysgenesis
         d) 45,X/46,XY mixed gonadal dysgenesis
         e) 47,XXY (seminiferous tubular dysgenesis)
      ii. True hermaphroditism
      iii. Sex reversal
         a) XX males (SRY±)
         b) XY female (SRY±)
         c) Smith–Lemli–Opitz Syndrome (SLOS)
         d) *DAX1* mutations
         e) *WT1* mutations

Clinical Features

1. Physical features suggestive of ambiguous genitalia (Lee et al. 2006)
   a. Overt genital ambiguity (e.g., cloacal exstrophy)
   b. Apparent female genitalia with enlarged clitoris and posterior labial fusion (e.g., CAH)
   c. Apparent male genitalia with undescended testes, hypospadias, or micropenis
2. Rules of thumb and clinical significance of internal genitalia (the gonads and the genital ducts) (Low et al. 2003)
   a. Testes descend, ovaries do not: Presence of a palpable gonad implies the presence of testicular tissue on the same side, which implies the presence of the *SRY* gene somewhere in the genome
   b. Testicular descent is directly linked to müllerian duct regression:
      i. Presence of two palpable gonads means there is no uterus.
      ii. With asymmetrical gonadal descent, similar ductal asymmetry internally can be predicted.
      iii. On the side of the descended gonad, there will be wolffian duct derivatives but no müllerian structures. Correspondingly, the contralateral hemi-uterus is likely to be present.
      iv. When there are no palpable gonads, the gonadal and ductal status is unknown.
   c. Presence of a uterus (digitally palpated or ultrasonically detected) means no müllerian

inhibiting substance/anti-müllerian hormone (MIS/AMH) action during the "sensitive" period in early gestation. This implies either no testes, dysgenetic nonfunctional testes, or defects in production or action of MIS/AMH as occurs in the rare syndrome of persistent müllerian duct syndrome (PMDS).

d. Testosterone, as well as MIS/AMH, functions as a locally acting exocrine hormone in the development of the internal genital ducts
   i. Gonadal asymmetry as occurs in true hermaphrodites and mixed gonadal dysgenesis results in corresponding duct asymmetry.
   ii. Circulating androgens in over-androgenized XX babies are insufficient to allow development of male internal genitalia.

3. Rules of thumb and clinical significance of external genitalia (Low et al. 2003)
   a. External virilization, of any degree, is due to the effect of androgens
      i. "Clitoromegaly" in an otherwise phenotypic female is always abnormal, indicating abnormal exposure to androgens
      ii. The genotype may be "XX" with virilization or "XY" with undervirilization
   b. The degree of external virilization proportionally predicts the degree of lower vaginal development
      i. A baby who is incompletely virilized externally, an incomplete vaginal remnant, is likely to be retained
      ii. In a 46 XX "female" baby, the greater the external virilization, the smaller the vaginal remnant and the higher its opening into the posterior urethra
   c. With the exception of the phallus, circulating androgens masculinize the external genitalia only during a critical period (8th–12th weeks)
      i. Scrotal fusion indicates the presence of early circulating androgens while an unfused scrotum means deficient early androgen effect
      ii. An enlarged phallus without urethral/scrotal fusion means there has been a delayed androgen effect (beyond 12 weeks)
      iii. Enlargement of the phallus to normal penile size means continued presence of an androgen effect throughout later gestation (12 weeks to term)

4. True hermaphroditism: contains both ovarian and testicular gonadal tissue separately or, more commonly, together as ovotestis
   a. During intrauterine life: presence of ovarian and testicular tissue with variability in hormonal production results in abnormal differentiation of internal and external genitalia
   b. At birth
      i. Variable degrees of genital ambiguity present in nearly all patients
      ii. Presence of labioscrotal folds, normally developed labia majora in most affected individuals
      iii. A hemiscrotum or even a normal scrotum in a minority of cases
      iv. A phallus of variable length with chordee and urethra generally opens as a urogenital sinus in majority of cases while less severe hypospadias in some cases
      v. Ovaries generally locate in ovarian position while testes locate in the scrotum generally, inguinal canal, or even intra-abdominally
      vi. Location of ovotestis depends on the amount of testicular or ovarian tissue present
      vii. Development of internal genitalia: variable depending on the neighboring gonad
         a) Presence of müllerian derivatives: an ovary is present and ovotestes in most cases
         b) Wolffian structures: observed in association with testes
      viii. A unicornate uterus is usually found
   c. At puberty
      i. Relative production rate of sex hormones vary depending on the composition of the gonads
      ii. Secondary sex characteristics depend on the type of predominant steroid hormone production
      iii. Breast development frequent after puberty
      iv. Menstruation occurring in approximately 50% of patients
      v. Ovulation common
      vi. Pregnancy reported in a few cases
   d. Pregnancy in true hermaphrodites (Schultz et al. 2009):
      i. Complications with preterm labor, neonatal death, or the delivery process itself

ii. Sex of the fetus likely male
iii. Recommendation to remove the remaining gonad(s) due to an increased risk of germ cell malignancies after thorough discussion of the risks, benefits, alternatives, and implications of future sterility and hormone deprivation

5. Recently proposed revised nomenclature (Lee et al. 2006)
   a. Disorders of sex development (DSD) replacing "intersex"
   b. 46,XY DSD replacing "male pseudohermaphrodite, undervirilization of an XY male, and undermasculization of an XY male"
   c. 46,XX DSD replacing "female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female"
   d. Ovotesticular DSD replacing "true hermaphrodite"
   e. 46,XX testicular DSD replacing "XX male or XX sex reversal"
   f. 46,XY complete gonadal dysgenesis replacing "XY sex reversal"

Diagnostic Investigations

1. Approach to the baby with ambiguous genitalia (Low et al. 2003)
   a. History:
      i. Careful history taking: indispensable to an accurate diagnosis
         a) Maternal steroid ingestion
         b) Antenatal diagnosis of an androgen-producing tumor
         c) A positive family history of a known intersex disorder will give important clues to the underlying disorder
         d) Majority of cases, however, will not yield a positive history
   b. Steps in the evaluation of a baby with ambiguous genitalia
      i. Document the degree of external virilization: The greater the degree of virilization, the greater the amount of early androgen exposure (between 8 and 12 weeks) and the greater the extent of vaginal regression.
      ii. Examine the urogenital sinus carefully by pulling it open. If skin tags with a slight bluish hue are seen, then the hymen and therefore the vagina is confirmed present.
      iii. Determine the presence and location of gonads
         a) Palpable gonads predict the presence of SRY, testicular development, and müllerian regression on the ipsilateral side
         b) The degree of testicular descent correlates with the degree of androgen exposure in the second half of pregnancy
      iv. Three possible clinical scenarios
         a) Both gonads palpable and symmetrical: Palpable gonads are almost always testes and the implication, in general, is that the baby is an inadequately virilized male and müllerian duct structures are absent. The differential diagnoses include inadequate testosterone production, receptor deficiency, 5-α-reductase deficiency, minor testicular dysplasia (an exception is the occurrence of bilateral symmetrical ovotestes in a true hermaphrodite).
         b) Gonadal asymmetry with only one gonad palpable: This implies that at least one testis is present. The other may be an ovary, an ovotestis or a streak gonad.
         c) When gonadal asymmetry is encountered, always consider true hermaphroditism or mixed gonadal dysgenesis.
      v. Impalpable gonads
         a) Gonadal and duct status: unknown.
         b) Additional clues may be obtained by careful examination to determine if the external inguinal rings are open, which are felt as inverted V-shaped defects superior and medial to the pubic tubercle. Open external rings indicate a high likelihood of an undescended canalicular testis, while a closed external ring is consistent with the presence of ovaries or extremely dysplastic testes with minimal testosterone production. Per rectal examination is also useful in this circumstance. A gentle examination with the little finger will easily palpate the cervix and confirm the presence of the uterus.
         c) Look for other clues in the general physical examination, such as facial

dysmorphism or developmental abnormalities that may be part of a sex chromosome abnormality. Hyperpigmentation may occur in congenital adrenal hyperplasia.

2. Pelvic ultrasonography: used to detect the presence of a uterus, as well as the presence and position of intra-abdominal gonads. However, visualization may be difficult in the small neonate.
3. Urogenital sinugram: to confirm the presence of and delineate the anatomy of the lower vagina.
4. MRI (Choi et al. 1998)
   a. Female pseudohermaphroditism: shows normal internal female genitalia with masculinized external genitalia
   b. Male pseudohermaphroditism: shows normal or mildly defective testes with incompletely masculinized external genitalia
   c. Gonadal dysgenesis: shows combinations of normal, dysgenetic, and streak gonads; no gonads are evident in gonadal agenesis
   d. True hermaphroditism: shows both testicular and ovarian tissue
5. Hormonal investigations
   a. Serum analysis of 17-hydroxyprogesterone.
   b. Serum profile of adrenal steroids, gonadal androgens, and its precursors.
   c. Human chorionic gonadotrophin stimulation tests may be needed to confirm the normal rise of gonadal hormones with stimulation, while testosterone/dihydrotestosterone ratios reflect 5-α-reductase activity.
6. Chromosomal analysis: to identify the genotype of the affected baby, either as XX, XY, or a mosaic pattern
7. FISH analysis with SRY probes to identify the presence of Y sequences on the X chromosome in cases of 46,XX hermaphroditism and ambiguous genitalia
8. Biopsy of the genital skin for androgen receptor assay
9. Panendoscopy and/or laparoscopy to delineate the internal genitalia
10. Gonadal biopsies on occasion
11. Diagnostic evaluation and potential diagnoses based upon symmetry of genitalia (Mieszczak et al. 2009)
    a. Symmetrical external genitalia
       i. Palpable gonad: gene testing of *SF1*
       ii. Nonpalpable gonad: ultrasound
          a) Uterus (lack of MIH): hormonal assessment (17α-hydroxyprogesterone, androstenedione, testosterone, plasma renin activity) for congenital adrenal hyperplasia and in utero androgen exposure
          b) No uterus (presence of MIH): hormonal assessment (MIH, LH, testosterone, FSH (follicle-stimulating hormone), inhibin B, androstenedione) for Leydig cell hypoplasia, 3β-HSD, 17β-HSD (hydroxysteroid dehydrogenase), androgen insensitivity, 5 α-reductase deficiency, and testicular regression
    b. Asymmetric external genitalia (virilization of labia different on each side): assessment includes:
       i. Fluorescence in situ hybridization for SRY (sex-determining region Y)
       ii. Hormonal assessment
          a) MIH
          b) LH
          c) Testosterone
          d) FSH
       iii. Inhibin B: androstenedione
       iv. Gene testing
          a) *SOX9* (17q24) – male gonadal dysgenesis, campomelic dysplasia, or XY sex reversal
          b) *WT1*(11p13) – XX male (SRY+), Frasier syndrome, or Denys–Drash syndrome with Wilms's tumor
          c) *DAX1* (Xp21.3) – mixed gonadal dysgenesis, XY female (SRY-), or congenital adrenal hypoplasia
          d) *WNT4* – XO/XY
          e) *DHH* – ovotesticular DSD
          f) *ATRX* – α-thalassemia X-linked mental retardation syndrome
          g) *SLOS* – Smith–Lemli–Opitz syndrome
       v. Imaging: ultrasound

Genetic Counseling

1. Recurrence risk: Recurrence risk depends on the inheritance pattern of the disorder (e.g., autosomal recessive disorders – congenital adrenal

hyperplasia, testosterone biosynthetic defects, Leydig cell hypoplasia; autosomal dominant disorders – campomelic dysplasia, Denys–Drash syndrome, Frasier syndrome; X-linked recessive disorders – androgen insensitivity syndrome, male pseudohermaphroditism due to testicular 17,20-desmolase deficiency)
   a. Patient's sib
      i. Autosomal recessive: 25%
      ii. Autosomal dominant: not increased unless a parent is affected or having gonadal mosaicism
      iii. X-linked recessive: 50% of male sibs affected if the mother is a carrier
   b. Patient's offspring
      i. Autosomal recessive: not increased unless the spouse is also a carrier
      ii. Autosomal dominant: 50%
      iii. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal
2. Prenatal diagnosis
   a. Prenatal ultrasonography: Pitfalls in sonographic fetal sex determination (Odeh et al. 2009) include:
      i. Fetuses with malformations of the external genitalia represent a diagnostic challenge
      ii. Clues to the presence of congenital malformations of the external genitalia include:
         a) Nonvisualization of the fetal bladder (Wilcox and Chitty 2001)
         b) Diagnosis of female genitalia at early gestation based on caudal orientation of the genital tubercle, followed at a later time by observation of male genitalia (Borneshtien et al. 1995)
         c) Marked phallic size discrepancy for gestational age; curvature of the phallus; scrotal-phallus malpositions
         d) Nondescended testis in the third trimester
         e) Absence of phallic, labial, or scrotal structures (Mandell et al. 1995)
         f) Abnormalities of the genitalia should also be suspected whenever a mismatch is found between the sonographic fetal sex and the karyotypic fetal sex (Stephens 1984; Cheikhelard et al. 2000)
   b. Prenatal diagnosis is possible for pregnancies at increased risk for various genetic syndromes when the disease-causing mutation in the family is known
3. Management
   a. Ambiguous genitalia: likely the most devastating condition to face any parent of a newborn.
   b. Dealing with emotional, psychosocial, cultural, diagnostic, and treatment issues.
   c. Factors to consider when discussing sex assignment with families (Lee et al. 2006):
      i. Diagnosis
      ii. Genital appearance
      iii. Potential for fertility
      iv. Surgical options
      v. Long-term hormone replacement therapy
      vi. Family views
      vii. Cultural practices
   d. Challenge facing clinicians : come to an accurate and expeditious diagnosis, and then to a rational sex assignment:
      i. The condition is rare
      ii. Clinical diagnosis frequently difficult
      iii. Understanding of normal sexual differentiation is crucial to understanding these disorders
   e. Hormone replacement therapy is often required to induce and sustain puberty, optimize bone mineral accrual and psychosexual development in individuals with ambiguous genitalia (Warne et al. 2005; Nabhan and Lee 2007):
      i. Intramuscular injections of either testosterone cypionate or ethanate are used for pubertal induction for hypogonadal boys. Other testosterone preparations such as gels and patches are available, but there is limited experience of their use for the induction of puberty (Rogol 2005).
      ii. Estrogen replacement orally or injection to induce secondary sexual characteristic development and menses for girls with hypogonadism. A progestin is usually added after breakthrough bleeding or after 1–2 years of continuous estrogen. In women without a uterus, there is no evidence that the addition of cyclic progesterone is beneficial.
   f. Surgical care:
      i. Feminizing genitoplasty, including vaginoplasty and clitoroplasty, in a virilized female
      ii. Surgical reconstruction in undervirilized males who typically have hypospadias: gender

reassignment may be considered in patients with male pseudohermaphrodism and genital inadequacy

iii. Testes in individuals with 46,XY gonadal dysgenesis or fragments of Y-chromosome material raised female should be removed to prevent testicular malignancy

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Fig. 1 Vaginal labia agglutination (adhesion) in a female infant

Fig. 3 Penoscrotal hypospadias with a chordee in a male infant

Fig. 2 Vaginal atresia in a female newborn

Fig. 4 Cloacal exstrophy with ambiguous genitalia in an infant

Fig. 5 Ambiguous genitalia with clitoromegaly in a female infant

Fig. 6 Ambiguous genitalia in a female infant with congenital adrenal hyperplasia

Fig. 7 Penoscrotal hypospadias in Smith–Lemli–Opitz syndrome

Fig. 8 A 17-year-old male was followed for 46,XX true hermaphroditism. He was born with low shaft hypospadias and *left* inguinal hernia. He underwent *left* groin exploration and *left* inguinal hernia repair. At operation, the patient was noted to have an odd testicle which looked like a typical ovotestis. Two biopsied specimen were obtained: one revealed immature ovary containing numerous follicles and other a fragment of immature testicle containing seminiferous tubules. He was followed at age of 11. He had Tanner III gynecomastia, Tanner III-IV pubic hair, and Prader 5–8 cc volume testes that were somewhat irregular in size and firm. The LH and FSH were 3.2 and 21 μ/ml (both were normal pubertal levels), respectively. A beta HCG was <3 mIU/ml, and testosterone level 351 ng/dl (normal pubertal levels), estrone 1.3 ng/dl, and estradiol 0.8 ng/dl (normal male levels). His bone age was between 12 and 12.5 years of age

Amniotic Deformity, Adhesions, Mutilations (ADAM) Complex

ADAM complex occurs in 1 of every 5,000–15,000 births and had been demonstrated in 1–2% of malformed infants (Heifetz 1984).

Synonyms and Related Disorders

Amniotic band disruption complex; Amniotic band syndrome; Amniotic constriction band; Congenital ring constrictions; Constriction ring syndrome; TEARS (The Early Amnion Rupture Spectrum)

Genetics/Basic Defects

1. Streeter intrinsic theory (Streeter 1930; Wiedrich 1998)
   a. An intrinsic defect of the subcutaneous germ plasm causes soft tissue to slough. The resulting external healing leads to the constriction ring.
   b. Significant rate of associated anomalies as indirect proof of existence of some genetic force at work to cause the syndrome
2. Torpin extrinsic theory (Torpin 1965) (currently most popular theory)
   a. Early amniotic rupture leading to the formation of mesodermal fibrous strands that entangle limbs and appendages
   b. Amnion rupture without injury to the chorion resulting in amniotic bands
   c. Oligohydramnios playing a major role in the development of the constricting bands
   d. Higher incidence of club feet possibly resulting from continuous pressure on the feet from the undersized uterus
   e. Amniotic bands essentially encircling the affected part resulting in constricting rings
   f. Supporting evidence
      i. Constriction rings often occurring in a straight line across multiple digits as if one external band affects multiple adjacent digits
      ii. Frequent involvement of the central digits
      iii. Occasional attachment of amnion in the constricting ring
      iv. Facial clefting which does not follow developmental planes
3. Other theory: simultaneous occurrence of both extrinsic and intrinsic factors in the development of constriction band syndrome
4. Other factors/mechanisms implicated in the etiology of amniotic band syndrome: The cause of amniotic band syndrome remains elusive and controversial (Bagatin et al. 1997).
   a. Simple oligohydramnios
   b. Fetal hypertension
   c. Venous stasis
   d. Localized fetal ischemia caused by uterine contractions
   e. Intrauterine hemorrhage as the precipitating event
   f. Vascular compromise (lack of distal blood flow demonstrated in association with forearm amputation defects)
   g. Cocaine drug abuse: cocaine acting as a teratogen by inducing fetal hypoxemia through impaired uteroplacental fetal blood flow and directly through its vasoconstrictive properties on the fetal vasculature
   h. Incompetent cervix

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i. Amniocentesis implicated. An increased incidence of anomalies related to amniotic band syndrome in association with prenatal amniocentesis in animal models
j. Familial occurrences reported despite no evidence for a genetic predisposition to amniotic band syndrome

Clinical Features

1. The nature and severity of deformities: related to the timing and initiating event of amniotic rupture (Heifetz 1984)
2. Triad of amniotic band syndrome
   a. Amnion-denuded placenta
   b. Fetal attachment or entanglement by amniotic remnants
   c. Fetal deformation, malformation, and/or disruption (Goldfarb et al. 2009)
      i. Fetal deformation
         a) Fetal compression secondary to oligohydramnios (talipes equinovarus, scoliosis, and various joint contractures)
         b) Fetal entanglement by amniotic bands
      ii. Fetal malformation resulting from amniotic band interfering with the normal sequence of embryologic development. Classic malformations include:
         a) Body-wall defects, internal organ abnormalities
         b) Craniofacial abnormalities
      iii. Fetal disruption secondary to cleavage of structures that have already developed normally. Classic disruptive findings are:
         a) Constriction bands
         b) Amputations
         c) Acrosyndactyly
3. Craniofacial disruptions (up to one-third of cases) (Bagatin et al. 1997)
   a. Facial clefting
      i. Most likely associated with swallowing of band at about 5 months of gestation
      ii. Unusual extensions with asymmetric locations, such as oblique facial clefting
   b. Orbital defects
      i. Anophthalmos
      ii. Microphthalmos
      iii. Enophthalmos
      iv. Hypertelorism
   c. Corneal abnormalities
      i. Anomalous eyelid configuration
      ii. Ineffective eye closure
   d. Other ocular abnormalities
      i. Strabismus due to defects in extraocular muscles
      ii. Epiphora related to either lachrymal system involvement or eyelid abnormalities
   e. CNS involvement: usually associated with amniotic band rupture before 45 days of gestation
      i. Neural tube defects (cranioschisis, atypical or asymmetrical meningocele, myelomeningocele, encephalocele, or anencephaly)
      ii. Ventriculomegaly
      iii. Pressure defects of the parenchyma
   f. Calvarial defects
   g. Cleft lip/palate
4. Limb abnormalities
   a. Limb reduction defects
   b. Intrauterine amputations
   c. Ring constrictions with or without distal lymphedema, clubbing, or syndactyly
      i. Deeper rings
      ii. Circumferential rings
   d. Club feet
   e. Digital anomalies: frequently involved
      i. Syndactyly
      ii. Acrosyndactyly
      iii. Digital hypoplasia
      iv. Symphalangism
      v. Symbrachydactyly
      vi. Camptodactyly
   f. Significant neurovascular impairment distal to the constricting band
5. Umbilical cord strangulation by amniotic bands
   a. Common occurrence (10%)
   b. Cord strangulation
   c. Severe strangulation of the umbilical cord at times resulting in fetal death
   d. Stillbirths observed in about 97% of umbilical cord strangulation by amniotic bands
6. Associated anomalies
   a. Hemangiomas
   b. Cardiac defect
   c. Limb/body wall defects

   d. Thoracoabdominal wall defects
      i. Thoracoschisis
      ii. Extrathoracic heart
      iii. Omphalocele
      iv. Gastroschisis
   e. Aplasia cutis
   f. Short umbilical cord
   g. Oligohydramnios sequence
7. Patterson's classification system of congenital ring constriction based on the severity of the syndrome
   a. Simple constriction rings
   b. Constriction rings associated with deformity of the distal part, with or without lymphedema
   c. Constriction rings associated with soft-tissue fusions of distal parts (acrosyndactyly)
   d. Intrauterine amputation
8. Hall's classification system for amniotic band syndrome
   a. Mild constriction without lymphedema
   b. Moderate constriction with lymphedema
   c. Severe constriction with amputation
9. Weinzweig's classification system for amniotic band syndrome (Weinzweig 1995)
   a. Mild constriction without lymphedema
   b. Moderate constriction with distal deformity, syndactyly, or discontinuous neurovascular or musculotendinous structures without vascular compromise
      i. Without lymphedema
      ii. With lymphedema
   c. Severe constriction with progressive lymphaticovenous or arterial compromise
      i. Without soft-tissue loss
      ii. With soft-tissue loss
   d. Intrauterine amputation
10. Lockwood's classification of fetal anomalies in amniotic band syndrome according to their presumed mechanism (Lockwood et al. 1989)
   a. Anomalies caused by interruption of embryonic morphogenesis
      i. Cleft lip and palate
      ii. Omphalocele
      iii. Cardiac anomalies
      iv. Renal agenesis or dysplasia
      v. Bladder exstrophy
      vi. Imperforate anus
   b. Anomalies caused by fetal vascular compromise
      i. Gastroschisis
      ii. Gallbladder agenesis
      iii. Single umbilical artery
   c. Anomalies caused by intrauterine constraint
      i. Club foot
      ii. Clubbed hands
      iii. Abnormal facies
      iv. Valgus-varus deformities
      v. Kyphoscoliosis
   d. Anomalies caused by disruption of normally developed structures
      i. Severe central nervous system or calvarial defect
      ii. Acrosyndactyly
      iii. Amputations
      iv. Constriction bands
      v. Facial clefts (anatomically inappropriate)
      vi. Aplasia cutis
11. Proposed prenatal classification in stages of amniotic band syndrome involving extremities (modified postnatal classification by Weinzweig 1995; Hüsler et al. 2009)
   a. Amniotic bands without signs of constriction
   b. Constriction without vascular compromise (normal vascular Doppler studies, when compared to opposite side) may have distal deformity
      i. Without or only mild lymphedema
      ii. With severe lymphedema
   c. Severe constriction with progressive arterial compromise. The flow has to be measured proximally, at and distally to the constriction band.
      i. Abnormal distal Doppler studies when compared to contralateral extremity
      ii. No vascular flow to extremity
   d. Bowing or fracture of long bones at constriction site
   e. Intrauterine amputation
12. Prognosis
   a. Prenatally diagnosed amniotic adhesion with a grim prognosis
   b. Most cases of cranial and body wall defects incompatible with extrauterine life
   c. Infants born with limited limb abnormalities: better prognosis with good results after surgical repair of the constrictions or syndactyly

Diagnostic Investigations

1. Radiography
   a. Syndactyly with amputation of distal parts
   b. Intrauterine amputation of limbs and digits
2. MRI imagings (Labor et al. 1998)
   a. Delineate the depth of the constriction band
   b. Delineate the extent of the resultant lymphedema
   c. Delineate the integrity of the musculature
   d. Define the vascular anatomy, which may be anomalous; may help to prevent injury to the vessels during surgery.
3. Histology (Day-Salvatore et al. 1995)
   a. Absence of amniotic membrane on the fetal surface of the chorionic sac, including the placental sac
   b. Presence of amnion remnant as a cuff of thick membrane at the base of the umbilical cord at its insertion site
   c. Amniotic squames and cellular debris are frequently embedded in the superficial soft tissue of the chorion indicating chronic amniotic rupture
   d. Constricting bands encircling digits

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: not increased
2. Prenatal diagnosis (Hüsler et al. 2009)
   a. Possible by ultrasonography during second and third trimester
   b. Possible as early as the first trimester in certain cases
   c. Degree of deformity depends on the severity and location of the band formation and the gestational age at amniotic rupture.
   d. Visualization of amniotic sheets or bands attached to the fetus. The diagnosis of amniotic band syndrome should not be made solely on the basis of a membrane observed in the uterine cavity.
   e. Restricted fetal movement
   f. Characteristic asymmetric fetal anomalies
   g. Constriction bands around the limbs
   h. Prenatal natural history of amniotic band sequence without body wall defect
      i. Prematurity
      ii. Preterm rupture of membranes
      iii. Low birth weight (<2,500 g)
      iv. May lead to compromised blood supply to the constricted body parts
      v. Constriction bands may spontaneously resolve (Pedersen and Thomsen 2001)
      vi. Fetal death associated with amniotic band strangulation of the umbilical cord reported (Heifetz 1984; Lurie et al. 2008)
3. Management
   a. Surgery not needed for shallow constriction bands that are not circumferential and without distal swelling
   b. Distal edema or impairment of neurovascular function requiring staged constriction band excision, Z-plasty, or W-plasty
   c. Digital amputation may be required for a ring so constrictive that distal edema is massive.
   d. Multiple plastic surgical procedures required for corrections of the complex craniofacial abnormalities
   e. Procedures for the upper-extremity deformities (Foulkes and Reinker 1994)
      i. Band release, Z- or W-plasty
      ii. Syndactyly/web space release
      iii. Skin graft
      iv. Stump revision
      v. Osteotomy/osteoclasis
      vi. Hardware removal
      vii. Ray resection/transposition
      viii. Distraction osteogenesis
      ix. Pollicization/osteocutaneous transfer
      x. Tendon transfer
      xi. Excision supernumerary digit
      xii. Amputation
   f. Procedures for the lower-extremity deformities (Foulkes and Reinker 1994)
      i. Band release, Z- or W-plasty
      ii. Syndactyly release
      iii. Simple revision
      iv. Amputation/excision toe
      v. Clubfoot procedure
      vi. Hip procedure
      vii. Tibial derotation
      viii. Removal of skin tag

g. Careful follow-up on congenital constriction band of the trunk because the evolution of this condition is benign.
h. Intrauterine release of extremity amniotic band should be indicated in severe cases with risk of intrauterine amputations or irreversible deformities when no other severe disorders are associated (Soldado et al. 2009). The most relevant risks that have to be assumed are premature rupture of membranes and complications related to prematurity.
i. In utero surgical intervention proposed to avoid amputation or permanent damage to the extremity of the fetus, provided the maternal and fetal risks of surgery are small

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Fig. 1 A small stillborn fetus (110 g) showing amniotic constriction band at *left* ankle. Amputation and pseudosyndactyly of fingers and toes are present

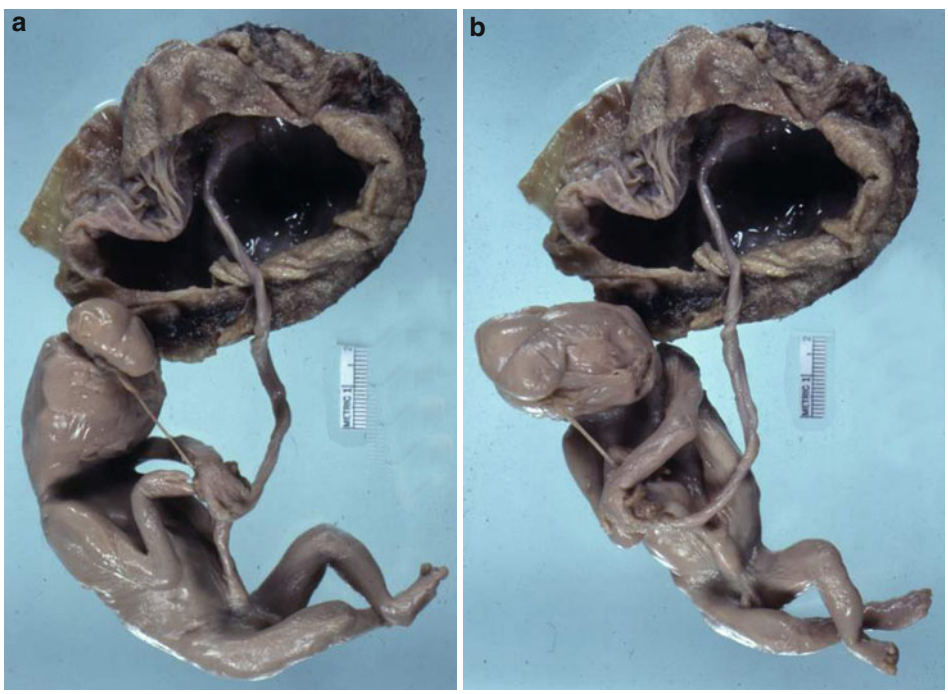

Fig. 2 (**a**, **b**) A small stillborn fetus (60 g) with a fibrous amniotic band constricting a portion of the head and facial cleft

Fig. 3 (**a**, **b**) A small fetus with a large amniotic band which caused anencephaly

Fig. 4 The *left* hand of a 1,100 g fetus showing in utero amputation of the third and fourth fingers

Fig. 6 Cord strangulation by amniotic band

Fig. 5 A placenta with a long strand of amniotic band which was pulled out of the mouth of the premature neonate at birth. The baby did not have amniotic band syndrome

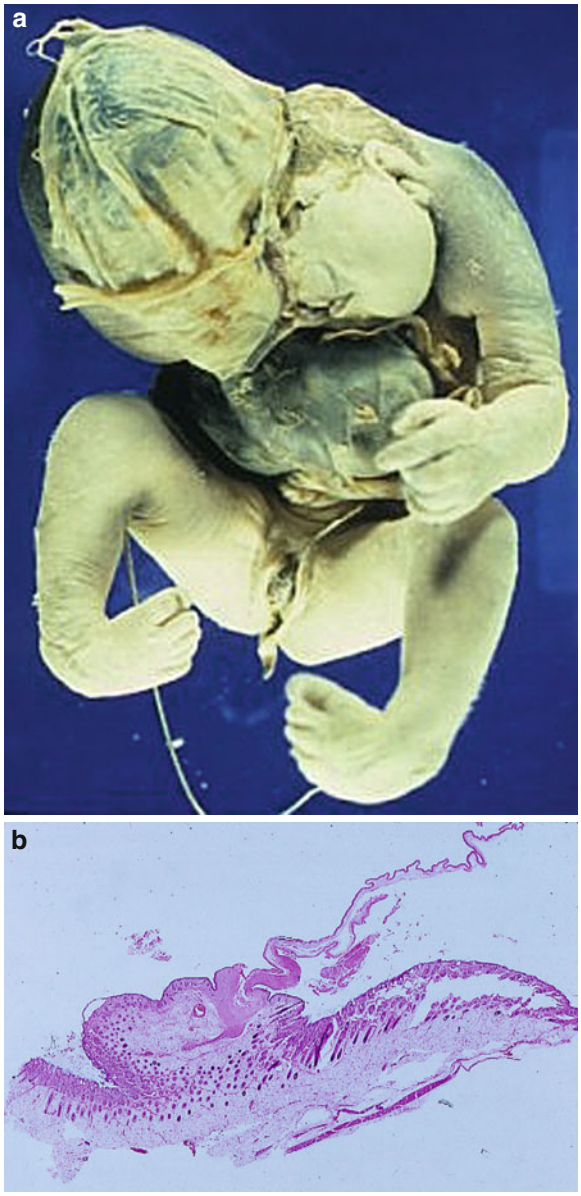

Fig. 7 (**a**, **b**) A fetus with a large meningoencephalocele and an amniotic band attaching to its base. Facial defects, a large gastroschisis, and talipes equinovarus were also present. Histology of the scalp shows an amniotic band fused with the soft tissue of the upper dermis. The amniotic epithelium of the band is visible as a darker line on the surface. The epidermis of the scalp is denuded at the site of band attachment

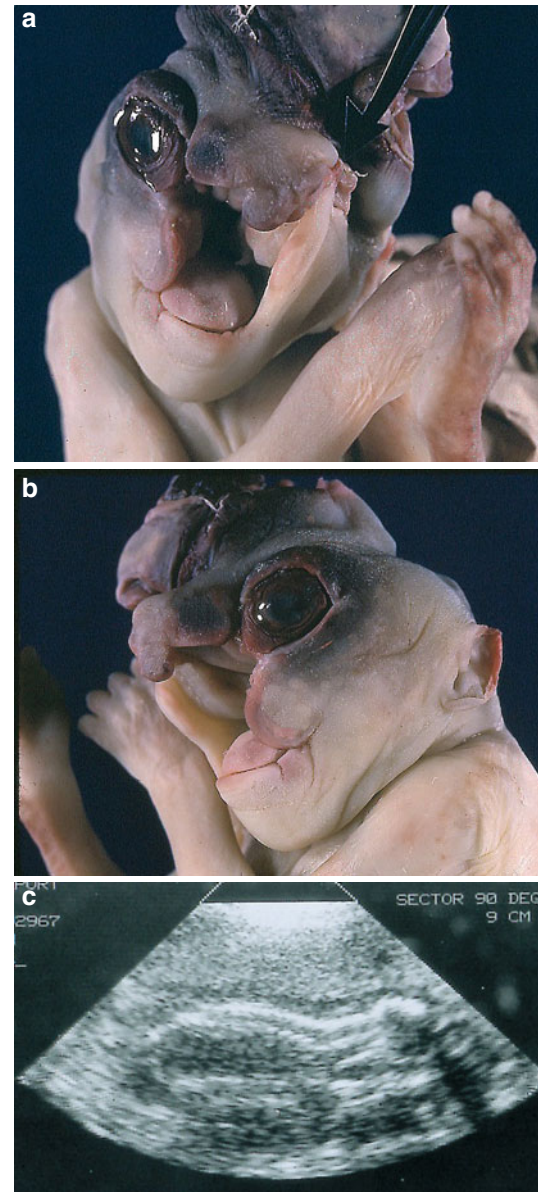

Fig. 8 (**a**–**c**) A fetus with marked craniofacial defects and the site of amniotic band attachment at the base of the skull. The fetus also had amputation of the distal *left* great toe (not shown). Prenatal ultrasonography showed a complex structure arising from the top and front of the craniofacial region

Fig. 9 An infant with marked craniofacial anomalies, a constricting ring of a finger with distal lymphedema, and an amputation of the fifth finger

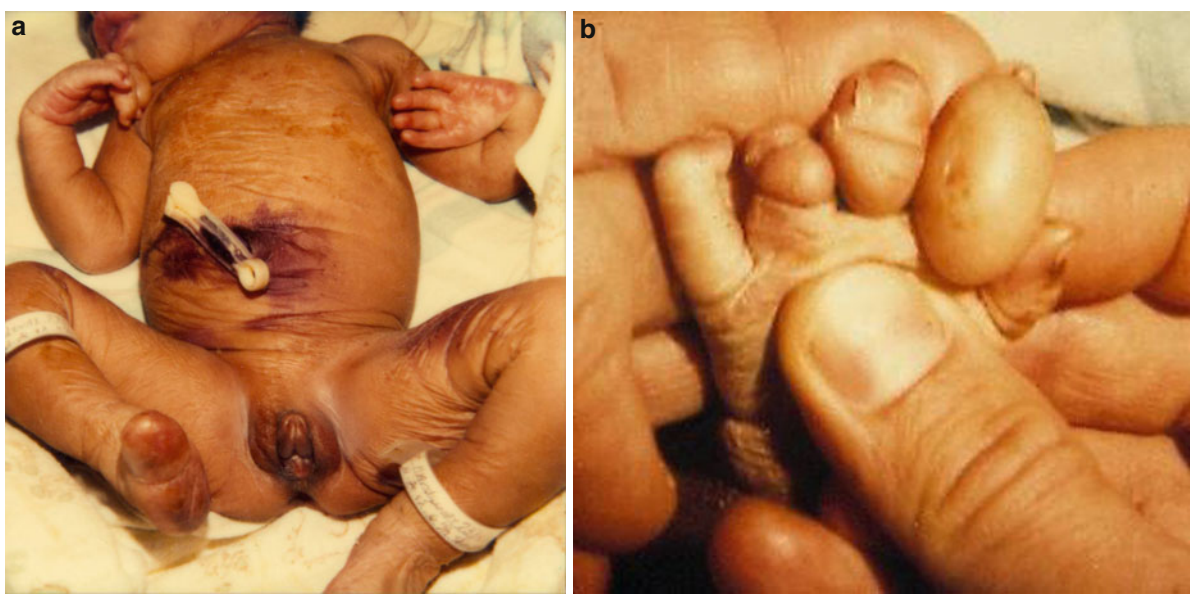

Fig. 10 (**a**, **b**) An infant with club *left* hand with a missing finger, constricting rings with marked distal lymphedema of the *right* index finger, and pseudosyndactyly of the *right* foot

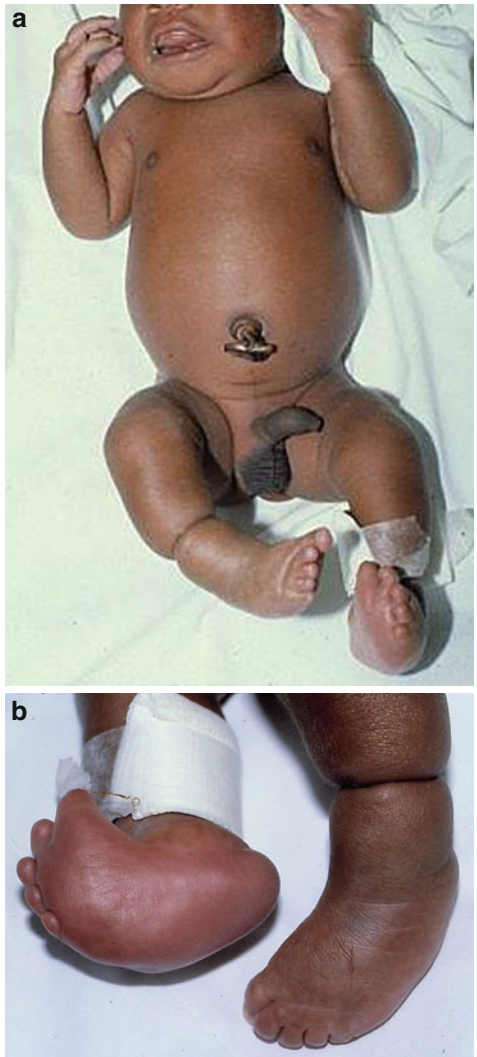

Fig. 11 (**a**, **b**) An infant with deep constricting groove around the lower one-third of both legs. The patient also had terminal amputation and constriction rings of fingers with a small amniotic band still attached to the constricting ring of the second finger (not shown)

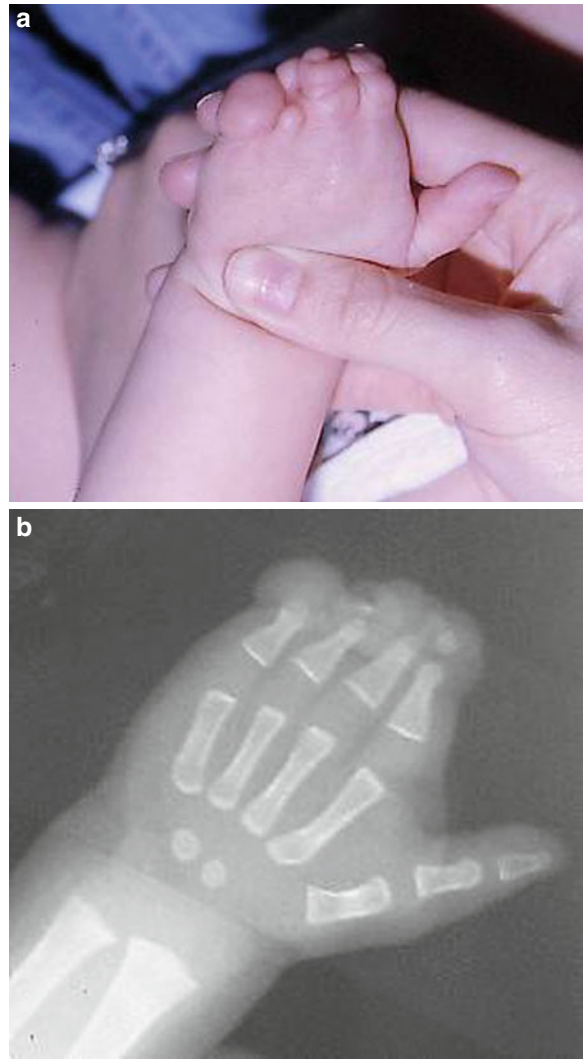

Fig. 12 (**a**, **b**) A hand of an infant with constriction bands of the fingers with amputations, shown by the radiograph

Androgen Insensitivity Syndrome

In 1953, Morris described the clinical phenotype of "testicular feminization" after reviewing 82 cases. Morris's phenotype included a female body habitus with normal breast development, minimal pubic and axillary hair, typically absent or rudimentary vagina or absent uterus. The term "testicular feminization syndrome" was based on the observation of the complete absence of signs of virilization in phenotypic females with testes and a 46,XY karyotype. The change in nomenclature from testicular feminization to androgen insensitivity syndrome (AIS) was prompted by the finding of normal urinary 17-ketosteroid levels, an androgen metabolite as well as by absence of treatment effect when 46,XY women were treated with methyltestosterone, suggesting androgen resistance rather than a deficiency (Wilkins 1950; Speroff and Fritz 2005; Oakes et al. 2009).

AIS probably represents the most common cause of male pseudohermaphroditism. It is an X-linked recessive disorder in 46,XY individuals with normal androgen production and metabolism. The prevalence of AIS is estimated to be 1 in 20,000–1 in 99,000 genetic males (Bangsboll et al. 1992; Boehmer et al. 2001; Grumbach et al. 2003). The prevalence of phenotypic females with inguinal hernias is estimated to be 0.8–2.4% (Gans and Rubin 1962; Nielsen and Bulow 1976).

Synonyms and Related Disorders

Androgen receptor deficiency; Dihydrotestosterone receptor deficiency; Testicular feminization syndrome

Genetics/Basic Defects

1. Inheritance
   a. X-linked recessive inheritance
      i. Affected XY individuals
      ii. Carrier XX females
   b. Manifesting carrier females (about 10% of carrier females)
2. Caused by mutations of androgen receptor (*AR*) gene (mapped to chromosomal locus Xq11-q12) (Lubahn et al. 1988)
   a. Mutations of androgen receptor: responsible for a variable degree of impaired androgen action
   b. De novo mutations
      i. De novo mutation rate close to 30%
      ii. Somatic or germ-line mosaicism observed for "de novo" mutations in which the mutation is present in some of the cells in one of the clinically unaffected parents
   c. Type of mutations
      i. Point mutations
      ii. Complete and partial gene deletions
      iii. Small insertion deletions
   d. Variable expressivity of a particular point mutation attributable to somatic mosaicism for the mutation
3. Pathogenesis
   a. Androgen insensitivity syndrome
      i. The result of an end-organ resistance to androgens caused by an abnormality of the androgen receptor
      ii. Normal production of testosterone and normal conversion to dihydrotestosterone

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(DHT) by the normal testes in affected individuals, differentiating this condition from 5α reductase deficiency
iii. Absence of fallopian tubes, uterus, or proximal (upper) vagina in affected individuals because testes produce normal amounts of müllerian-inhibiting factor (MIF)

b. Complete androgen insensitivity syndrome (CAIS)
i. Most severe form
ii. Complete resistance to all actions of testosterone and dihydrotestosterone

c. Incomplete androgen insensitivity syndrome (IAIS): partial resistance to the action of testosterone and dihydrotestosterone

d. Reifenstein syndrome: Variable resistance to the action of testosterone and dihydrotestosterone

e. Mild androgen insensitivity syndrome (MAIS): Resistance to the action of androgen varies in different tissues

Clinical Features

1. Variable phenotypic expression allowing the classification of AIS into complete and partial forms, and a rare group of phenotypically normal men with azoospermia.
2. Complete androgen insensitivity syndrome
   a. Presumptive diagnosis of CAIS (Gottlieb et al. 2007)
      i. Absence of extragenital abnormalities
      ii. Two nondysplastic testes
      iii. Absent or rudimentary müllerian structures (absence of fallopian tubes, uterus, or cervix)
      iv. A short vagina
      v. Under-masculinization of the external genitalia at birth
      vi. Impaired spermatogenesis (sterility) and/or somatic virilization at puberty
   b. External phenotype
      i. Invariably presenting as a normal female external appearance (female habitus)
      ii. Female external genitalia ("testicular feminization"; Tfm)
      iii. Underdeveloped, short blind-ending vagina
      iv. Normal breast and female adiposity development
      v. Unaffected sexual identity and orientation
      vi. Scant or absent pubic and/or axillary hair
   c. Urogenital tract
      i. Absent or rudimentary wolffian duct derivatives (epididymides and/or vas deferens)
      ii. Inguinal or labial masses subsequently identified as testes in a phenotypic female infant or child
      iii. Inguinal hernia: the commonest presentation of CAIS in childhood (Deeb and Hughes 2005)
      iv. 1.1% incidence rate of CAIS in a child with a premenarcheal inguinal hernia while 80–90% of girls with CAIS eventually develop an inguinal hernia (Gans and Rubin 1962; Viner et al. 1997; Sarpel 2005)
   d. Other features
      i. Primary amenorrhea in a phenotypic female adolescent: most typical presentation
      ii. Complete androgen insensitivity syndrome almost always runs true in families (i.e., affected XY relatives usually have normal female external genitalia and seldom have any sign of external genital masculinization, such as clitoromegaly or posterior labial fusion).
3. Partial androgen insensitivity syndrome (PAIS)
   a. Predominantly female external genitalia (incomplete androgen insensitivity syndrome)
      i. Signs of external genital masculinization
         a) Clitoromegaly
         b) Partial fusion of the labioscrotal folds
      ii. Female habitus and breast development
      iii. Normal axillary and pubic hair
      iv. Inguinal or labial testes as in CAIS
      v. Wolffian duct derivatives emptying into the vagina
      vi. Distinct urethral and vaginal openings or a urogenital sinus
      vii. No müllerian duct derivatives
   b. Ambiguous external genitalia (Reifenstein syndrome)
      i. Microphallus (<1 cm) with clitoris-like underdeveloped glans
      ii. Labia majora-like bifid scrotum
      iii. Descended or undescended testes
      iv. Perineoscrotal hypospadias or urogenital sinus
      v. Gynecomastia in puberty

   c. Predominantly male external genitalia (Reifenstein syndrome)
      i. Simple (glandular or penile) or severe (perineal) "isolated" hypospadias with a normal-sized penis and descended testes or severe hypospadias with micropenis
      ii. Bifid scrotum
      iii. Either descended or undescended testes
      iv. Gynecomastia in puberty
4. Mild androgen insensitivity syndrome
   a. Two phenotypic forms at puberty
      i. Impaired spermatogenesis and fertility
      ii. Normal or sufficient spermatogenesis to preserve fertility
   b. Clinical features common to both forms
      i. Male external genitalia ("undervirilized male syndrome")
      ii. Gynecomastia in puberty
      iii. High-pitched voice
      iv. Sparse sex hair
      v. Impotence
5. Manifesting carrier females
   a. Asymmetric distribution and sparse or delayed growth of pubic or axillary hair
   b. A history of late (15 years) or delayed (16 years or older) menarche
6. Differential diagnosis (Oakes et al. 2008)
   a. Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome (müllerian agenesis)
      i. A more common cause of primary amenorrhea: an incidence rate of 1 in 5,000 (Aittomaki et al. 2001)
      ii. Normal breast development
      iii. Underdeveloped vagina
      iv. Normal axillary and pubic hair (Speroff and Fritz 2005)
      v. A 46,XX karyotype
   b. Swyer syndrome (XY gonadal dysgenesis)
      i. Lack of breast development
      ii. Short stature
      iii. Localize testes and to rule out testicular tumors by ultrasound and MRI

Diagnostic Investigations

1. Diagnostic workup
   a. Diagnosis of CAIS usually based on:
      i. Clinical findings
      ii. Laboratory evaluation
      iii. Imaging studies including transabdominal pelvic ultrasound and MRI: to document internal anatomy
   b. Diagnosis of PAIS and MAIS based on:
      i. Clinical findings
      ii. Laboratory evaluation
      iii. Family history consistent with X-linked recessive inheritance
2. Laboratory investigations
   a. AIS
      i. Chromosome analysis: 46,XY karyotype
      ii. Evidence of normal or increased synthesis of testosterone by the testes
      iii. Evidence of normal conversion of testosterone to 5α-dihydrotestosterone
      iv. Evidence of normal or increased luteinizing hormone production by the pituitary gland
      v. Evidence of deficient or defective androgen-binding activity of genital skin fibroblasts
   b. CAIS, IAIS, Reifenstein syndrome, and MAIS
      i. Chromosome analysis: 46,XY karyotype
      ii. Testosterone: Normal or high male plasma levels and production rates
      iii. Estrogen: Plasma levels and production rates higher than in normal men
      iv. Gonadotropin: Elevated plasma LH levels (may be normal in MAIS)
   c. Additional findings of sporadic cases of predominantly male phenotype of PAIS
      i. Impaired development of the prostate and of the wolffian duct derivatives demonstrated by ultrasonography or genitourography
      ii. Less than normal decline of sex hormone–binding globulin in response to a standard dose of the anabolic androgen, Stanozolol
      iii. Higher than normal levels of anti-müllerian hormone during the first year of life or at the beginning of puberty
3. Histologic investigations
   a. CAIS
      i. Testes: apparently normal in early life but begin to lose their germ cell population in late childhood
      ii. Development of testicular hamartomas (composed of Sertoli and Leydig cells, spindle cells, stroma, and germ cells in varying

proportion), benign and malignant tumors beginning in the postpubertal period
iii. Germinal cell tumors, usually seminomas, in approximately 8% of CAIS cases
b. IAIS
i. Histologic appearance of the gonads similar to that of CAIS
ii. Cryptorchid testes, usually containing spermatocytes and rare observation of spermatozoa in a minority of patients
c. MAIS with oligospermia or azoospermia in phenotypically normal males with testicular biopsy showing:
i. Presence of Sertoli cell only
ii. Arrest of spermatogenesis at the spermatid stage

4. Detection of known mutations of the androgen receptor gene clinically available by sequencing
a. CAIS: detected in >95% of patients
b. PAIS: detected in <50% of patients
c. MAIS: proportion of patients with detected mutations unknown

Genetic Counseling

1. Recurrence risk: genetic counseling according to X-linked recessive inheritance (Gottlieb et al. 2007)
a. Patient's sib
i. Recurrence risk: low but greater than that of the general population because the possibility of germ-line mosaicism exists provided the mother is not a carrier
ii. 50% of sibs inheriting the mutation from the carrier mother
a) Sibs with a 46,XY karyotype who inherit the mutation will be affected
b) Sibs with a 46,XX karyotype who inherit the mutation will be carriers
b. Patient's offspring
i. 46,XY individuals with AIS (i.e., CAIS, PAIS, MAIS): almost always infertile
ii. Manifesting carrier females: 50% risk of transmitting the AR gene mutation in each pregnancy
c. Offspring of a known *AR* mutation carrier female
i. 25% of 46,XY children: affected
ii. 25% of 46,XY children: unaffected
iii. 25% of 46,XX children: carrier
iv. 25% of 46,XX children: not a carrier
v. A wide range of phenotypes observed for the same mutation in different families making genetic counseling more difficult

7. Carrier detection
a. Family pedigree
b. Clinical features
i. Asymmetric distribution and sparse or delayed growth of pubic or axillary hair in manifesting carriers (10% of carriers), resulting from skew X chromosome inactivation
ii. Normal pubic and axillary hair do not rule out the 46,XX carrier state
c. Deficient or defective androgen-binding activity of single-cell clones from a genital skin fibroblast line, provided an affected 46,XY family member is known to have deficient or defective androgen-binding activity in a genital skin fibroblast cell line
d. Molecular genetic testing (Davies et al. 1995)
i. A complete screening strategy of the entire androgen receptor gene needed to find the mutation in a new case of androgen insensitivity syndrome. Once the mutation is identified in the proband, carrier detection of other family members is possible.
ii. Intragenic polyglutamine and polyglycine trinucleotide repeats in the N-terminal region of the androgen receptor may be used as polymorphisms to follow the affected X chromosome through the family and used for carrier status determination.

8. Prenatal diagnosis
a. Request for prenatal diagnosis uncommon
i. Finding of discordance between chromosomal and phenotypic sex by ultrasonographic and cytogenetic analysis
ii. AIS does not affect intellect
iii. Only some treatment modalities available
b. Prenatal diagnosis by mutation analysis: clinically available in families in which the disease-causing allele has been identified in an affected family member
c. Fetal sex determination by amniocentesis or CVS
i. XX fetus: additional testing not warranted
ii. XY fetus: extract DNA for mutation analysis

9. Management (Gottlieb et al. 2007)
a. Psychological support

i. Probably the most important aspect of medical care
ii. Psychologist or psychiatrist consultations to help adjust to child's condition, including support on how to inform the child, over time and in an age-appropriate manner
iii. Androgen Insensitivity Syndrome Support Group (http://www.medhelp.org/www/ais)

b. CAIS
i. Remove testes (gonadectomy) as soon as the diagnosis is made: current recommendation, however, is for removal of gonads after puberty (Oakes et al. 2008).
ii. The rationale for postpubertal gonadectomy: testicular malignancy seldom occurs before puberty unlike that of usual cryptorchid testes.
iii. Estrogen replacement therapy necessary to initiate puberty, maintain feminization, and avoid osteoporosis
iv. Dilatation of short vaginal length (vaginoplasty) to avoid dyspareunia
v. Systemic disclosure of the condition to parents and patients in an empathic setting

c. PAIS with predominantly female genitalia
i. Management issues similar to CAIS
ii. Prepubertal gonadectomy helps avoid discomfort of increasing clitoromegaly at the time of puberty.

d. PAIS with ambiguous genitalia or predominantly male genitalia
i. Sex of rearing based on the genital phenotype, genital reconstructive surgery, and hormone therapy
ii. Sex assignment in infants with ambiguous genitalia requires delicate decision-making by parents and health-care personnel and should be resolved as early as is feasible.
iii. A male sex of rearing demands a therapeutic trial with pharmacologic doses of androgen to predict potential androgen responsiveness at puberty and to facilitate reconstructive surgery.
iv. Reduction mammoplasty for gynecomastia developing in puberty

e. MAIS
i. Reduction mammoplasty often required for gynecomastia
ii. A trial of androgen pharmacotherapy to improve virilization

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Fig. 1 (**a**–**d**) A 24-year-old 46,XY individual with incomplete androgen insensitivity syndrome showing female habitus, normal axillary and pubic hair, and clitoromegaly

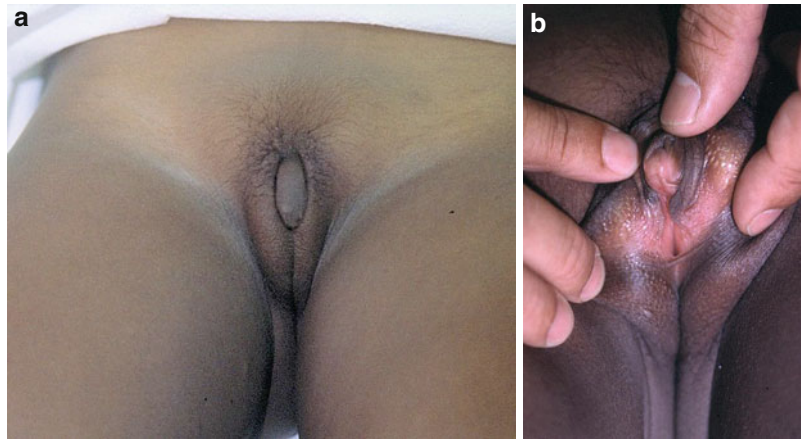

Fig. 2 (**a**, **b**) A 14-year-old sibling (46,XY) with incomplete androgen insensitivity syndrome showing the same phenotype

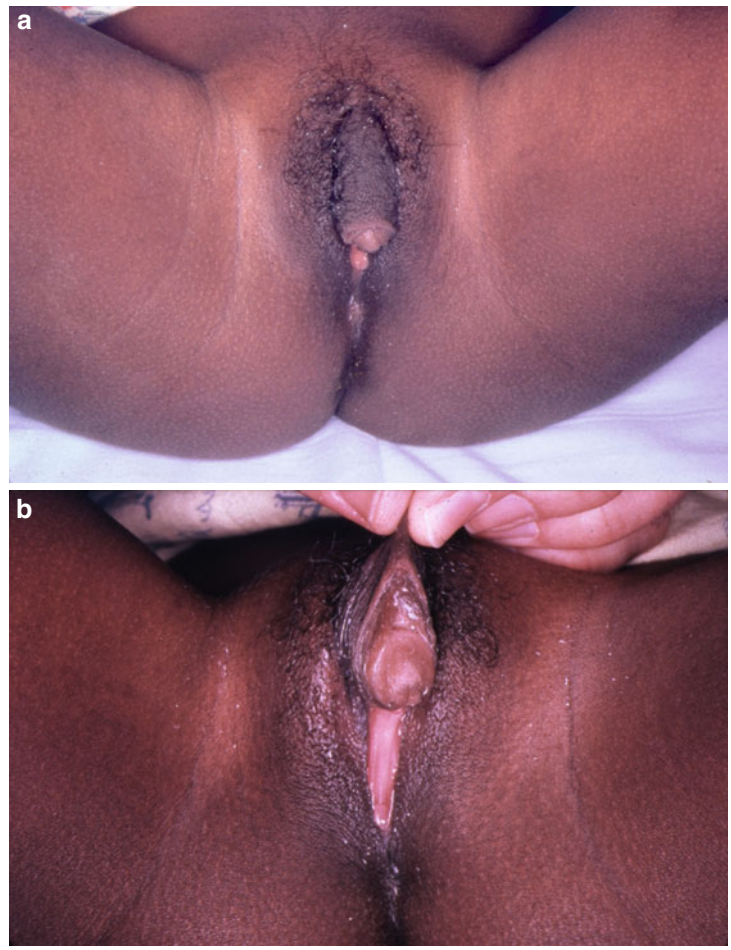

Fig. 3 (**a**, **b**) Appearance of external genitalia of another patient with androgen insensitivity syndrome

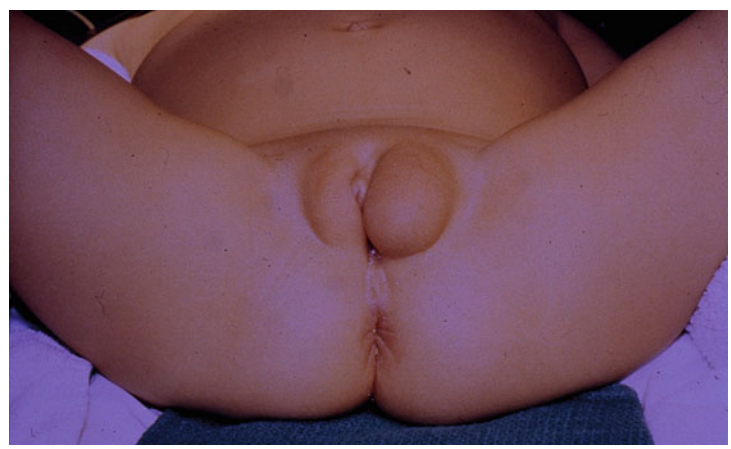

Fig. 4 A neonate with androgen insensitivity syndrome showing a mass in the left labioscrotal fold which proved to be a testis

Angelman Syndrome

In 1965, Angelman reported three children with a similar pattern of severe learning disability, seizures, ataxic jerky movements, easily provoked laughter, absent speech, and dysmorphic facial features. The syndrome, which bears his name, was originally called the "happy puppet" syndrome. The incidence is estimated to be 1 in 12,000 to 1 in 20,000 (Clyton-Smith and Pembrey 1992; Petersen et al. 1995; Steffenburg et al. 1996).

Synonyms and Related Disorders

Happy puppet syndrome

Genetics/Basic Defects

1. Inheritance
   a. Sporadic in most cases
   b. Rare familial transmission (always transmitted through maternal lineage)
2. Caused by deficiency of gene expression from abnormality on the maternally derived chromosome 15 because of genomic imprinting
   a. The relevant region on chromosome 15q
      i. Normally expressed on the maternally derived chromosome
      ii. Normally imprinted on the paternally derived chromosome
   b. Inability of the imprinted paternal allele to produce functional protein since the normally expressed maternal copy is often deleted in Angelman syndrome
3. Genetic mechanisms responsible for the disorder (Buiting 2010)
   a. Chromosome deletions and translocations
      i. Deletion (de novo) of the maternally derived chromosome region 15q11–q13 (~70%), which affects several imprinted genes including *UBE3A* (E6AP-3A ubiquitin-protein ligase gene) and *SNRPN* (small nuclear ribonucleoprotein polypeptide N)
         a) Abnormal methylation analysis with presence of paternal band only
         b) Other diagnostic tests: high-resolution cytogenetics or FISH analysis
      ii. Rare families with deletion due to unique chromosome 15 rearrangement within 15q11–q13 (<1%)
         a) Abnormal methylation analysis with presence of paternal band only
         b) Other diagnostic tests: high-resolution cytogenetics or FISH analysis
   b. *UBE3A* and other presumed single gene mutations (20–25%)
      i. Imprinting of the *UBE3A* gene with paternal silencing in human brain
      ii. Inability to degrade unwanted proteins
      iii. Compromised cellular functions secondary to absence of *UBE3A*
      iv. Resulting in abnormal cortical functioning with severe mental retardation
      v. Diagnostic tests for mutations
         a) Normal methylation analysis with presence of both maternal and paternal bands
         b) Other diagnostic tests: screening of *UBE3A* for mutations

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c. Paternal uniparental disomy (UPD) (both copies of a chromosome come from the father) of the chromosome 15 (1–2%)
   i. Affected individuals having two alleles of all genes (both derived from the father) but remain silenced with no production of functional protein
   ii. Milder phenotypic manifestations (lower incidence of seizures)
   iii. Abnormal methylation analysis with presence of paternal band only
   iv. Other diagnostic tests: RFLP analysis
d. Imprinting defects (2–4%)
   i. A mutation within the "imprinting center," located within 15q11–q13 on chromosome 15, renders the imprinting center unable to function properly (2%). Normally imprinting center regulates which segments of DNA are imprinted.
      a) Abnormal methylation analysis with presence of paternal band only
      b) Positive screening for imprinting center for mutation
   ii. Imprinting defect without imprinting center mutation (2%)
      a) Abnormal methylation analysis with presence of paternal band only
      b) Negative screening for imprinting center for mutation
   iii. Mosaic imprinting defect (frequency unknown)
      a) Abnormal methylation analysis with presence of faint maternal band
      b) Usually negative screening for imprinting center for mutation
   iv. Microdeletions reported in the imprinting center
e. No genetic abnormality identified: Patients with clinical features of Angelman syndrome but no demonstrable cytogenetic or molecular abnormality of chromosome 15q11–q13

Clinical Features

1. Consistent cardinal features (100%) (Clayton-Smith and Laan 2003; Williams et al. 2006)
   a. Normal newborn phenotype
      i. Normal prenatal and birth history
      ii. Normal head circumference
      iii. Absence of major birth defects
   b. Developmental delay
      i. Starting around 6 months of age
      ii. Eventually classified as severe developmental delay and/or mental retardation
   c. Profound speech impairment
      i. Absent or minimal use of words
      ii. Receptive and nonverbal communication skills better than verbal capability
   d. Movement or balance disorder
      i. Abnormal ataxic gait
      ii. Puppet-like jerky movements of limbs
      iii. Hand flapping movement
   e. Typical behavioral pattern
      i. An easily excitable personality, often with hand flapping movements
      ii. Short attention span
      iii. A happy, sociable disposition
      iv. Inappropriately happy affect
      v. Bouts of inappropriate laughter
      vi. Hypermotoric behavior
2. Frequent features (>80%)
   a. Delayed, disproportionate growth in head circumference, usually resulting in microcephaly by age 2
   b. Seizures (80%)
      i. Onset usually before 3 years of age (1–5 years)
      ii. Variety of seizures (tonic-clonic, atypical absences, complex partial, myoclonic, atonic, tonic seizures to status epilepticus)
   c. Characteristic EEG with large amplitude slow spike waves and triphasic waves
3. Associated features (20–80%)
   a. Characteristic craniofacial appearance
      i. Flat occiput
      ii. Occipital groove
      iii. Strabismus
      iv. Tongue thrusting
      v. Prognathia
      vi. Wide mouth
      vii. Widely spaced teeth
      viii. Frequent drooling
      ix. Excessive chewing/mouthing behaviors
   b. Swallowing disorder
   c. Feeding problems during infancy
   d. Hypopigmented skin
   e. Light hair and eye color, compared to other family members, seen only in deletion cases

f. Hyperactive lower limb deep tendon reflexes
g. Uplifted, flexed arm position especially during ambulation
h. Increased sensitivity to heat
i. Sleep disturbance
j. Attention to and fascination with water
k. Hypotonia at birth

4. Adolescent and adult phenotype
   a. More striking facial features
      i. Marked mandibular prognathism
      ii. Pointed chin
      iii. Macrostomia
      iv. Prominent lower lip
      v. Deeply set eyes
      vi. Keratoconus secondary to eye rubbing
   b. Scoliosis and joint contractures increasing with age
   c. Improved hyperactivity and concentration
   d. Persistent sociable disposition
   e. A good quality of life maintained despite the above problems
   f. Lifespan not greatly reduced
5. Phenotype–genotype correlations
   a. Patients with chromosome 15 deletions: in general, the most severely affected
      i. Higher incidence of seizures, microcephaly, and hypopigmentation. Severe epilepsy seen in these patients is considered to be the result of the absence of one copy of the *GABA* receptor genes.
      ii. Greater delay in motor milestones
      iii. Absent speech
      iv. Severe clinical features thought to be the result of haploinsufficiency for a number of genes within the 15q11–q13 region
   b. Phenotype in the non-deletion cases: milder than in the deletion cases
   c. Phenotype in the paternal UPD: milder than that of the deletion cases
      i. A low incidence of seizures, microcephaly, and hypopigmentation
      ii. Able to say a few words in many patients
      iii. Better growth parameters
      iv. Less obvious dysmorphic features
      v. Typical behavioral pattern
   d. Imprinting defects
      i. Less likely to have microcephaly, hypopigmentation, or seizures
      ii. More able than the deletion group with less delay in motor milestones and better communication skills
      iii. Growth better than the deletion patients
      iv. Obesity relatively common within this group
   e. Milder phenotype associated with incomplete imprinting defect or cellular mosaicism (displayed as Angelman syndrome methylation pattern)
   f. Point mutations in the *UBE3A*
      i. Phenotype between the deletion group and the UPD group
      ii. Frequently with mild or absence of ataxia, epilepsy, and microcephaly
      iii. Not hypopigmented
      iv. Better motor and communication skills than the deletion group
6. Consensus criteria for the clinical diagnosis of Angelman syndrome by developmental history and clinical findings (Williams et al. 2006)
   a. Developmental history
      i. Normal prenatal and birth history
      ii. Normal head circumference
      iii. Absence of major birth defects
      iv. Feeding difficulties may be present in the neonate and infant
      v. Developmental delay evident by 6–12 months of age
      vi. Sometimes associated with truncal hypotonus
      vii. Unsteady limb movements and/or increased smiling may be evident
   b. Consistent clinical findings (100%)
      i. Developmental delay, functionally severe
      ii. Movement or balance disorder, usually ataxia of gait, and/or tremulous movement of limbs. Movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions
      iii. Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping, or waving movements; hypermotoric behavior
      iv. Speech impairment, none or minimal use of words; receptive and nonverbal communication skills higher than verbal ones
   c. Frequent clinical findings (>80%)
      i. Delayed, disproportionate growth in head circumference, usually resulting in

microcephaly (_2 SD of normal OFC) by age 2 years. Microcephaly is more pronounced in those with 15q11.2–q13 deletions.
ii. Seizures, onset usually <3 years of age. Seizure severity usually decreases with age but the seizure disorder lasts throughout adulthood.
iii. Abnormal EEG, with a characteristic pattern, as mentioned in the text. The EEG abnormalities can occur in the first 2 years of life and can precede clinical features, and are often not correlated to clinical seizure events.

d. Associated clinical findings (20–80%)
i. Flat occiput
ii. Occipital groove
iii. Protruding tongue
iv. Tongue thrusting; sucking/swallowing disorders
v. Feeding problems and/or truncal hypotonia during infancy
vi. Prognathia
vii. Wide mouth, wide-spaced teeth
viii. Frequent drooling
ix. Excessive chewing/mouthing behaviors
x. Strabismus
xi. Hypopigmented skin, light hair, and eye color (compared to family), seen only in deletion cases
xii. Hyperactive lower extremity deep tendon reflexes
xiii. Uplifted, flexed arm position especially during ambulation
xiv. Wide-based gait with pronated or valgus-positioned ankles
xv. Increased sensitivity to heat
xvi. Abnormal sleep-wake cycles and diminished need for sleep
xvii. Attraction to/fascination with water; fascination with crinkly items such as certain papers and plastics
xviii. Abnormal food-related behaviors
xix. Obesity (in the older child)
xx. Scoliosis
xxi. Constipation

7. Differential diagnosis (Williams et al. 2010a)
a. Nonspecific psychomotor delay and/or seizures including cerebral palsy, static encephalopathy, and mitochondrial encephalomyopathy: tremulousness and jerky limb movements seen in most infants with Angelman syndrome are not seen in these conditions
b. Mowat–Wilson syndrome
i. Findings suggesting Angelman syndrome
a) Happy affect
b) Prominent mandible
c) Diminished speech
d) Microcephaly
e) Constipation
ii. Typically results from heterozygous mutations in *ZEB2*
c. Christianson syndrome (Christianson et al. 1999; Gilfillan et al. 2008)
i. An X-linked disorder
ii. Caused by mutations in the *SLC9A6* gene
iii. Clinical features
a) Apparently happy disposition
b) Severe cognitive delays
c) Ataxia
d) Microcephaly
e) Seizure disorder
f) A rapid (10–14 Hz) background frequency EEG, compared to a generalized high amplitude, slow spike/wave (1.5–3 Hz) pattern seen in patients with *SLC9A6* mutations
g) Cerebellar and brain stem atrophy in some cases
h) Individuals with *SLC9A6* disorder may have thinner body appearance and may lose ambulation beyond 10 years of age.
d. Adenylosuccinate lyase deficiency (Spiegel et al. 2006; Gitiaux et al. 2009)
i. Results in accumulation of succinylpurines leading to:
a) Psychomotor retardation
b) Autistic features
c) Hypotonia
d) Seizures
ii. The following behavior profile may mimic Angelman syndrome:
a) Motor apraxia
b) Severe speech deficits
c) Excessive laughter
d) A very happy disposition

e) Hyperactivity
f) A short attention span
g) Mouthing of objects
h) Tantrums
i) Stereotyped movements

e. Pitt–Hopkins syndrome
i. Characteristic features
a) Mental retardation
b) Distinctive facial features including wide mouth
c) Intermittent hyperventilation followed by apnea (Zwier et al. 2007). Diurnal hyperventilation is a salient feature in some and occurs after 3 years of age (Peippo et al. 2006).
ii. Mutation and deletion screening for the TCF4 gene: available

f. Rett syndrome
i. Seizures and severe speech impairment of Rett syndrome: resemble infant girls with Angelman syndrome but children with Angelman syndrome do not have a regressive course and do not lose purposeful use of their hands, as do girls with Rett syndrome.
ii. Testing for mutations of *MECP2*: clinically available

g. Prader–Willi syndrome: Infants with Angelman syndrome who present with feeding difficulties and muscle hypotonia may be misdiagnosed as having Prader–Willi syndrome because the 15q11.2–q13 deletion, detected by comparative genomic hybridization (CGH) or fluorescent in situ hybridization (FISH), was not proven by DNA methylation analysis to be of maternal origin.

h. Other microdeletion syndromes
i. Microdeletion of 22q13.3 deletion (Phelan–McDermid) syndrome (Precht et al. 1998)
a) Nondysmorphic facial features
b) Absent or minimal speech
c) Moderate to severe developmental delay
d) Behavioral features in the autism spectrum
ii. Microdeletions of the 2q23.1 region (van Bon et al. 2010; Williams et al. 2010b)
a) Severe speech delay
b) Seizures
c) Behavioral disorders
d) Microcephaly. Some individuals present with an AS-like phenotype.
e) Other new microdeletion disorders, detected by CGH, may be associated with some features of Angelman syndrome (Brunetti-Pierri et al. 2008; Sharkey et al. 2009).

Diagnostic Investigations

1. Normal metabolic, hematologic, and chemical laboratory profiles
2. Normal brain imagings (MRI, CT) with occasional mild cortical atrophy and dysmyelination
3. Abnormal EEG
a. High amplitude slow spike-wave activities (most common)
b. Hypsarrhythmia (infantile spasm)
4. Cytogenetic studies
a. To detect visible chromosome rearrangement (<1%)
i. Translocation
ii. Inversion
b. High-resolution chromosome studies to demonstrate large del(15)(q11–q13)
c. Fluorescence in situ hybridization (FISH) to identify 15q11–q13 microdeletions, using D15S10 and/or *SNRPN* probes: detects about 70% of patients
5. DNA methylation studies
a. To demonstrate characteristic DNA methylation pattern (i.e., paternal imprint only) of 15q11–q13 cloned DNA sequences using methylation-sensitive restriction endonucleases
i. Diagnose about 80% of classic Angelman syndrome including patients with a deletion, uniparental disomy, or an imprinting defect
ii. Certain maternally inherited genes are extensively methylated and thus inactivated while the paternal alleles are unmethylated and active in normal individuals.
iii. Unmethylated *SNRPN* alleles in patients with Angelman syndrome, caused by:
a) Uniparental disomy
b) Imprinting center defects
c) Typical 15q11–q13 deletion

iv. Inability to distinguish the molecular classes (15q11–q13 deletion, uniparental disomy, or imprinting center defect)

b. *UBE3A* mutation analysis
   a) Detect mutations in the E6-AP ubiquitin-protein ligase gene
   b) Detect additional 11% of patients

6. DNA polymorphisms to demonstrate absence of maternal alleles at 15q11–q13 loci, which may result either from maternal deletion or from paternal uniparental disomy
   a. Determined by analysis of simple sequence repeats (microsatellites) in the parents and affected individual
   b. Determine parental origin of 15q11–q13 and the rest of chromosome 15
   c. Detect patients with deletions and uniparental disomy but not the *UBE3A* mutation class of patients
   d. Detect biparental inheritance of 15q11–q13 with abnormal DNA methylation in patients with imprinting center defects
7. Simple algorithm for genetic testing in patients with clinical suspicion of Angelman syndrome (Clayton-Smith and Laan 2003; Williams et al. 2010a)
   a. Abnormal methylation analysis
      i. FISH analysis or array-CGH
         a) Presence of del(15)(q11.3–q13) (5–7 Mb deletion)
         b) Absence of del(15)(q11–q13)
      ii. RFLP analysis if FISH analysis is negative
         a) Presence of UPD
         b) Absence of UPD
      iii. Angelman syndrome imprinting center deletion analysis (2–200 kb deletions) if UPD is absent
   b. Normal methylation analysis
      i. Screen *UBE3A* mutation (sequence analysis for sequence variants and gene or Intragenic deletion study for partial or whole-gene deletions) in clinically typical patients
         a) If positive, check parents
         b) If negative, keep on reviewing patient's findings
      ii. No further testing required for clinical normal patients (not Angelman syndrome)
8. Currently, about 10% of patients with classic phenotypic features of Angelman syndrome are not amenable to diagnostic testing due to presently unidentified genetic mechanisms.
9. Consensus criteria for the diagnosis of Angelman syndrome by laboratory findings and genetic test abnormalities (Williams et al. 2006)
   a. Normal metabolic, hematologic, and chemical laboratory profiles
   b. Structurally normal brain using MRI or CT (may have mild cortical atrophy or dysmyelination)
   c. Characteristic Angelman syndrome pattern of DNA methylation of the *SNURF-SNRPN* exon 1/promoter. Detects cases due to 15q11.2–q13 deletion, UPD, and imprinting defects (may have mosaic methylation pattern in non-deletion imprinting defects)
   d. Abnormal FISH indicating a deletion of 15q11.2–q13 DNA sequences within the common Angelman syndrome deletion overlap region
      i. Use of a pericentromeric FISH probe enhances the ability to detect subtle translocation.
      ii. Array-CGH can be used to detect the deletion but confirmation by FISH is currently required.
      iii. Class I and II deletions can be distinguished by array-CGH or FISH using appropriate clones.
   e. DNA polymorphism analysis within 15q11.2–q13 showing paternal UPD
   f. Deletion in the Imprinting Center, demonstrated by real-time PCR, single copy FISH, or other analysis methods of the Angelman syndrome Imprinting Center smallest region of overlap (SRO)
   g. Pathogenic DNA sequence change in the *UBE3A* gene
10. Diagnostic approach (van Buggenhout and Fryns 2009)
   a. Cytogenetic study: large deletion/translocation/duplication: Rare (<1%)
   b. Molecular diagnosis: DNA methylation test
      i. Abnormal
         a) FISH and CGH (5–7 Mb deletion) to demonstrate deletion region 15q11.2–q13 (60–70% of the patients)
         b) UPD study to demonstrate paternal UPD (2–5% of the patient)

c) Imprinting Center deletion study to demonstrate: Imprinting Center defect (2–5%)

ii. Normal: Sequence analysis of the *UBE3A* gene detects mutations in about 10% of the patients.

Genetic Counseling

1. Recurrence risks : depending on the genetic mechanism involved and on whether the mother is shown to carry genetic abnormalities of 15q11–q13 (Laan 1999; Buiting 2010; Williams et al. 2008, 2010a)
   a. Reasons of difficulty in providing recurrence risk estimation
      i. Causal heterogeneity of Angelman syndrome
      ii. Maternal germ cell mosaicism
   b. Patient's sib
      i. For proband with a large deletion: <1% risk to sibs. However, germline mosaicism for these large deletions has been reported (Kokkonen and Leisti 2000).
      ii. For proband with an inherited small interstitial deletion or an unbalanced chromosome translocation: The risk to sibs depends on whether the rearrangement is inherited or de novo (Horsthemke et al. 1996; Stalker and Williams 1998). Possibly as high as 50%
      iii. For proband with paternal UPD (in families in which Angelman syndrome is the result of paternal UPD and in which no Robertsonian chromosomal translocation is identified): The risk to sibs of having Angelman syndrome is <1% (The risk figure is based on the lack of recurrence among all known cases of UPD in Angelman syndrome with normal chromosomes).
      iv. For proband with paternal UPD and with predisposing parental translocation: approaching 100% if father has a 15;15 Robertsonian translocation
      v. For proband with imprinting defect
         a) No imprinting center deletion: <1%
         b) With inherited imprinting center deletion: 50%
      vi. For proband with *UBE3A* mutation
         a) De novo mutation: <1%
         b) With inherited mutation from mother: 50%
      vii. For proband without identifiable molecular abnormality: undetermined risk
   c. Patient's offspring: To date, only one individual with Angelman syndrome reported to have reproduced (Lossie and Driscoll 1999)
      i. Females with Angelman syndrome are fully capable of reproduction: The mother and fetus inherited large deletions of maternal 15q11–13.
      ii. Demonstrated paternal-only DNA methylation imprints along 15q11–13.
      iii. *UBE3A* was paternally expressed (not imprinted) in eye tissue from the fetus with Angelman syndrome.
2. Prenatal diagnosis
   a. Possible when the underlying genetic mechanism is as follows:
      i. A deletion
      ii. Uniparental disomy
      iii. An imprinting defect
      iv. A *UBE3A* mutation
      v. A chromosome rearrangement
   b. Combined use of methylation analysis, chromosomal/FISH analysis, and DNA marker studies through analysis of fetal cells obtained by CVS or amniocentesis: to identify the common ~4 Mb deletion, paternal UPD, or imprinting mutation in about 70–80% of cases with Angelman syndrome
   c. Mutation analysis for *UBE3A*
   d. Readily accomplished if a disease-causing mutation is identified and is present in the mother
   e. Preimplantation genetic diagnosis
      i. Available for families in which the underlying mechanism has been identified in the proband to be UBE3A mutations or imprinting center deletions
      ii. The relative hypomethylation of the early embryo makes PGD problematic for DNA methylation testing.
3. Management
   a. Routine management
      i. Feeding difficulties
      ii. Constipation
      iii. Gastroesophageal reflux
      iv. Strabismus

b. Seizure control difficult with antiepileptic drugs, especially in childhood
   i. Sodium valproate as monotherapy or in combination with clonazepam or other benzodiazepines
   ii. Experience with the newer antiepileptic drugs very limited
c. Physical therapy for unstable or nonambulatory children
d. Occupational therapy for improving fine motor and oral-motor control
e. Speech and communication therapy
   i. Augmentative communication aids, such as picture cards or communication boards
   ii. Sign language
f. Consistent behavioral modifications
g. Orthopedic management
   i. Subluxed or pronated ankles
   ii. Tight Achilles tendons
   iii. Scoliosis

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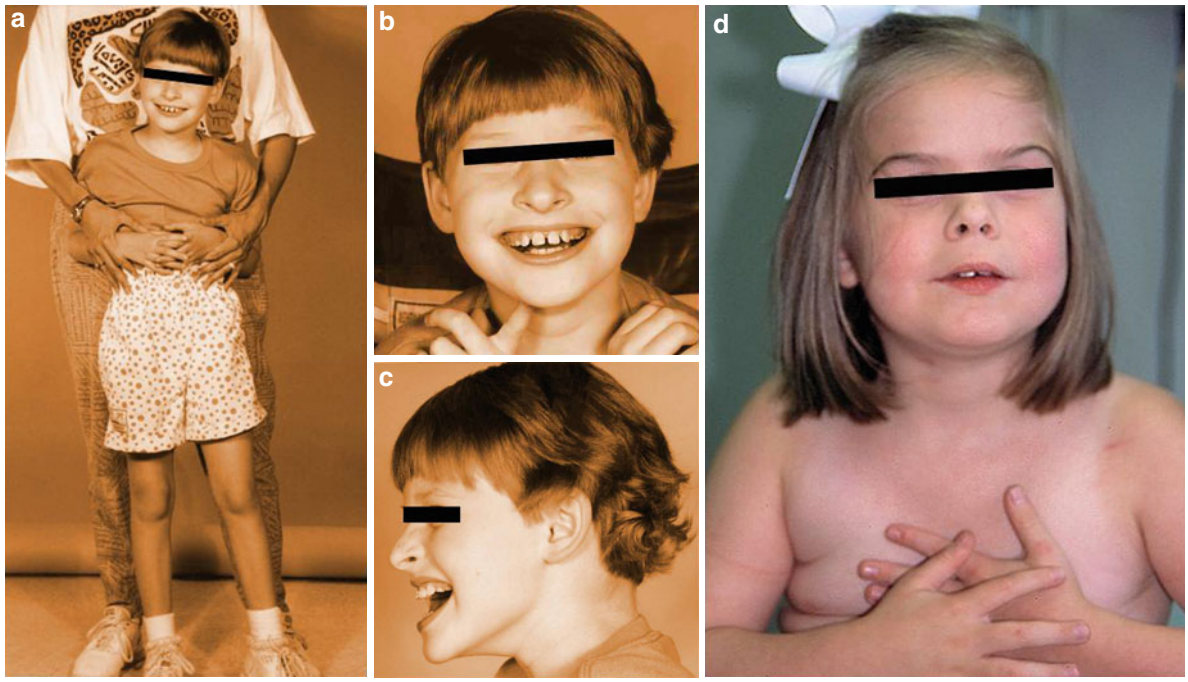

Fig. 1 (**a**–**d**) Two children with Angelman syndrome showing happy disposition, an open mouth expression, widely spaced teeth, and a pronounced mandible. The diagnoses were confirmed cytogenetically [del(15)(q11–13)]

Apert Syndrome

Apert syndrome is named after the French physician who described the syndrome acrocephalosyndactylia in 1906. Apert syndrome is a rare autosomal dominant disorder characterized by craniosynostosis, craniofacial anomalies, and severe symmetrical syndactyly (cutaneous and bony fusion) of the hands and feet. It probably is the most familiar and best-described type of acrocephalosyndactyly. Prevalence is estimated at 1 in 65,000 (approximately 15.5 in 1,000,000) live births (Cohen and Kreiborg 1992, 1993a). Apert syndrome accounts for 4.5% of all cases of craniosynostosis.

Synonyms and Related Disorders

Acrocephalosyndactyly types 1 and 2; Apert-Crouzon disease; Vogt cephalodactyly

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant
   b. Sporadic in majority (>98%) of cases, resulting from new mutations with a paternal age effect
   c. Rarity of familial cases can be explained by reduced genetic fitness of individuals because of severe malformations and the presence of mental retardation in many cases.
2. Cause
   a. Caused by specific missense substitution mutations, involving adjacent amino acids (i.e., Ser252Trp or Pro253Arg) in the linker between the second and third extracellular immunoglobulins domains of *FGFR2*, which maps to chromosome bands 10q25–q26 (more than 98% of cases with Apert syndrome)
   b. Remaining cases are caused by Alu-element insertion mutations in or near exon 9 of *FGFR2*.
3. Pathogenesis
   a. Unique fibroblast growth factor receptor 2 (*FGFR2*) mutations
      i. Leading to an increase in the number of precursor cells that enter the osteogenic pathway
      ii. Ultimately leading to increased subperiosteal bone matrix formation and premature calvaria ossification during fetal development
   b. Fusion of the cranial sutures
      i. The order and rate of suture fusion determine the degree of deformity and disability.
      ii. Once a suture becomes fused, growth perpendicular to that suture becomes restricted, and the fused bones act as a single bony structure.
      iii. Compensatory growth occurs at the remaining open sutures to allow continued brain growth.
      iv. Complex, multiple sutural synostosis frequently extends to premature fusion of the sutures at the base of the skull, causing midfacial hypoplasia, shallow orbits, a foreshortened nasal dorsum, maxillary hypoplasia, and occasional upper airway obstruction.
   c. Syndactyly of Apert syndrome
      i. A keratinocyte growth factor receptor (KGFR)-mediated effect, provided by the observation of the correlation between KGFR expression in fibroblasts and severity of syndactyly
      ii. Different phenotypic expression in patients with Ser252Trp and those with Pro253Arg.

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The syndactyly is more severe with Pro253Arg mutation for both hands and feet, whereas cleft palate is significantly more common with Ser252Try mutation.

d. During early infancy (younger than 3 month of age)
   i. Premature closure of the coronal suture area, evident by a bony condensation line beginning at the cranial base and extending upward with a characteristic posterior convexity
   ii. Widely patent anterior and posterior fontanelles
   iii. Presence of a gaping defect of the midline of the calvaria, extending from the glabellar area to the posterior fontanelle via the metopic suture area, anterior fontanelle, and sagittal suture area. The skull with gaping midline defect appears to permit adequate accommodation of the growing brain.
   iv. Normal lambdoidal sutures in all cases
e. During the first 2–4 years of life
   i. Obliteration of the midline defect by coalescence of the enlarging bony islands without evidence of any proper formation of sutures
   ii. Very early onset in fetal life of growth inhibition in the sphenofrontal and coronal suture area, suggested by an extremely short squama and orbital part of the frontal bone together with the posterior convexity of the coronal bone condensation line

Clinical Features

1. History
   a. Headache and vomiting: signs of acute increase of intracranial pressure, especially in cases of multiple suture involvement
   b. Stridor and sleep apnea indicates upper airway problems, due to craniosynostosis of the base of the skull
   c. Visual disturbance due to exposure keratitis and conjunctivitis
   d. Mental retardation in many patients, though patients with normal intelligence have been reported
2. Skull
   a. Craniosynostosis
   b. Coronal sutures most commonly involved, resulting in acrocephaly, brachycephaly, turribrachycephaly, flat occiput, and high prominent forehead
   c. Large late-closing fontanels
   d. Gaping midline defect
   e. Rare cloverleaf skull anomaly in approximately 4% of infants
3. Facial features
   a. Horizontal grooves above the supraorbital ridges that disappear with age
   b. A break in the continuity of the eyebrows
   c. A trapezoid-shaped mouth at rest
   d. Flattened, often asymmetric face
   e. Maxillary hypoplasia with retruded midface
   f. Eyes
      i. Down-slanting palpebral fissures
      ii. Hypertelorism
      iii. Shallow orbits
      iv. Proptosis
      v. Exophthalmos
      vi. Lateral ptosis
      vii. Widened palpebral fissures
      viii. Tearing secondary to exposure keratitis
      ix. Prolonged corneal exposure resulting in corneal scars and opacification
      x. Partially open eye during sleep
      xi. Strabismus
      xii. Amblyopia
      xiii. Optic atrophy
      xiv. Keratoconus
      xv. Ectopic lentis
      xvi. Congenital glaucoma
      xvii. Lack of pigment in the fundi with occasional papilledema
      xviii. Rare luxation of the eye globes as an extreme complication of severe exorbitism, producing possible strangulation of the circulation of the globe and blindness
   g. Mouth
      i. A prominent mandible
      ii. Down-turned corners
      iii. High arched palate
      iv. Bifid uvula
      v. Cleft palate
      vi. Crowded upper teeth
      vii. Malocclusion
      viii. Delayed dentition

ix. Ectopic eruption
x. Shovel-shaped incisors
xi. Supernumerary teeth
xii. V-shaped maxillary dental arch
xiii. Bulging alveolar ridges

h. Ears
i. Apparent low-set ears
ii. Occasional conductive hearing loss
iii. Congenital fixation of stapedial footplate

4. Extremities and digits
a. The upper limbs affected more severely than lower limbs
b. Coalition of distal phalanges and synonychia of the hands (never present in the feet)
c. The glenohumeral joint and proximal humerus affected more severely than the pelvic girdle and femur
d. The elbow involved much less severely than the proximal portion of the upper limb
e. Syndactyly of the hands and feet with partial-to-complete fusion of the digits, often involving second, third, and fourth digits. These often are termed mitten hands and socked feet. In severe cases, all digits are fused, with the palm deeply concave or cup-shaped and the sole supinated.
f. Hitchhiker posture or radial deviation of short or broad thumbs resulting from abnormal proximal phalanx
g. Brachydactyly
h. Contiguous nailbeds (synonychia)
i. Subacromial dimples and elbow dimples during infancy
j. Limited mobility at the glenohumeral joint with progressive limitation in abduction, forward flexion, and external rotation
k. Limited elbow mobility common with decreased elbow extension, flexion, pronation, and supination
l. Short humeri, a constant finding beyond infancy
m. Limited genu valga present in many cases

5. Other skeletal and cartilaginous segmentation defects
a. Congenital cervical spinal fusion (68%), especially C5–C6
b. Aplasia or ankylosis of shoulder, elbow, and hip joints
c. Tracheal cartilage anomalies
d. Rhizomelia

6. CNS
a. Intelligence varying from normal to mental deficiency, though a significant number of patients are mentally retarded. Malformations of the CNS may be responsible for most cases.
b. Common CNS malformations
i. Megalencephaly
ii. Agenesis of the corpus callosum
iii. Malformed limbic structures
iv. Variable ventriculomegaly. Progressive hydrocephalus is uncommon.
v. Encephalocele
vi. Gyral abnormalities
vii. Hypoplastic cerebral white matter
viii. Pyramidal tract abnormalities
ix. Heterotopic gray matter
x. Papilledema and optic atrophy with loss of vision in cases with insidious intracranial pressure increase

7. Cardiovascular (10%)
a. Atrial septal defect
b. Patent ductus arteriosus
c. Ventricular septal defect
d. Pulmonary stenosis
e. Overriding aorta
f. Coarctation of aorta
g. Dextrocardia
h. Tetralogy of Fallot
i. Endocardial fibroelastosis

8. Genitourinary (9.6%)
a. Polycystic kidneys
b. Duplication of renal pelvis
c. Hydronephrosis
d. Stenosis of bladder neck
e. Bicornuate uterus
f. Vaginal atresia
g. Protuberant labia majora
h. Clitoromegaly
i. Cryptorchidism

9. Gastrointestinal (1.5%)
a. Pyloric stenosis
b. Esophageal atresia and tracheoesophageal fistula
c. Ectopic or imperforate anus
d. Partial biliary atresia with agenesis of gallbladder

10. Respiratory (1.5%)
a. Anomalous tracheal cartilage
b. Tracheoesophageal fistula
c. Pulmonary aplasia

d. Absence of right middle lobe of the lung
e. Absence of interlobular lung fissures
11. Skin
a. Hyperhidrosis (common)
b. Acneiform lesions frequent after adolescence
c. Interruption of the eyebrows
d. Hypopigmentation
e. Hyperkeratosis in the plantar surface
f. Paronychial infections more commonly affected in feet than hands and observed more commonly in institutionalized patients
g. Excessive skin wrinkling of forehead
h. Skin dimples at knuckles, shoulders, and elbows
12. At risk for complications resulting from elevated intracranial pressure despite surgical attempts to increase cranial capacity in infancy
13. Early death
a. Upper airway compromise
i. Reduction in nasophrynx size
ii. Choanal patency
iii. Obstructive sleep apnea
iv. Cor pulmonale
b. Lower airway compromise due to anomalies of the tracheal cartilage
14. Differential diagnosis
a. Beare–Stevenson syndrome
i. Mental retardation
ii. Associated cutaneous disorders
a) Cutis gyrata
b) Acanthosis nigricans (hands and feet)
iii. Caused by *FGFR2* mutations
b. Carpenter syndrome (see the chapter)
i. An autosomal recessive disorder
ii. A peculiar face
iii. Preaxial polydactyly of hands, feet, or both
iv. Absence of osseous fusion of hand bones
c. *FGFR3* -associated coronal synostosis syndrome
i. Variable clinical presentation overlapping with Pfeiffer, Jackson–Weiss, or Saethre–Chotzen syndrome phenotypes
ii. Some individuals with a disease-causing mutation may have no clinical problems
d. Jackson–Weiss syndrome
i. Caused by *FGFR2* mutations
ii. Enlarged or broad great toes with varus deviation
iii. Tarsal or metatarsal fusion
iv. Lack of thumb abnormalities
v. Midface hypoplasia
e. Pfeiffer syndrome
i. Identifiable mutations in *FGFR1* and *FGFR2* (~67% of patients)
ii. Hand and foot abnormalities
a) Broad thumbs and halluces
b) Occasional cutaneous syndactyly
iii. Lack of osseous fusion of the phalanges
iv. Craniofacial features
a) Turribrachycephaly
b) Occasional clover-leaf skull
c) Ocular hypertelorism
d) Shallow orbits
e) Sown-slanting palpebral fissures
f) Proptosis
g) Strabismus
h) Low nasal bridge
i) Small nose
j) Maxillary hypoplasia
k) Mandibular prognathism
f. Saethre–Chotzen syndrome (see the chapter)
i. Characteristic facies
ii. Relatively mild cranial deformity
iii. Lack of osseous fusion of the hand bones
iv. Identifiable mutations in the *TWIST* gene (~75% of patients)

Diagnostic Investigations

1. Psychometric evaluation
2. Hearing assessment
3. Imaging studies
a. Skull radiography to evaluate craniostenosis, which usually involves coronal sutures and maxillary hypoplasia
i. Sclerosis of suture line
ii. Bony bridging and beaking along the suture line
iii. An indistinct suture line
iv. Turribrachycephaly
v. Shallow orbits
vi. Hypoplastic maxillae
b. Spine radiography
i. Spinal fusions, most commonly at the levels of C3-4 and C5-6, appearing to be

progressive and occurring at the site of subtle congenital anomalies
ii. Small-sized vertebral body and reduced intervertebral disc space: indicators of subsequent bony fusion

c. Limb radiography
i. Multiple epiphyseal dysplasia
ii. Short humeri
iii. Glenoid dysplasia
iv. Cutaneous and osseous syndactyly
v. Complete syndactyly involving the second and fifth digits (mitten hands)
vi. Multiple progressive synostosis involves distal phalanges, proximal fourth and fifth metacarpals, capitate, and hamate.
vii. Progressive symphalangism of interphalangeal joints
viii. Shortened and radial deviation of distal phalanx
ix. Delta-shaped deformity of proximal phalanx of the thumbs
x. Complete syndactyly involving the second and fifth toes (socked feet)
xi. Fusion of tarsal bones, metatarsophalangeal and interphalangeal joints, and adjacent metatarsals
xii. Delta-shaped proximal phalanx of the first toes
xiii. Occasional partial or complete duplication of the proximal phalanx of the great toes and first metatarsals

d. Computed tomography
i. CT scan with comparative 3-dimensional reconstruction analysis of the calvaria and cranial bases: the most useful radiological examination in identifying skull shape and presence or absence of involved sutures
ii. Precise definition of the pathological anatomy, permitting specific operative planning

e. Magnetic resonance imaging
i. Demonstration of the anatomy of the soft-tissue structures and associated brain abnormalities
ii. Visualization of the spatial arrangement of the bones

4. Molecular analysis
a. Exquisitely specific molecular mechanism with a narrow mutational spectrum
b. More than 98% of cases: caused by specific missense substitution mutations, involving adjacent amino acids (Ser252Trp, Ser252Phe, or Pro253Arg) in exon 7 of *FGFR2*
c. The remaining cases: due to Alu-element insertion mutations in or near exon 9

Genetic Counseling

1. Recurrence risk
a. Patient's sib
i. A negligible recurrence risk for patient's sib when parents are not affected except in the case of germinal mosaicism in which the risk for future sibs depends on the proportion of germ cells bearing the mutant allele
ii. 50% risk, if a parent is also affected.
b. Patient's offspring: a 50% recurrence risk for an affected individual to have an affected offspring
c. Advanced paternal age effect in new mutations has been shown clinically and demonstrated conclusively at the molecular level.

2. Prenatal diagnosis
a. Prenatal ultrasonography in low-risk pregnancies with finding of abnormal fetal skull shape
i. Prenatal diagnosis of Apert syndrome suspected with findings of fetal "mitten hands" associated with abnormal skull shape and midfacial hypoplasia and confirmed by molecular diagnosis. Craniosynostosis is usually not detected until the third trimester.
ii. Low yield for testing mutations in the *FGFR2* gene
iii. Mutation identification not helpful in determining the prognosis of a fetus, which is largely determined by the clinical diagnosis and not by the molecular diagnosis
b. Prenatal MRI: a useful and sometimes indispensable, additional diagnostic tool (Weber et al. 2010)
c. Fetoscopy to visualize fetal anomalies comparable to Apert syndrome in a pregnancy at risk: an invasive procedure not used currently
d. Molecular genetic analysis
i. An affected parent with identified mutation of *FGFR2* gene: prenatal diagnosis available on fetal DNA obtained through amniocentesis or chorionic villus sampling

ii. An affected parent without identified mutation of *FGFR2* gene: linkage analysis available to an informative family with at least two affected family members based on an accurate clinical diagnosis and an accurate understanding of genetic relationships in the family

3. Management
   a. Protection of the cornea
      i. Instill lubricating bland ointments in the eyes at bedtime to protect corneas from desiccation
      ii. Artificial teardrops during the day
      iii. Lateral or medial tarsorrhaphy in severe cases to narrow the palpebral fissure cosmetically and protect the corneas and the vision
   b. Upper airway obstruction during the neonatal period
      i. Remove excessive nasal secretions
      ii. Treat upper airway infection
      iii. Humidification with added oxygen
      iv. Judicious use of topic nasal decongestants
      v. Rarely requires orotracheal intubation
   c. Sleep apnea
      i. Polysomography (a sleep recording of multiple physiologic variables), currently the most reliable method for determining the presence of sleep apnea
      ii. Continuous positive pressure
      iii. Tracheostomy indicated in severely affected children
   d. Chronic middle ear effusion associated with bilateral conductive hearing deficit
      i. Antimicrobial therapy
      ii. Bilateral myringotomy and placement of ventilation tubes: the most effective treatment
   e. Craniofacial surgery
      i. Cranium
         a) Removes synostotic sutures
         b) Reshapes the calvaria
         c) Allows more normal cranial development to proceed with respect to shape, volume, and bone quality
         d) Relieves increased intracranial pressure
      ii. Orbits
         a) Correction of ocular proptosis: the primary objective of orbital surgery
         b) Reduction of increased interorbital distance (hypertelorism)
         c) Correction of increased interior malrotation
      iii. Nose
         a) Infants and child: nasal reconstruction focusing on correction of the excessively obtuse nasofrontal angle, flat nasal dorsum, and ptotic nasal tip
         b) Teenager and adult: reduction of the nasal tip bulk
      iv. Midface
         a) Normalization of midface appearance
         b) Expansion of the inferior orbit
         c) Volumetric expansion of the nasal and nasopharyngeal airways
         d) Establishment of a normal dentoskeletal relationship
      v. Mandible: mandibular osteotomies to improve dentoskeletal relations for masticatory and esthetic benefit
   f. Surgical reconstruction of syndactyly
   g. Psychological and social challenges confronted by individuals with Apert syndrome
      i. Emotional adjustment
      ii. Body image development
      iii. Impact of surgery and hospitalization on children with Apert syndrome

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Fig. 1 (**a**–**d**) An infant with Apert syndrome showing characteristic facial appearance and typical mitten hands and socked feet

Fig. 2 (**a**–**d**) A 13-year-old girl with Apert syndrome showing characteristic facial appearance and postoperative status of the fingers and toes

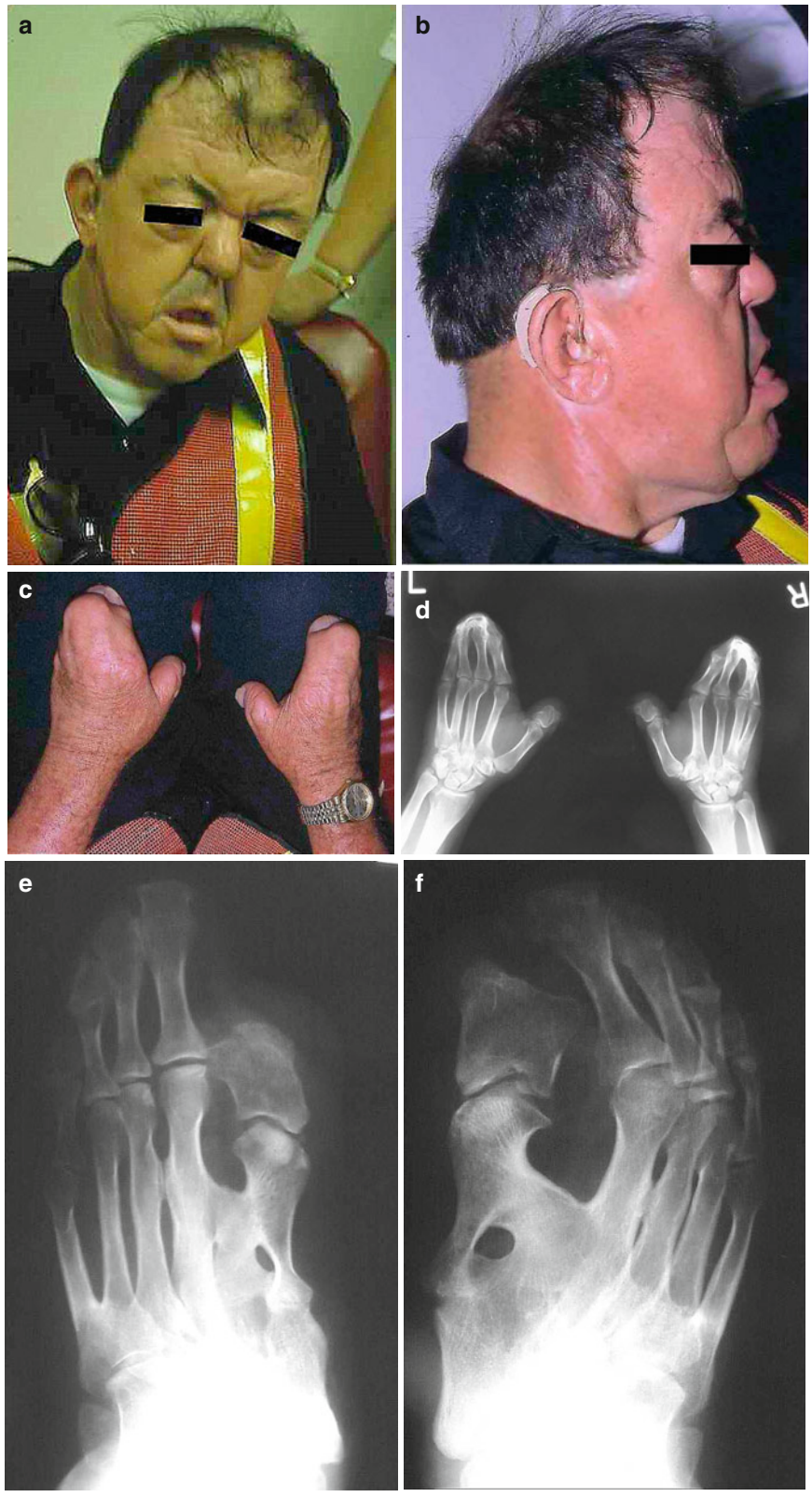

Fig. 3 (**a**–**f**) An adult with Apert syndrome showing typical craniofacial appearance, hearing loss (wearing hearing aids), and mitten hands. Radiographs showed cutaneous and osseous syndactyly, complete syndactyly involving the second through fifth digits (mitten hands), symphalangism of interphalangeal joints, delta-shaped proximal phalanx of the thumbs, complete syndactyly involving the second through fifth digits (socked feet), and partial duplication of the proximal phalanx of the great toes and first metatarsals

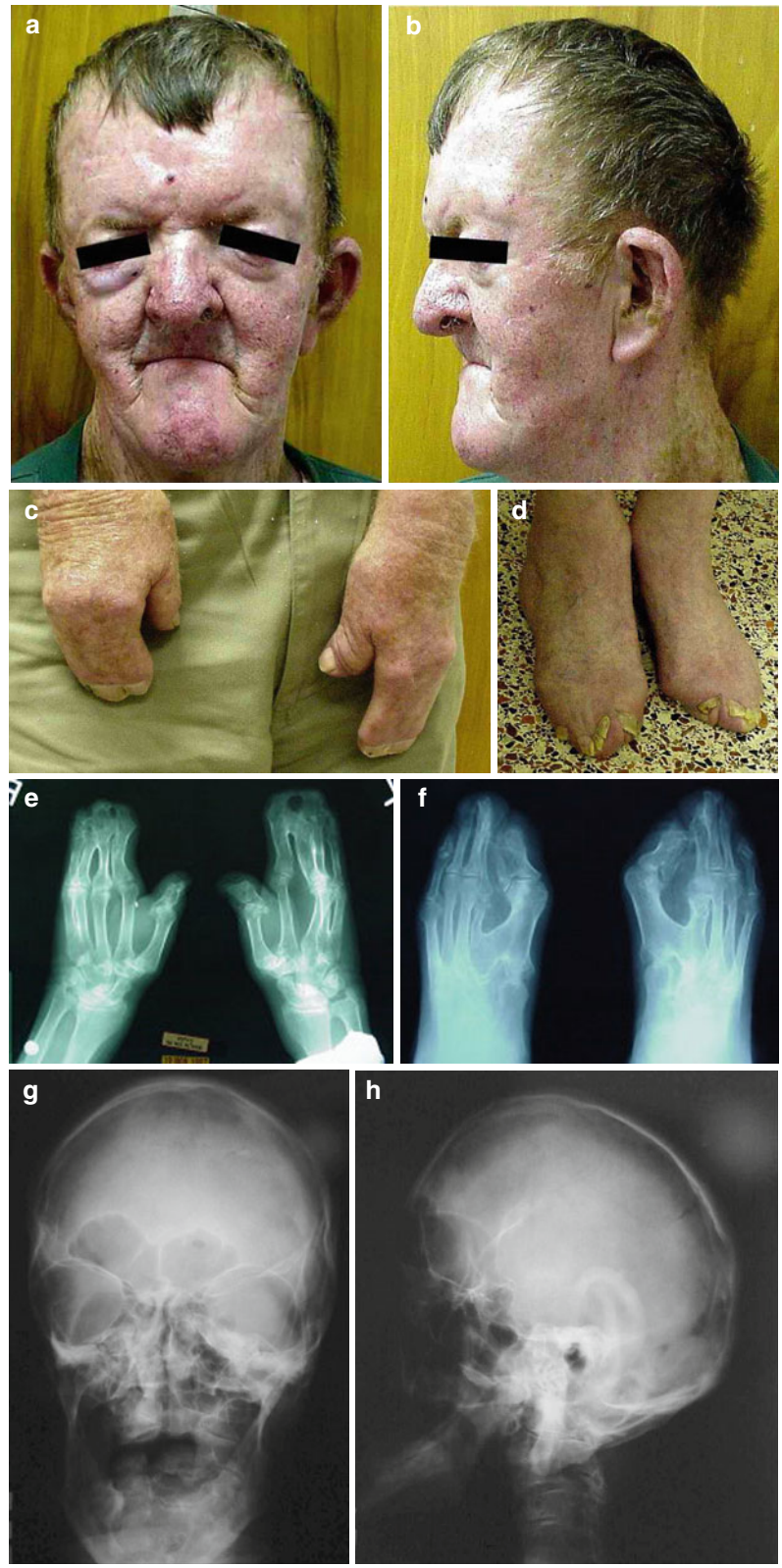

Fig. 4 (**a**–**h**) An adult with Apert syndrome showing typical craniofacial appearance with mitten hands and socked feet. Radiographs of hands and feet and skull showed cutaneous and osseous syndactyly, turribrachycephaly, shallow orbits, and hypoplastic maxilla

Fig. 5 (**a**–**h**) A daughter and a mother with Apert syndrome showing characteristic craniofacial features, mitten hands, and socked feet

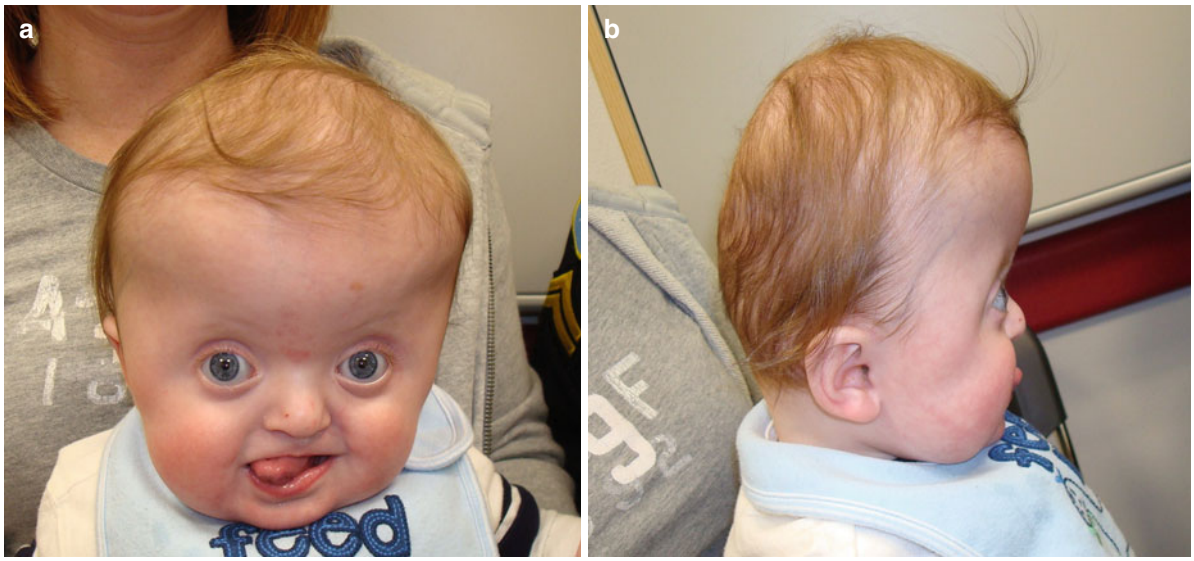

Fig. 6 (**a**, **b**) A 6-month-old male infant was evaluated for Apert syndrome which was diagnosed prenatally. The fetus was noted to have abnormal craniofacial features with mitten hands by ultrasonography. Molecular testing from cultured amniocytes indicated the presence of a C > G transversion at nucleotide 755 (c.755 C > G) of the fibroblast growth factor receptor 2 (*FGFR2*) gene. This change substitutes a tryptophan for a serine at amino acid 252 (p.S252W). The presence of this mutation is consistent with a clinical diagnosis of Apert syndrome. The infant showed severe acrocephaly, palpable coronal suture ridge, ocular hypertelorism with proptotic eyes, low-set ears, depressed nasal bridge, small soft palate cleft, hitchhiker like thumbs, mitten hands, and sock feet

Fig. 7 Mitten-shaped hands with cutaneous syndactyly and synonychia

Fig. 8 Radiograph of the right hand showing coalition of distal phalanges, symphalangism, cutaneous and osseous syndactyly, and delta-shaped deformity of the proximal phalanx of the thumb

Fig. 10 Radiograph of the right foot showing complete cutaneous syndactyly involving the second, third, fourth digits, and delta-shaped deformity of the proximal phalanx of the first toe

Fig. 9 Both feet showing socket-shaped feet, syndactyly of the feet with partial-to-complete fusion of the digits, involving second, third, and forth digits

Aplasia Cutis Congenita

Aplasia cutis congenita (ACC) is a clinical description of the absence of the skin at birth, first described by Cordon in 1767. It is a heterogeneous group of disorders characterized by absence of epidermis, dermis, and, sometimes, subcutaneous tissue, muscle, or bone on one or more parts of the body. The incidence is estimated to be 1 in 10,000 births.

Synonyms and Related Disorders

Aplasia cutis congenita associated with epidermolysis bullosa (simplex, junctional, dystrophic); Congenital scalp defect; Congenital skull and scalp defect

Genetics/Basic Defects

1. Etiological theories
   a. Amniogenic theory (Frieden 1986)
      i. Adhesion of the amniotic membrane to the fetal skin might tear off, leaving absent areas of skin
      ii. Not supported by the study of placentas because most placentas are normal
   b. Vascular theory: assumes thromboplastic material from a fetus papyraceus (mummified dead fetus) as the causes of skin damage
   c. Placental abnormalities
   d. Biomechanical forces on the vertex during the embryogenesis
   e. Intrauterine trauma: a history of trauma in only a minority of cases
   f. Intrauterine infections
      i. Varicella
      ii. Herpes simplex
   g. Intrauterine involution of a hemangioma
   h. Teratogens
      i. Methimazole
      ii. Misoprostol
   i. Genetic factors
2. Frieden's classification of aplasia cutis congenita (Frieden 1986)
   a. Group I: ACC of the scalp without multiple anomalies: sporadic occurrence or autosomal dominant inheritance
   b. Group II: ACC of the scalp with associated limb abnormalities: autosomal dominant inheritance
   c. Group III: ACC of the scalp with associated epidermal, organoid nevus, or epidermal nevus syndrome: sporadic occurrence
   d. Group IV: ACC overlying embryologic malformations: inheritance depending on underlying conditions
   e. Group V: ACC with associated fetus papyraceous or placental infarcts: sporadic occurrence
   f. Group VI: ACC associated with epidermolysis bullosa: autosomal dominant or recessive inheritance depending on the type of the epidermolysis bullosa
   g. Group VII: ACC localized to extremities without blistering: autosomal dominant or recessive inheritance

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   h. Group VIII: ACC caused by specific teratogens: scalp (methimazole), any area (varicella, herpes simplex)
   i. Group IX: ACC associated with malformation syndromes
      i. Trisomy 13
      ii. Trisomy 18
      iii. Monosomy 4
      iv. Ectodermal dysplasias
      v. Johanson-Blizzard syndrome
      vi. Focal dermal hypoplasia
      vii. 46,XY gonadal dysgenesis
      viii. Amniotic band disruption complex
3. Aplasia cutis congenita associated with epidermolysis bullosa (Achiron et al. 1992)
   a. Simplex
      i. An autosomal dominant disorder
      ii. Lysis of the epidermis occurring within the cytoplasm of the basal cell layer
   b. Junctional
      i. An autosomal recessive disorder
      ii. Damage at the level of the lamina lucida
   c. Dystrophic (scarring)
      i. An autosomal dominant or recessive disorder
      ii. Defect situated in the anchoring fibrils attaching the basal lamina to the dermis

Clinical Features

1. Aplasia cutis of the scalp (aplasia cutis vertices) (Cambiaghi et al. 1998)
   a. The most common form
   b. Single or multiple noninflammatory ulcers
   c. Occurrence at or near the scalp vertex
   d. Variable in shape and size
   e. Heals leaving a hairless scar
   f. Occurrence
      i. An isolated condition
      ii. Associated with other congenital abnormalities
2. Aplasia cutis with extracranial symmetrical involvement (a distinctive type of "non-scalp" aplasia cutis congenita)
   a. Linear lesions with a symmetrical pattern of distribution on the trunk and limbs
   b. Aplasia cutis with fetus papyraceous: usually associated with in utero death of a monozygotic twin during pregnancy, with or without the presence of a fetus papyraceous (persistence of a mummified dead fetus)
   c. Other terms
      i. Truncal aplasia cutis
      ii. Bilateral abdominal aplasia cutis
3. Associated congenital anomalies
   a. Craniofacial anomalies
      i. Underlying skull bony defect: 15–20% of cases of scalp ACC and as high as 75% in cases of extensive scalp ACC (Burkhead et al. 2009)
      ii. Microphthalmia
      iii. Colobomas
      iv. Myopia
      v. Epibulbar dermoid
      vi. Cleft lip
      vii. Cleft palate
      viii. Ear malformations
   b. CNS malformation
      i. Hydrocephalus
      ii. Mental retardation
      iii. Spastic paralysis
   c. Ectodermal dysplasia
      i. Hypoplasia of the teeth
      ii. Delayed dentition
      iii. Nail hypoplasia
      iv. Skin blisters
      v. Skin hyperpigmentation
      vi. Cutis marmorata
   d. Gastrointestinal abnormalities (Al-Sawan et al. 1999; Lane and Zanol 2000)
      i. Tracheoesophageal fistula/esophageal atresia
      ii. Omphalocele
      iii. Gastroschisis
      iv. Pyloric atresia: especially in association with junctional (atrophicans) type of epidermolysis bullosa
      v. Ileal atresia
      vi. Mesenteric herniation
      vii. Biliary atresia
      viii. Midgut atresia
      ix. Intestinal lymphangiectasia
   e. Musculoskeletal abnormalities
      i. Terminal transverse limb defects (Adams-Oliver syndrome) (Snape et al. 2009)
      ii. Arthrogryposis
      iii. Polydactyly
      iv. Syndactyly

4. Prognosis
   a. Scalp lesion (1–3 cm): resolves spontaneously in majority of cases (85%)
   b. Prognosis usually determined by underlying anomalies and extent of the lesions

Diagnostic Investigations

1. Imaging
   a. Radiography
      i. Scalp/skull
      ii. Hands
      iii. Feet
   b. CT scan or MRI of the brain
2. Karyotyping to detect chromosome abnormality
3. Histology: heterogeneous appearance of lesions
   a. Ulcerated lesions at birth
      i. Complete absence of all layers of skin
      ii. Occasionally extending to the bone or dura
   b. In utero healing of some lesions
   c. Healed lesions
      i. Flattened epidermis
      ii. Proliferation of fibroblasts in a loose connective tissue stroma
      iii. Newly formed capillaries
      iv. Complete absence of adnexal structures
4. Culture/serology
   a. Varicella zoster
   b. Herpes simplex virus
5. Amniotic fluid findings in some cases (Dror et al. 1994)
   a. Elevated amniotic fluid AFP levels
   b. Positive acetylcholinesterase

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal dominant: not increased unless a parent is affected
      ii. Autosomal recessive: 25%
   b. Patient's offspring
      i. Autosomal dominant: 50%
      ii. Autosomal recessive: not increased unless the spouse is a carrier
2. Prenatal diagnosis
   a. Ultrasonography for at risk family with aplasia cutis congenita associated with epidermolysis bullosa and pyloric atresia (Achiron et al. 1992)
      i. Hydramnios
      ii. A dilated stomach
      iii. A deformed external ear
      iv. A contracted fisted hand
   b. Amniocentesis for associated chromosomal abnormality
3. Management
   a. Careful and standard wound treatment for small defects involving only epidermis: usually uneventful healing of the lesion
   b. Control of infection
   c. Control of electrolyte abnormalities, especially with larger wounds
   d. Requires a scalp flap for most lesions
   e. A split-thickness skin grafting or full-thickness pedicle grafts (for defects of the scalp extending to the dura mater)
   f. Reconstruction of skull and scalp for a large lesion involving scalp, skull, and dura
   g. Emergency intervention to control life-threatening hemorrhage
   h. Surgical intervention also useful later in life for revision of scars and correction of alopecia with rotation flaps, simple excision and closure, scalp reduction techniques, or local hair transplantation
   i. Management of associated anomalies

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Fig. 1 (**a**, **b**) An infant with aplasia cutis congenita with epidermolysis bullosa showing lesions on the face, trunk, and extremities

Arthrogryposis Multiplex Congenita

Arthrogryposis multiplex congenita comprises nonprogressive conditions characterized by multiple joint contractures throughout the body at birth. The term encompasses a very heterogeneous group of disorders having the common feature of multiple congenital joint contractures. The overall prevalence of arthrogryposis is approximately 1 in 3,000 live births (Hall 1985a, b; Fahy and Hall 1990).

Synonyms and Related Disorders

Amyoplasia; Distal arthrogryposis (distotarlar dysmorphism, Freeman-Sheldon syndrome, Sheldon-Hall syndrome, Gordon syndrome, Hecht syndrome, Beals syndrome)

Genetics/Basic Defects

1. Major causes
   a. Arthrogryposis as a physical sign observed in many specific clinical conditions
      i. Single gene defects
      ii. Chromosomal abnormalities
      iii. Known or unknown syndromes or conditions
      iv. Environmental effects
   b. Fetal akinesia due to fetal abnormalities
      i. Neurogenic abnormalities: the most common cause of arthrogryposis
         a) Meningomyelocele
         b) Anencephaly
         c) Hydranencephaly
         d) Holoprosencephaly
         e) Spinal muscular atrophy
         f) Cerebro-oculo-facial-skeletal syndrome
         g) Marden-Walker syndrome
      ii. Muscular abnormalities: relatively rare causes of arthrogryposis
         a) Congenital muscular dystrophies
         b) Congenital myopathies
         c) Intrauterine myositis
         d) Mitochondrial disorders
      iii. Connective tissue abnormalities in tendon, bone, joint, or joint lining restricting fetal movements, resulting in congenital contractures. Examples include:
         a) Synostosis
         b) Lack of joint development
         c) Aberrant fixation of joints (as in diastrophic dysplasia and metatropic dwarfism)
         d) Aberrant laxity of joints with dislocations (as in Larsen syndrome)
         e) Aberrant soft tissue fixations (as in popliteal pterygium syndrome)
         f) Failure of normally developed tendon to attach to the appropriate place around the joint or bone in some forms of distal arthrogryposis, resulting in abnormal lack of movement of the joints with secondary contractures at birth.
      iv. Mechanical limitations to movement. Limited space for fetal movement inside the uterus may contribute to development of contractures. Examples include:
         a) Multiple births
         b) Uterine structural abnormalities such as bicornuate uterus
         c) Umbilical cord wrapping

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d) Oligohydramnios in renal agenesis
e) Early persistent leakage of amniotic fluid

v. Intrauterine vascular compromise resulting in loss of nerve and muscle function with development of fetal akinesia and secondary joint contractures. Examples include:
a) Severe maternal bleeding during pregnancy
b) Failed attempts at termination of pregnancy

c. Fetal akinesia due to maternal disorders, examples include:
i. Infections
a) Rubella
b) Poliomyelitis
ii. Drugs/chemicals
a) Methocarbamol
b) Alcohol
c) Carbon monoxide poisoning
iii. Trauma
iv. Vitamin deficiency
v. Hyperthermia (e.g., prolonged sauna)
vi. Radiation
vii. Other maternal illnesses
a) Maternal autoantibodies
b) Diabetes mellitus
c) Myotonic dystrophy
d) Maternal multiple sclerosis

2. Pathophysiology
a. Joint development
i. Almost always normal during early embryogenesis
ii. Fetal motion essential for normal development of joints and their contiguous structures
b. Lack of fetal movement
i. Causing extra connective tissue to develop around the joint
ii. Resulting in fixation of the joint
iii. Limiting movement further aggravates the joint contracture.
iv. Contractures secondary to fetal akinesia: more severe in patients who are diagnosed early in pregnancy and who experience akinesia for longer periods of time during gestation

Clinical Features

1. Family history (Hall 1997)
a. Presence of congenital contractures in the family
i. Affected siblings
ii. Other affected family members
b. Marked intrafamilial variability
i. Mildly affected parent
ii. A parent with contractures early in infancy
c. Consanguinity
i. Increasing the chance that the parents will both carry the same disease gene
ii. Observed more frequently in families with rare recessive diseases than in those with common recessive diseases
d. Increased parental age
i. Some chromosomal abnormalities: increasing dramatically with advanced maternal age
ii. Single-gene dominant mutations: increasing with advanced paternal age
e. History of previous miscarriages or stillbirths
2. Pregnancy history
a. Diminished fetal movement
b. Infants born to mothers affected with the following disorders:
i. Myotonic dystrophy: A child who inherits the gene and is severely affected with resistant contractures.
ii. Myasthenia gravis and multiple sclerosis: Children may be born with congenital contractures.
c. Maternal infections leading to CNS or peripheral nerve destruction with secondary congenital contractures
i. Rubella
ii. Rubeola
iii. Coxsackievirus
iv. Enterovirus
v. Akabane
d. Maternal fever or hyperthermia causing contractures due to abnormal nerve growth or migration

e. Exposure to teratogens leading to decreased fetal movement
   i. Drugs
   ii. Alcohol
   iii. Curare
   iv. Methocarbamol
   v. Phenytoin
   vi. Radiation
f. Amniotic fluid volume
   i. Oligohydramnios: causes fetal constraint and secondary deformational contractures
   ii. Polyhydramnios: indicating fetal compromise
g. Uterine abnormalities
   i. Bicornuate uterus with a septum
   ii. Uterine fibroid
h. Other maternal complications
   i. Toxemia
   ii. Severe hypotension at critical time
   iii. Severe hypoxia (e.g., carbon monoxide poisoning) during pregnancy
   iv. Abnormal fetal lies
   v. Threatened abortion
   vi. Attempted termination
   vii. Trauma such as trauma to the abdomen

3. Delivery history
   a. Breech or transverse fetal position
      i. Relatively common
      ii. Usually normal length of gestation
      iii. Induction of labor often prolonged
      iv. Fracture of a limb during traumatic delivery in 5–10% of cases
   b. Abnormal placenta, membranes, or cord insertion in case of amniotic bands or vascular compromise. The umbilical cord may be shortened or wrapped around a limb, leading to compression.
   c. Prematurity
   d. Multiple births or twins
      i. Lack of movement due to uterine crowding
      ii. The death of one twin may lead to vascular compromise in the remaining twin.
4. Common physical characteristics
   a. Involved extremities
      i. Fusiform or cylindrical in shape
      ii. Thin subcutaneous tissue
      iii. Absence of skin creases
   b. Deformities
      i. Usually symmetric
      ii. Severity increasing distally
      iii. Hands and feet typically being the most deformed.
   c. Joint rigidity
   d. Associated joint dislocations, especially the hips and, occasionally, the knees
   e. Muscles
      i. Atrophy
      ii. Absence
   f. Sensation
      i. Usually intact
      ii. Diminished or absent deep tendon reflexes
5. Contractures
   a. Distal joints affected more frequently than proximal joints
   b. Types of contractures
      i. Flexion versus extension
      ii. Limitation of movement (fixed vs passive vs active)
      iii. Complete fusion vs ankylosis and soft-tissue contracture
   c. Intrinsically derived contractures
      i. Frequently associated with polyhydramnios
      ii. Symmetric contractures
      iii. Accompanied by taut skin
      iv. Pterygia across joints
      v. Lack of flexion creases
      vi. Recurrence risk and prognosis dependent on etiology
   d. Extrinsically derived contractures
      i. Associated with positional limb anomalies, large ears, loose skin, and normal or exaggerated flexion creases
      ii. Excellent prognosis
      iii. A low recurrence risk
6. Deformities
   a. Limb deformities
      i. Pterygium (webbing)
      ii. Shortening
      iii. Amniotic bands
      iv. Compression (e.g., due to cord wrapping)
      v. Absent patella
      vi. Dislocated radial heads
      vii. Dimples

b. Face deformities
   i. Asymmetry
   ii. Flat nasal bridge
   iii. Hemangioma
   iv. Jaw deformities including micrognathia and trismus
c. Other deformities
   i. Scoliosis
   ii. Genital deformities
      a) Cryptorchidism
      b) Microphallus
      c) Lack of labia
   iii. Hernias
      a) Inguinal
      b) Umbilical
d. Other features of the fetal akinesia sequence
   i. Intrauterine growth retardation
   ii. Pulmonary hypoplasia
   iii. Craniofacial anomalies
      a) Hypertelorism
      b) Cleft palate
      c) Depressed nasal tip
      d) High nasal bridge
   iv. Functional short gut with feeding problems
   v. Short umbilical cord
e. Absent or distorted crease abnormalities resulting from aberrant form or function in early hand or foot development

7. Malformations
   a. Craniofacial malformations
      i. CNS
         a) Structural malformations
         b) Seizures
         c) Mental retardation
      ii. Skull
         a) Craniosynostosis
         b) Asymmetry
         c) Microencephaly
      iii. Eyes
         a) Small and malformed eyes
         b) Corneal opacities
         c) Ptosis
         d) Strabismus
      iv. Palate
         a) High-arched
         b) Cleft
         c) Submucous cleft
   b. Respiratory problems affecting lung function
      i. Tracheal and laryngeal clefts and stenosis
      ii. Hypoplasia or weak muscles of diaphragm
   c. Limb malformations
      i. Reduction anomalies
      ii. Radioulnar synostosis
      iii. Syndactyly
      iv. Shortened digits
   d. Skin/vasculature abnormalities
      i. Hemangiomas and cutis marmorata
      ii. Cold and blue distal limbs
   e. Cardiac problems
      i. Congenital heart defects
      ii. Cardiomyopathy
   f. Urogenital structural anomalies
      i. Kidneys
      ii. Ureters
      iii. Bladder
   g. Nervous system problems
      i. Loss of vigor
      ii. Lethargy
      iii. Slow, fast, or absent deep tendon reflexes
      iv. Sensory deficits
   h. Muscle malformations
      i. Decreased muscle mass
      ii. Soft muscle texture
      iii. Fibrous bands
      iv. Abnormal tendon attachments
      v. Muscle changing with time
8. Connective tissue abnormalities
   a. Skin webs (pterygia) across joints with limitation of movement
   b. Skin dimples observed frequently over joints where movement is limited
   c. Soft, doughy, thick, or extensible skin
   d. Decreased or increased subcutaneous fat
   e. Inguinal, umbilical, or diaphragmatic hernias
   f. Thickness in joints
   g. Symphalangism
   h. Abnormalities in tendon attachment and length
   i. Associated skin defects including scalp defects, amniotic bands on limbs, and nail defects
9. Disorders with mainly limb involvement (Hall 1997)
   a. Amyoplasia (Bevan et al. 2007)
      i. The most common type of arthrogryposis seen in clinical practice and constitutes about one third of cases.
      ii. Incidence: about 1 in 10,000 live births

iii. A sporadic condition, not observed in siblings or offspring (recurrence risk not increased)
iv. Characterized by typical and symmetric positioning of the limbs
v. Internally rotated and adducted shoulders
vi. Fixed extended elbows
vii. Pronated forearms
viii. Flexed wrists and fingers
ix. A severe talipes equinovarus deformity
x. Muscles: hypoplastic and usually replaced by fibrous and fatty tissue
xi. Normal intelligence

b. Distal arthrogryposes
i. Type I (distotarlar dysmorphism)
a) An autosomal dominant disorder
b) Medially overlapping fingers
c) Tightly clenched fists at birth
d) Ulnar deviation of fingers and camptodactyly in adults
e) Positional foot contractures
f) Usually normal intelligence
ii. Type IIA (Freeman–Sheldon syndrome, also known as whistling face syndrome)
a) An autosomal dominant disorder
b) A mask-like face with a small mouth, giving a whistling face appearance
c) Deep-set eyes
d) Small nose with a broad nasal bridge
e) Epicanthal folds
f) Strabismus
g) High-arched palate
h) Small tongue
i) An H-shaped cutaneous dimpling on the chin
j) Flexion of fingers
k) Equinovarus feet with contracted toes
l) Kyphoscoliosis
iii. Type IIB (Sheldon–Hall syndrome) (Toydemir and Bamshad 2009)
a) An autosomal dominant disorder
b) Contractures of the distal joints of the limbs
c) Triangular face
d) Down-slanting palpebral fissures
e) Small mouth
f) High-arched palate
g) Caused by mutations in either *MYH3*, *TNNI2*, or *TNNT3* (~50% of cases)
iv. Type III (Gordon syndrome)
a) Short stature (90%)
b) Cleft palate
c) Bifid uvula
d) Epicanthal folds
e) Congenital ptosis
f) Short neck
g) Camptodactyly
v. Type IV
a) Scoliosis
b) Finger contractures
vi. Type V
a) Ophthalmoplegia (limited ocular motility)
b) Ptosis
c) Finger contractures
vii. Type VI
a) Sensorineural hearing loss
b) Finger contractures
viii. Type VII (Hecht syndrome)
a) Trismus pseudocamptodactyly
b) Inability to fully open mouth
c) Facultative camptodactyly
ix. Type VIII (autosomal dominant multiple pterygium syndrome)
a) Multiple pterygium
b) Finger contractures
x. Type IX (Beals syndrome, congenital contractural arachnodactyly)
a) An autosomal dominant disorder
b) Joint contractures
c) A long, thin body builds
d) Crumpling ears
e) Lacking cardiovascular and ocular abnormalities of Marfan syndrome
xi. Type X (congenital plantar contractures)

c. Bony fusion likely to be confused with arthrogryposis
i. Symphalangism (e.g., fusion of phalanges)
ii. Coalition (e.g., fusion of the carpals and tarsal bones)
iii. Synostosis (e.g., fusion of long bones)

d. Other associated syndromes and conditions
i. Absence of dermal ridges
ii. Absence of distal interphalangeal (DIP) joint creases
iii. Amniotic bands
iv. Antecubital webbing
v. Camptodactyly

vi. Congenital clapsed thumbs
vii. Familial impaired pronation and supination of forearm
viii. Humeroradial synostosis
ix. Liebenberg syndrome
x. Nail-patella syndrome
xi. Nievergelt-Pearlman syndrome
xii. Poland anomaly
xiii. Radioulnar synostosis
xiv. Tel-Hashomer camptodactyly

10. Disorders with involvement of limbs and other body parts (Hall 1997)
    a. Multiple pterygium syndrome (Chen et al. 1980)
        i. Autosomal recessive type: characterized by multiple joint contractures with marked pterygia, dysmorphic facies (flat, sad, motionless facial appearance), and cervical vertebral anomalies
        ii. Autosomal dominant type: characterized by multiple pterygia with or without mental retardation
    b. Multiple pterygium syndrome (pterygia with flexion contractures) associated with scoliosis, cleft palate, and malignant hyperthermia
    c. Multiple pterygium syndrome, Escobar type (Escobar et al. 1978)
        i. Webbing of the neck that increases with age
        ii. Webbing of the knees and elbows that develops before adolescence
        iii. Multiple joint contractures
        iv. Lumbar lordosis
    d. Lethal multiple pterygium syndrome (Hall 1984c; Chen et al. 1984; Chen 2011)
        i. An autosomal recessive disorder
        ii. Characteristic features
            a) Early lethality
            b) Hydrops fetalis
            c) Cystic hygroma
            d) Dysmorphic facies (hypertelorism, markedly flattened nasal bridge with hypoplastic nasal alae, cleft palate, micrognathia, low-set ears)
            e) Marked webbing and flexion contractures of multiple joints
            f) Short neck
            g) Small chest
            h) Hypoplastic lungs
        iii. Classification by Hall (1984a, b, c and Entezami et al. (1998)
            a) Type I (Gillin-Pryse-Davis syndrome): multiple pterygia, pulmonary hypoplasia, genital anomalies, and marked flexed extremities with a reduced muscle mass
            b) Type II (Chen syndrome) (Chen et al. 1984): multiple pterygia, hygroma colli, facial anomalies, undermodeled long bones, cartilaginous fusion of joints and bony fusion of the spinous processes of the vertebrae, polyhydramnios, hypoplastic lungs and heart, and diaphragmatic hernia
            c) Type III (van Regemorter syndrome): multiple pterygia, pulmonary hypoplasia, facial anomalies, thin extremities with reduced muscle mass, and fusions of the long tubular bones
            d) Type IV (Herva syndrome): multiple pterygia, degeneration of the anterior horn cells of the spinal cord, and observed particularly in Finland
    e. Popliteal pterygium syndrome
        i. An autosomal dominant disorder
        ii. Popliteal webs
        iii. Cleft lip or palate
        iv. Webs in the mouth
        v. Unusual nails
    f. Lethal popliteal pterygium syndrome (Bartsocas-Papas syndrome)
        i. An autosomal recessive disorder
        ii. Severe webs across the knee
        iii. Associated with facial clefting and fused digits (synostosis of the hand and foot bones) in the newborn period
        iv. Usually lethal
    g. Osteochondrodysplasias known to be associated congenital contractures
        i. Camptomelic dysplasia
        ii. Conradi-Hünermann (chrondrodysplasia punctata)
        iii. Diastrophic dysplasia
        iv. Focal femoral dysplasia
        v. Geleophysic syndrome
        vi. Kniest dysplasia
        vii. Metaphyseal dysplasia, Jansen type
        viii. Metatropic dysplasia

ix. Larsen dysplasia
x. Nail-patella syndrome
xi. Oculodentodigital syndrome
xii. Orocraniodigital syndrome
xiii. Osteogenesis imperfecta type II
xiv. Otopalatodigital syndrome
xv. Parastremmatic dysplasia
xvi. Perinatal lethal osteogenesis imperfecta
xvii. Pfeiffer syndrome
xviii. Saul–Wilson syndrome
xix. Synspondylism
xx. Spondyloepiphyseal dysplasia congenita
xxi. Otospondylomegaepiphyseal dysplasia

h. Other associated syndromes and conditions
i. Hand-muscle wasting and sensorineural deafness
ii. Holt–Oram syndrome
iii. Kuskokwim syndrome
iv. Leprechaunism
v. Megalocornea with multiple skeletal anomalies
vi. Möbius syndrome
vii. Nemaline myopathy
viii. Ophthalmomandibulomelic dysplasia
ix. Prader-Willi habitus/osteoporosis/hand contractures
x. Pseudothalidomide syndrome
xi. Puretic-Murray syndrome
xii. Sacral agenesis
xiii. Schwartz-Jampel syndrome
xiv. Sturge–Weber syndrome
xv. Tuberous sclerosis
xvi. VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia) complex
xvii. Weaver syndrome
xviii. Winchester syndrome
xix. X-trapezoidocephaly with midfacial hypoplasia and cartilage abnormalities

11. Disorders with limb involvement and CNS dysfunction (Hall 1997)
a. Associated chromosome abnormalities
i. Sex chromosome anomalies (45,X, 47, XXY/48,XXXY, 49,XXXXX, 49, XXXXY)
ii. Autosomal trisomies (4p, 8, 8 mosaicism, 9, 9q, 10p, 10q, 11q, 13, 14, 15, 18, 21)
iii. Other chromosome anomalies
b. Cerebro-oculo-facio-skeletal syndrome
i. A common lethal condition
ii. Contractures
iii. Brain anomalies
iv. Dysmyelination
v. Microphthalmia
vi. Cataracts
vii. Renal anomalies
viii. Other visceral anomalies
c. Neu-Laxova syndrome
i. A lethal autosomal recessive disorder
ii. Dramatic contractures
iii. Intrauterine growth retardation
iv. Microcephaly
v. Open eyes
vi. Tight ichthyotic skin
vii. Severe CNS anomalies
d. Restrictive dermopathy
i. A lethal autosomal recessive disorder
ii. Contractures and failure of fetal skin to grow normally restricting fetal movement and leading to secondary contractures
e. Pena-Shokeir phenotype: Phenotype is caused by fetal akinesia rather than a specific syndrome
i. Short, fixed limbs
ii. Pulmonary hypoplasia
iii. Intrauterine growth retardation
iv. Polyhydramnios
v. Short umbilical cord
vi. Unusual craniofacies

12. Other associated syndromes and conditions
a. Adducted thumbs
b. Bowen-Conradi syndrome
c. C syndrome
d. Congenital myotonic dystrophy
e. Congenital myasthenia gravis
f. Faciocardiomelic syndrome
g. Fetal alcohol syndrome
h. FG syndrome
i. Marden-Walker syndrome
j. Meckel syndrome
k. Meningomyelocele
l. Mietens-Weber syndrome
m. Miller–Dieker syndrome
n. Neu-Laxova syndrome
o. Neurofibromatosis
p. Popliteal pterygium with facial clefts
q. Potter syndrome

r. Pseudotrisomy 18
s. Spinal muscular atrophy
t. Syndrome of cloudy cornea, diaphragmatic defects, and distal limb deformities
u. Syndrome of craniofacial and brain anomalies and intrauterine growth retardation
v. Syndrome of cryptorchidism, chest deformity, and contractures
w. Toriello–Bauserman syndrome
x. Walker–Warburg syndrome
y. X-linked lethal arthrogryposis
z. Zellweger syndrome

13. Prognosis
    a. Poor prognosis for ventilator-dependent neonates
    b. Prenatal factors that potentially predict respiratory insufficiency
        i. Decreased fetal movements
        ii. Polyhydramnios
        iii. Micrognathia
        iv. Thin ribs
        v. Decreased fetal movement often resulting in delayed developmental milestones
    c. Skeletal changes secondary to the original deformities
        i. Scoliosis
        ii. Deformed carpal and tarsal bones
        iii. Under growing of limbs after longstanding contractures
        iv. External genitalia often abnormal (e.g., cryptorchidism, absent labia majora) because of abnormal hip position
    d. Intrinsically or extrinsically derived defects
        i. Extrinsically derived contractures: an excellent prognosis
        ii. Intrinsically derived contractures: a prognosis dependent on etiology
    e. Prognosis depending on the condition's natural history
        i. Developmental landmarks (attainment of motor, social, and language milestones)
        ii. Growth of affected limbs
        iii. Progression of contractures
        iv. CNS damage (lethal, stable, improving)
        v. Asymmetry of contractures (improving, worsening)
        vi. Changes in trunk or limbs
        vii. Intellectual ability
        viii. Socialization
    f. Prognosis depending on the patient's response to therapy
        i. Spontaneous improvement
        ii. Response to physical therapy
        iii. Response to casting
        iv. Types of surgery at appropriate time
        v. Development of motor strength proportionate to limb size

Diagnostic Investigations

1. Lab studies (Hall 1981)
    a. Laboratory tests, in general, are not useful
    b. Creatine phosphokinase (CPK) levels when the following conditions are present:
        i. Generalized weakness
        ii. Doughy or decreased muscle mass
        iii. Progressive worsening
    c. Viral cultures for an infectious process (intrauterine growth retardation, eye involvement, and hepatosplenomegaly)
    d. Immunoglobulin M levels and specific viral titers (e.g., coxsackievirus, enterovirus, Akabane virus) in the newborn for intrauterine infection
    e. Maternal antibodies to neurotransmitters in the infant indicating myasthenia gravis
    f. Cytogenetic study indicated in the following situations:
        i. Multiple organ or system involvement
        ii. Presence of CNS abnormalities, such as microcephaly, mental retardation, lethargy, degenerative changes, or eye anomalies
        iii. Fibroblast chromosome study if lymphocyte chromosomes are normal and the patient has mental retardation without diagnosis
    g. Nuclear DNA mutation analysis to identify certain disorders, such as spinal muscular dystrophy
    h. Mitochondrial mutation analysis to identify certain disorders, such as mitochondrial myopathy
2. Imaging studies
    a. Patient's photographs
        i. To document the extent of deformities (range of motion and position of arthrogryposis)
        ii. To assess progress during treatment
    b. Radiographs to evaluate the following skeletal and joint abnormalities:
        i. Bony abnormalities (e.g., gracile bones, fusions, extra or missing carpals, and tarsals)

ii. Disproportionately short stature (i.e., skeletal dysplasias)
iii. Scoliosis
iv. Ankylosis
v. Absence of patella
vi. Humeroradial synostosis

c. Ultrasonography
i. To evaluate the CNS and other viscera for anomalies
ii. To establish potential muscle tissue

d. CT scan to evaluate the CNS and the muscle mass
e. MRI to evaluate muscle mass obscured by contractures
f. Ophthalmological evaluation for opacity and retinal degeneration

3. Histologic studies (Banker 1985)
a. Neurogenic types
i. Muscle fiber type predominance or disproportion is the most common neurogenic abnormality in arthrogryposis (26%). These are nonspecific alterations.
ii. Dysgenesis of the motor nuclei of the spinal cord and brainstem causes the replacement of fasciculi of muscle fibers by small muscle fibers and adipose tissue. Examples include Pierre Robin syndrome and Möbius syndrome.
iii. Dysgenesis of the CNS: the second most common neurogenic abnormality in arthrogryposis (23%), with disorganization and decrease in neurons of the cortex and motor nuclei of the brainstem and spinal cord. Clinical syndromes with this abnormality include trisomy 18, partial deletion of the long arm of chromosome 18 syndrome, and Zellweger syndrome.
iv. Dysgenesis of the anterior horn, another common neurogenic abnormality in arthrogryposis
v. Spinal muscular atrophy (e.g., Werdnig–Hoffmann disease): another neurogenic abnormality in arthrogryposis

b. Myopathic types
i. Central core disease: a form of arthrogryposis in which the central portion of each muscle fiber contains a zone in which oxidative enzyme activity is absent
ii. Nemaline myopathy indicated by abnormal thread-like structures in muscle cells. In type I nemaline myopathy, nemaline rods are present. In type II, the number of fibers with central nuclei is increased.
iii. Congenital muscular dystrophy indicated by muscle fibers that demonstrate a rounded configuration and conspicuous variation in diameter. Perimysial and endomysial connective tissues are increased markedly.
iv. Mitochondrial cytopathy indicated by numerous ragged-red fibers on muscle biopsy. It is associated with CNS abnormalities consistent with mitochondrial disease (Gordon 1998).
v. Myoneural junction abnormality (e.g., congenital myasthenia gravis): another myopathic type of arthrogryposis

4. Procedures
a. Skin biopsy for culture of fibroblasts to be used for chromosome analysis and metabolic studies
b. Muscle biopsy
i. Probably the most important diagnostic procedure. It should be included in all autopsies and at time of surgery.
ii. Distinguish myopathic from neuropathic conditions by obtaining muscle specimens from normal and affected areas.
iii. Special histopathologic and electron micrographic studies to evaluate fatty and connective tissue replacement of muscle fibers and variations in fiber size, such as decreased fiber diameter. All are nonspecific signs of muscle atrophy.

c. Electromyography (EMG) in normal and affected areas useful in differentiating neurogenic and myopathic causes (Gordon 1998)
d. Nerve conduction tests to measure conduction velocities in motor and sensory nerves. These should be performed when a peripheral neuropathy is suspected.
e. An autopsy to investigate the following:
i. CNS (i.e., brain neuropathology)
ii. Spinal cord (number and size of anterior horn cells, presence or absence of tracts at various levels)
iii. Ganglia and peripheral nerves
iv. Eye (i.e., neuropathology)
v. Muscle tissue from different muscle groups (i.e., electron microscopy and special stains)

vi. Fibrous bands replacing muscle
vii. Tendon attachments
viii. Other visceral anomalies, malformations, deformations, and disruptions

Genetic Counseling

1. Recurrence risk: Recurrence risk depends on whether the contractures are extrinsically or intrinsically derived. Extrinsically derived contractures have a low recurrence risk, while the recurrence risk for intrinsically derived contractures depends on etiology. Arthrogryposis may be inherited in the following ways with different recurrence risks:
   a. Patient's sib
      i. Autosomal recessive: 25%
      ii. Autosomal dominant: not increased unless a parent is affected or having gonadal mosaicism
      iii. X-linked recessive: 50% of male sibs affected if the mother is a carrier
   b. Patient's offspring
      i. Autosomal recessive: not increased unless the spouse is also a carrier
      ii. Autosomal dominant: 50%
      iii. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal.
   c. Multifactorial: Combined effects of multiple genes and environmental factors cause multifactorial traits. For most multifactorial diseases, empirical risks (risks based on direct observation of data) have been derived. For example, empirical recurrence risks of neural tube defects for siblings of an affected individual range from 2% to 5% in most populations.
   d. Mitochondrial: A small but significant number of diseases are caused by mitochondrial mutations. Because of the unique properties of mitochondria, these diseases display characteristic modes of inheritance (i.e., inherited exclusively through the maternal line) with wide phenotypic variability. Only females can transmit the disease mutation to their offspring (e.g., distal type IIB arthrogryposis).
   e. Sporadic: For those families in which a specific diagnosis cannot be made, the empiric recurrence risk to unaffected parents of an affected child, or to the affected individual with arthrogryposis, is about 3–5%.
2. Prenatal diagnosis
   a. Prenatal ultrasonography to detect the following:
      i. Diminished fetal movement (main manifestation shared by various conditions with congenital contractures)
      ii. Joint contractures (bilateral fixed flexion deformities of the hands, elbows, shoulders, hips and knees, or talipes)
      iii. Detection of subcutaneous edema (fetal hydrops)
      iv. Cystic hygroma
      v. Increased nuchal translucency
      vi. Abnormal fetal lie
      vii. Polyhydramnios or oligohydramnios
      viii. Other associated anomalies (e.g., distended bladder in early urethral obstruction sequence; microcephaly, hydrocephaly, or hydranencephaly in "cerebral dysgenesis"–induced congenital contractures)
   b. Chromosome analysis by amniocentesis or CVS for chromosome disorders
   c. Molecular genetic analysis for certain genetic disorders with demonstrable mutations
3. Management (Shriner's Manual)
   a. No completely successful approach to treatment
   b. Overall goals
      i. Proper alignment of the lower limbs
      ii. Upper limb function for self-care
   c. Early vigorous physical therapy to stretch contractures
      i. To improve joint motion
      ii. To avoid muscle atrophy
      iii. Excellent functional outcome in patients with amyoplasia or distal arthrogryposis
      iv. May be harmful in diastrophic dysplasia because it may lead to joint ankylosis
      v. Frequent recurrence of deformities following stretching, often requires surgery
   d. Splinting combined with physical therapy
      i. Preferable to continuous casting
      ii. Night splinting after surgical procedures indicated to maintain increased range of motion
   e. Feeding assistance and intubation needed in patients with severe trismus

f. Specific joint problems
   i. Should be addressed with regard to treatment of other joints and the goals for the patient
   ii. Early soft-tissue surgery with osteotomies when the growth is completed
   iii. Tenotomies accompanied by capsulotomies in soft-tissue release procedures
   iv. Long-term bracing and assistive devices usually needed
g. Feet
   i. A rigid talipes equinovarus deformity: the most common deformity
   ii. Goal of treatment: a plantigrade, braceable foot
h. Knees
   i. Goal of treatment: an extended knee for ambulation
   ii. Flexion knee deformities more common than fixed knee deformities and more resistant to treatment
i. Hips
   i. Hip surgery follows foot and knee surgery, especially in the presence of knee extension deformities.
   ii. Hip surgery in patients younger than 1 year to facilitate ambulation. In some patients with bilateral hip dislocations and extremely mobile hips, open reduction may be attempted.
j. Upper extremities
   i. Treatment involves development of self-help skills (e.g., feeding and toileting) and mobility skills (e.g., pushing out of chair and using crutches).
   ii. Consider overall function of the entire extremity rather than function of the individual joints in evaluating the upper extremities.
   iii. Consider upper extremity surgery until the patient is older than 5–6 years.
k. Elbows
   i. Goals: passive or active flexion capability (feeding arm) and extension capability (toilet arm)
   ii. Achieve elbow mobility before correcting a wrist deformity because the elbow is crucial to hand function.
l. Wrists
   i. Stretching and splinting for the major wrist deformity (flexion with ulnar deviation)
   ii. Proximal row carpectomy with or without fusion for a severe deformity
m. Fingers
   i. Passive stretching and splinting for minimal to moderate flexion deformities
   ii. Soft-tissue releases with proximal interphalangeal joint fusions for more severe deformities
   iii. Thumb-in-palm deformity to be corrected to provide opposition-improved grasp
n. Spine
   i. The spine affected in about one third of patients
   ii. Scoliosis beginning early and progressing to become a long, severe, rigid, C-shaped curve. This curve responds poorly to orthoses, as it is progressive.
   iii. Curves greater than 35°: treated with spinal fusion and instrumentation
o. Complications
   i. Anesthesia: difficult to administer because vascular access often is restricted
   ii. Intubation: posing problems for patients with a small underdeveloped jaw, limited movement of the temporomandibular joint, or a narrow airway
   iii. Osseous hypoplasia associated with decreased mechanical use in developing bone: prone to fracture at multiple sites. Multiple perinatal fractures have been observed in osteopenic bones.
p. Physical activity
   i. Limited because of existing orthopedic problems
   ii. As a group, patients cope well socially and participate in social activities corresponding to their needs.
   iii. More restricted walking in patients with flexion contractures of the lower extremities than in those with extension contractures. Flexion contractures of the hips severely impair walking ability.
   iv. Contracture of the elbow causing a significant degree of disability in hand function
   v. Impossible to use crutches in patients with upper extremity involvement associated with severe spinal deformity
   vi. Dependent on help from other people to a higher degree in patients with more severe

joint involvement than those with less severe joint involvement

vii. Independent living with productive lives for most children with normal intelligence despite severe handicaps. However, many remain partially dependent on others, such as parents, relatives, and government subsidy. Dependency is related more closely to personality, education, and overall coping skills than to the degree of physical deformity.

viii. Good family support, a proper educational environment, and promotion of independence at an early age: required to achieve maximal function in addition to appropriate surgical correction

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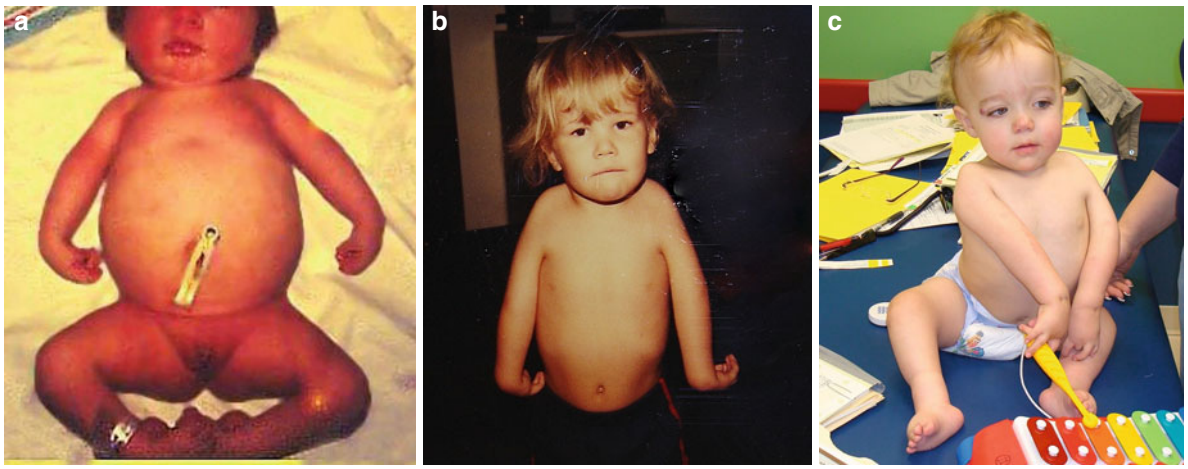

Fig. 1 (**a–c**) Three infants with amyoplasia congenita showing typical, symmetrical positioning of the limbs, internally rotated and adducted shoulders, fixed extended elbows, pronated forearms, flexed wrists and fingers, and severe talipes equinovarus deformity

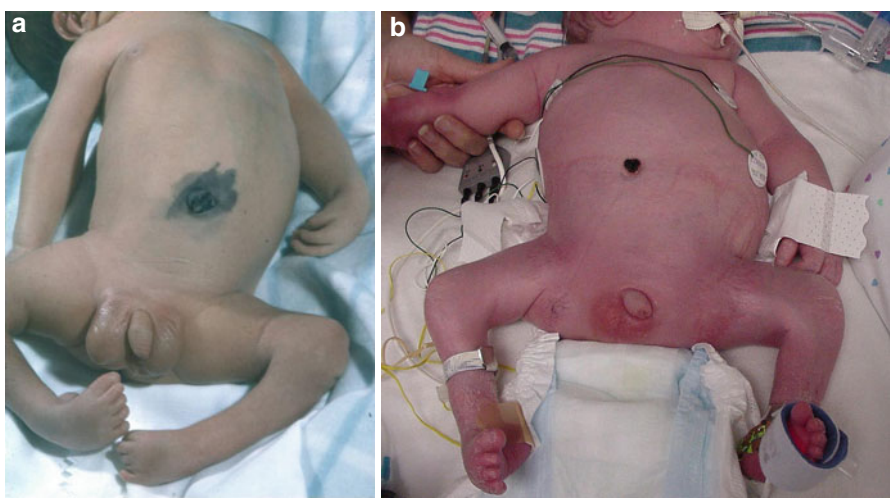

Fig. 2 (**a–b**) Two infants with arthrogryposis multiplex congenita characterized by flexion contractures of the knees and fingers, and equinovarus deformities of the feet

Fig. 3 (**a–b**) An infant with distal arthrogryposis showing predominantly distal contractures with overlapping finger contractures, ulnar deviation of fingers, and clubfeet

Fig. 4 (**a–c**) A 33-year-old female was followed for arthrogryposis multiplex congenita. At birth, flexion contractures of the fingers and hands, dysplastic hips, bilateral rocker bottom feet, and "generalized stiffness" were noted. At recent visit, flexion contractures of the elbows, limitation of supination of the wrists, contractures of the thumbs and PIP joints, and operation scars of webbing release between 1st and 2nd fingers and Achilles tendon release were noted

Asphyxiating Thoracic Dystrophy

In 1955, Jeune et al. described familial asphyxiating thoracic dystrophy (ATD) in a pair of siblings with severely narrow thoraxes. This condition is also known as Jeune syndrome. Incidence is estimated at 1 per 100,000–130,000 live births (den Hollander et al. 2001).

Jeune syndrome, a potentially lethal congenital dwarfism, is a rare autosomal recessive disorder characterized by typical skeletal dysplasias, such as a narrow thorax and micromelia, with respiratory and renal manifestations. Respiratory manifestations vary widely from respiratory failure and infantile death to a latent phenotype without respiratory symptoms.

Synonyms and Related Disorders

Jeune Syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Genetically heterogeneous
   a. One locus mapped to chromosome 15q13 (Morgan et al. 2003).
   b. Families with both mild and severe forms of ATD mapped to 15q13.
   c. Five consanguineous families sharing a 1.2 cM region of homozygosity between D15S165 and D15S1010.
   d. Mutations in the intraflagellar transport 80 (*IFT80*) gene have been recently identified in 3/39 families originating from Pakistan and Turkey, ascribing ATD to the ciliopathy group (Morgan et al. 2003). However, *IFT80* was excluded in a series of 26 fetuses and children belonging to 14 families diagnosed with either ATD or short rib-polydactyly syndrome, type III (SRP III) (Dagoneau et al. 2009).
   e. *DYNC2H1* Mutations: cause asphyxiating thoracic dystrophy (also cause SRP III) (Dagoneau et al. 2009)
      i. Studying a consanguineous family from Morocco, another locus was mapped to chromosome 11q14.3-q23.1 in a 20.4 Mb region and identified homozygous mutations in the cytoplasmic dynein 2 heavy chain 1 (*DYNC2H1*) gene in the affected children.
      ii. Compound heterozygosity for *DYNC2H1* mutations was also identified in four additional families.
      iii. Among the five families, 3/5 were diagnosed with ATD and 2/5 included pregnancies terminated for SRP type III
      iv. *DYNC2H1* is a component of a cytoplasmic dynein complex and is directly involved in the generation and maintenance of cilia.
      v. ATD and SRP type III are variants of a single disorder belonging to the ciliopathy group.

Clinical Features

1. Wide phenotypic variability
2. Classification of ATD
   a. Lethal form
   b. Severe form
   c. Mild form
   d. Latent form

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3. Short-limbed dwarfism
4. Growth retardation
5. Respiratory distress
   a. Respiratory distress secondary to a small thorax
      i. Motionless thorax
      ii. Abdominal respiration
      iii. Considerable supraclavicular, suprasternal, and intercostal space retraction on inspiration
   b. Severe dyspnea and extreme cyanosis in severe cases
   c. Some infants with only respiratory symptoms in conjunction with infection
   d. Some individuals lack respiratory symptoms in infancy or childhood.
6. Chest deformity of varying degree
   a. A long, narrow, and abnormally small thorax with reduced thoracic cage capacity
   b. Lung hypoplasia and respiratory distress usually leading to early death
   c. The symptoms of small thorax usually improves with age for those who survive early childhood
7. Limbs
   a. Variable micromelia and short digits with bulbous terminal phalanges
   b. Occasional postaxial polydactyly of the hands and feet
8. Eyes: occasional retinal degeneration.
9. Occasional intestinal malabsorption.
10. Renal failure developing during infancy, early adolescence, or second decade of life.
11. Polyuria, polydipsia, and hypertension occur during the second or third year of life.
12. Occasional involvement of the liver
    a. Prolonged neonatal jaundice
    b. Polycystic liver disease
    c. Hyperplasia of the bile ducts
    d. Congenital hepatic cirrhosis
13. Occasional involvement of the heart
    a. Cardiac failure secondary to increased pulmonary vascular resistance, thoracic constriction, and alveolar hypoplasia
    b. Possible intrinsic myocardial disease
14. Cystic changes of pancreatic ducts and pancreatic exocrine insufficiency occur in long-term survivors.
15. Occasional involvement of the teeth, nails, and other organs.
16. Prognosis
    a. Difficult to predict in each individual case because frequent pulmonary complications and cystic renal lesions are not always directly related to severity of skeletal changes.
    b. The skeletal dysplasia of this entity is compatible with life, though respiratory failure and infections are often fatal during infancy.
    c. Considerable variation in the severity of thoracic constriction: For those patients who survive infancy, the thorax tends to revert to normal with improving respiratory function. This suggests that the lungs have a normal growth potential and the respiratory problems are secondary to restricted rib cage deformity.
    d. Renal failure: Renal involvement is the major prognostic factor in those patients who survive the respiratory insufficiency during infancy.
    e. Short stature in survivors.
17. Morbidity and mortality
    a. Alveolar hypoventilation
       i. The most common and prominent clinical presentation
       ii. Caused by impaired chest expansion as a result of short horizontally placed ribs
    b. Bilateral microcystic renal disease gradually progressing to tubular atrophy and renal failure
    c. Most patients (approximately 60–70%) dying from respiratory failure in early infancy and early childhood
    d. Chronic renal failure ensuing in survivors
    e. Few patients reaching adolescence or adulthood
18. ATD overlapping with SRP III (Verma-Naumoff syndrome)
    a. Both conditions share the same radiological features (including the polydactyly)
    b. SRP type III (Ho et al. 2000; Superti-Furga and Unger 2007)
       i. More severe condition
       ii. Early prenatal expression and lethality
       iii. Variable malformations
          a) Cleft lip and/or palate
          b) Polycystic kidneys
          c) Gastrointestinal, urogenital, brain, and/or cardiac malformations
       iv. Severely shortened tubular bones having round metaphyseal ends with lateral spikes

Diagnostic Investigations

1. Laboratory studies
   a. Urinalysis
      i. Hematuria
      ii. Proteinuria
      iii. Defective urine concentrating capacity
   b. Arterial blood gas (ABG): hypoxia and hypercarbia in room air reflecting severe restrictive lung disease
2. Imaging studies
   a. Newborn and infant radiography
      i. Small and bell-shaped thorax with reduced transverse and anterior-posterior diameter
      ii. Abnormal clavicles ("bicycle handlebar shaped")
      iii. Short and horizontally oriented ribs with irregular costochondral junctions and bulbous and irregular anterior ends
      iv. Abnormal pelvis
         a) Short squared iliac wings
         b) Trident appearance of acetabular margin
      v. Short limbs relative to trunk
      vi. Variable limb shortening
      vii. Short phalanges, metacarpals, or metatarsals with or without polydactyly
      viii. Premature ossification of the capital femoral epiphyses
   b. Childhood radiology
      i. Relatively larger thorax with growth of ribs compared to infancy
      ii. Short ilium with normal flaring of iliac wings
      iii. Striking cone-shaped epiphyses and early fusion between the epiphyses and metaphyses of the distal and middle phalanges
      iv. Short distal and middle phalanges
      v. Varying shortening of extremities relative to trunk
      vi. Subtypes of ATD
         a) Type I: irregular metaphyseal ends
         b) Type II: smooth metaphyseal ends
3. Pulmonary function test to detect severe restrictive lung disease
4. Histology
   a. Lungs: Hypoplastic due to a marked reduction in the number of alveolar ducts and alveoli (hypoplasia of alveoli)
   b. Cartilages: retarded endochondral ossification in both types
      i. ATD type I: irregular cartilage-bone junction with patchy distribution of physeal growth zone of chondrocytes
      ii. ATD type II: smooth cartilage-bone junctions
   c. Kidneys
      i. Cystic renal dysplasia and hypoplasia
      ii. Nephronophthisis or interstitial nephritis
         a) Diffuse interstitial and periglomerular fibrosis
         b) Round cell lymphocytic infiltration
         c) Hyalinized glomeruli
         d) Pericapsular thickening
         e) Thickened basement membrane
         f) Dilated or atrophic tubules
      iii. Pyelonephritis with scarring
      iv. Distortion of renal parenchyma
   d. Liver
      i. Periportal hepatic fibrosis
      ii. Bile duct proliferation
      iii. Early cirrhosis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: usually lethal, not surviving to reproductive age
2. Prenatal diagnosis by ultrasonography
   a. Detection of affected second- and third-trimester fetuses of at-risk families
   b. Characteristic ultrasonographic findings
      i. Narrow thorax
      ii. Short hypoplastic ribs
      iii. Short tubular bones
      iv. Renal cystic changes
   c. Other ultrasonographic findings
      i. Polyhydramnios
      ii. Absent or feeble fetal respiratory movements
      iii. Increased nuchal translucency
      iv. With or without polydactyly
      v. Ventriculomegaly
      vi. A single umbilical artery
3. Management
   a. Medical care
      i. Supportive care

ii. Mechanical ventilation
   a) Urgently required in the most severe cases, those when respiratory distress develops immediately after birth
   b) Less severe cases gradually progressing to respiratory failure as a result of multiple recurrent pulmonary infections
iii. Treat respiratory infections vigorously with antibiotics, endotracheal suctioning, and postural drainage
iv. Nasogastric or gastrostomy feedings if needed
v. Ursodeoxycholic acid used to control the progression of the hepatic dysfunction

b. Surgical care
   i. Surgery indicated only in the most severe cases in which failure to intervene will result in progressive pulmonary damage and eventual death. No data is currently available on long-term follow-up care of patients who have been surgically treated.
   ii. Expansion thoracoplasty utilizing various surgical techniques (Kaddoura et al. 2001)
      a) Splitting the sternum or the rib cage and maintaining the separation with methacrylate
      b) Rib grafts
      c) Homologous bone grafts
      d) Lateral rib cage expansion using staggered superiosteal rib osteotomies and rigid titanium miniplate and screw augmentation and stabilization
      e) Modified bailey rib approximator to provide a calibrated dynamic separation for the sternum after the primary procedure of midsternotomy and methylmethacrylate sternoplasty
   iii. Dialysis and renal transplantation indicated for renal failure. Recently, cadaver renal transplantation was successful in a 10-year-old boy with Jeune syndrome type 2 (Amirou et al. 1998).
   iv. Surgical complications
      a) Pneumothorax
      b) Mucous plugging of a bronchus
      c) Repeated infections
      d) Progressive herniation of lung through sternal defect
      e) Cardiac insufficiency

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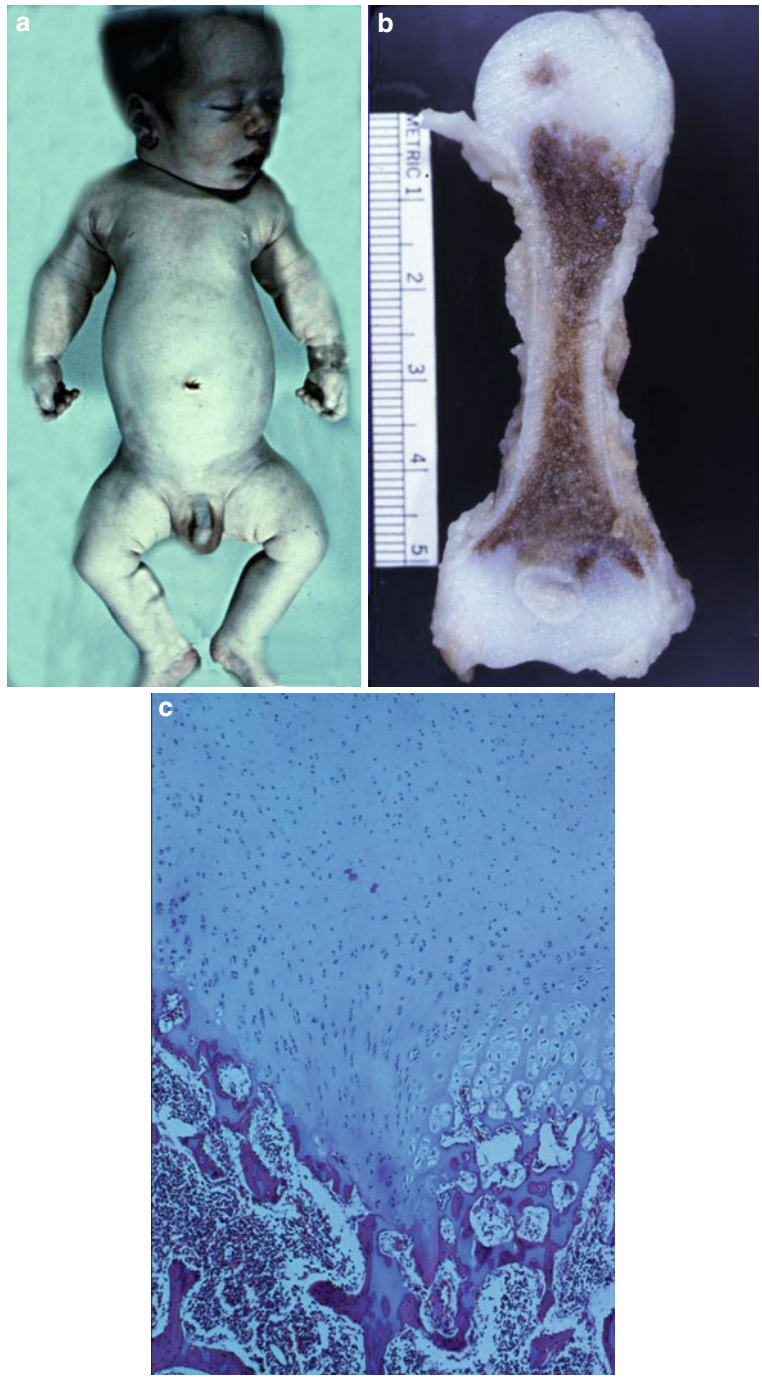

Fig. 1 (**a–c**) A neonate died of respiratory insufficiency. The chest is severely narrow and limbs are mildly shortened (Yang et al. 1976). The longitudinal section of the humerus shows irregular cartilage-bone junctions. There is a premature ossification center in the proximal epiphysis. The photomicrograph of the physeal growth zone shows scattered areas (*left* 2/3rd of the picture) of severe retardation and disorganization. Consequently, the cartilage-bone junction is irregular

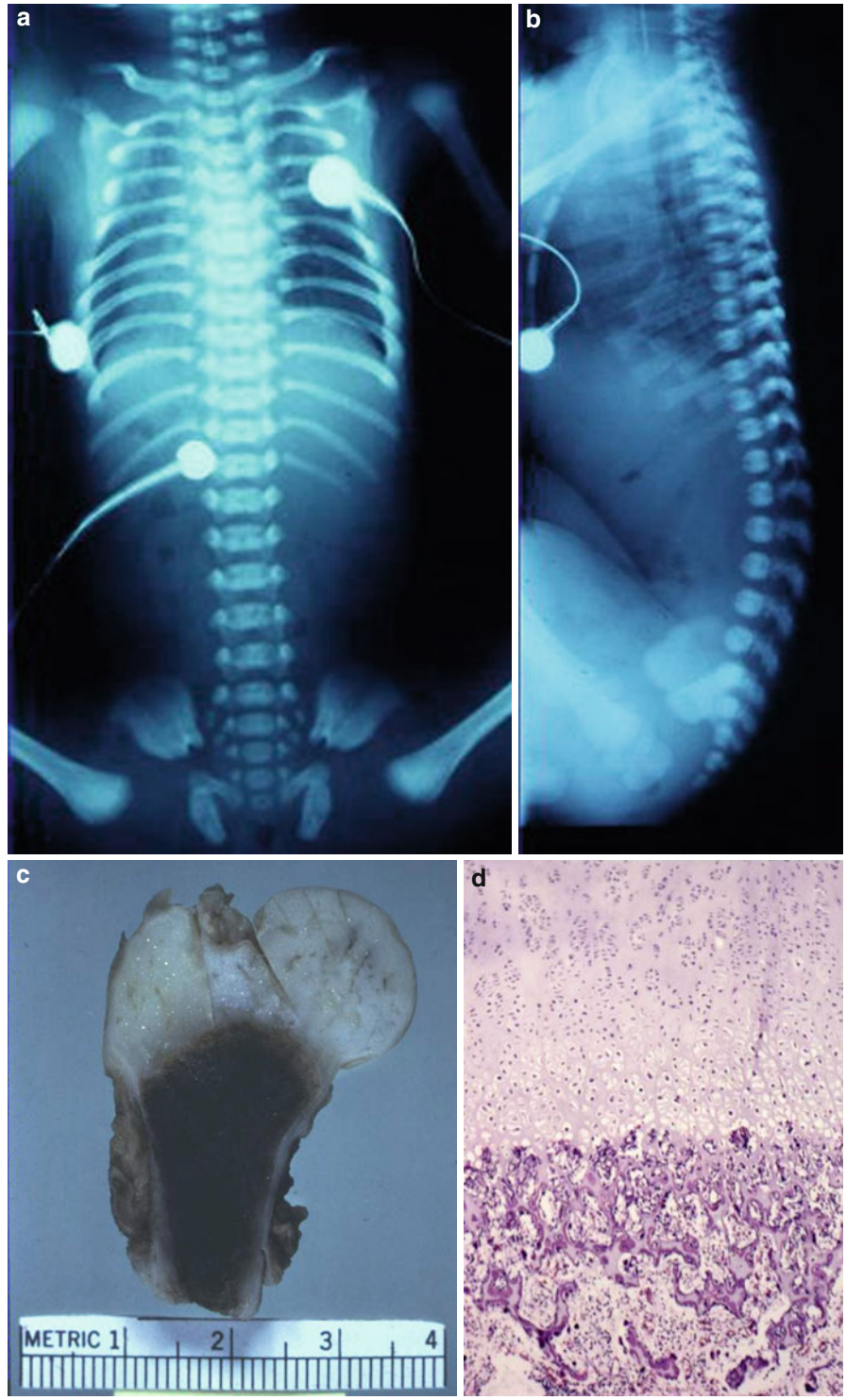

Fig. 2 (**a-d**) Radiographs of the skeletal system of a neonate with type II asphyxiating thoracic dystrophy. The ribs are short. The ilia are vertically shortened. The findings are similar in both types I and II. However, the metaphyseal ends of tubular bones do not show irregularity or spurs as in type I. Photomicrograph of the proximal femur shows generalized retardation and disorganization of the physeal growth zone. The cartilage columns in the metaphysis form a lattice-like meshwork

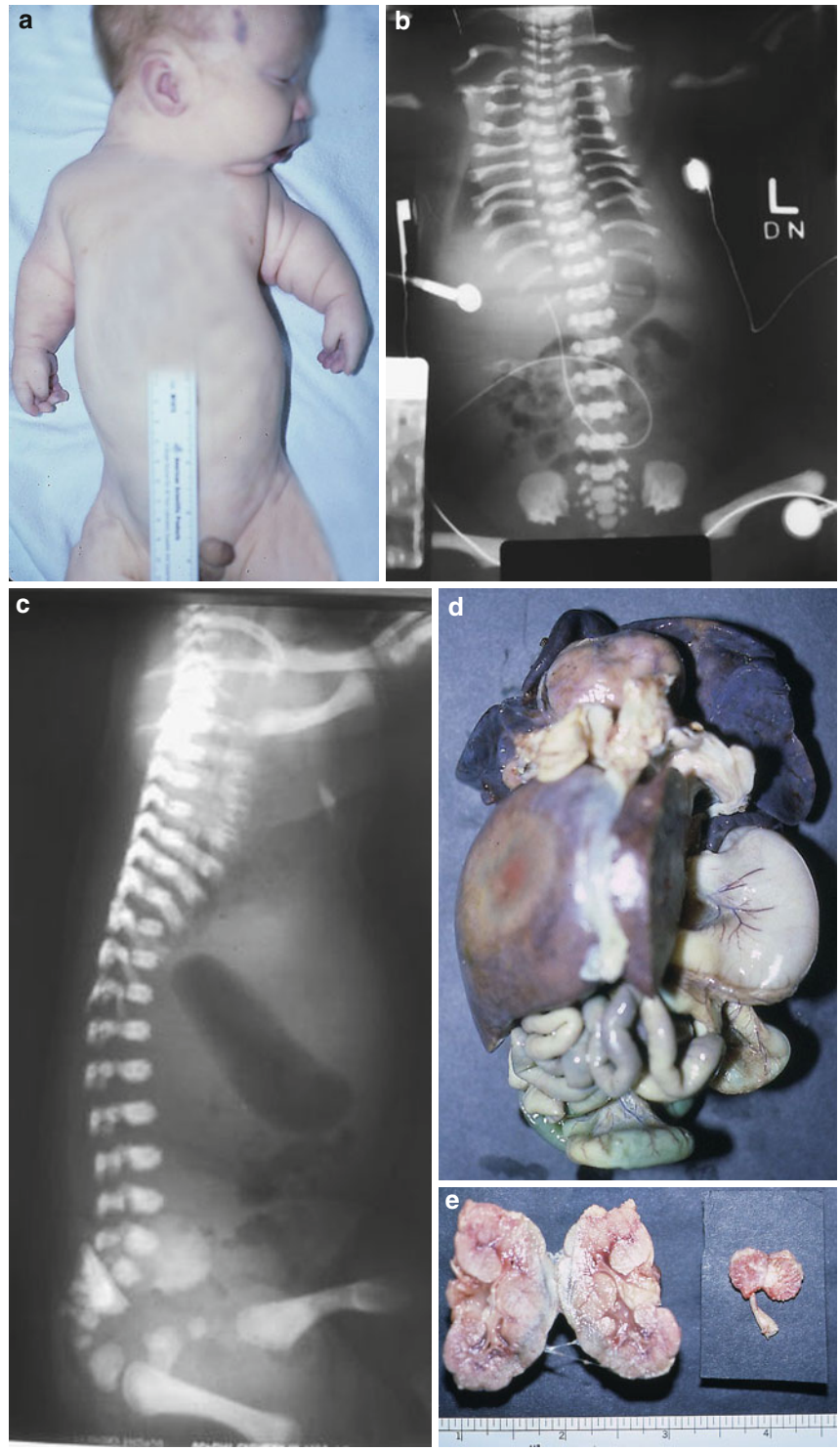

Fig. 3 (**a–e**) An infant with type II asphyxiating thoracic dystrophy showing a narrow thorax and short *upper* extremities. The radiographs showed the handlebar clavicles, short horizontal ribs with widened/cupped anterior rib ends, and *square-shaped* iliac bones with the medial spurs of both acetabular roofs. The necropsy showed lung hypoplasia and renal cystic dysplasia and hypoplasia

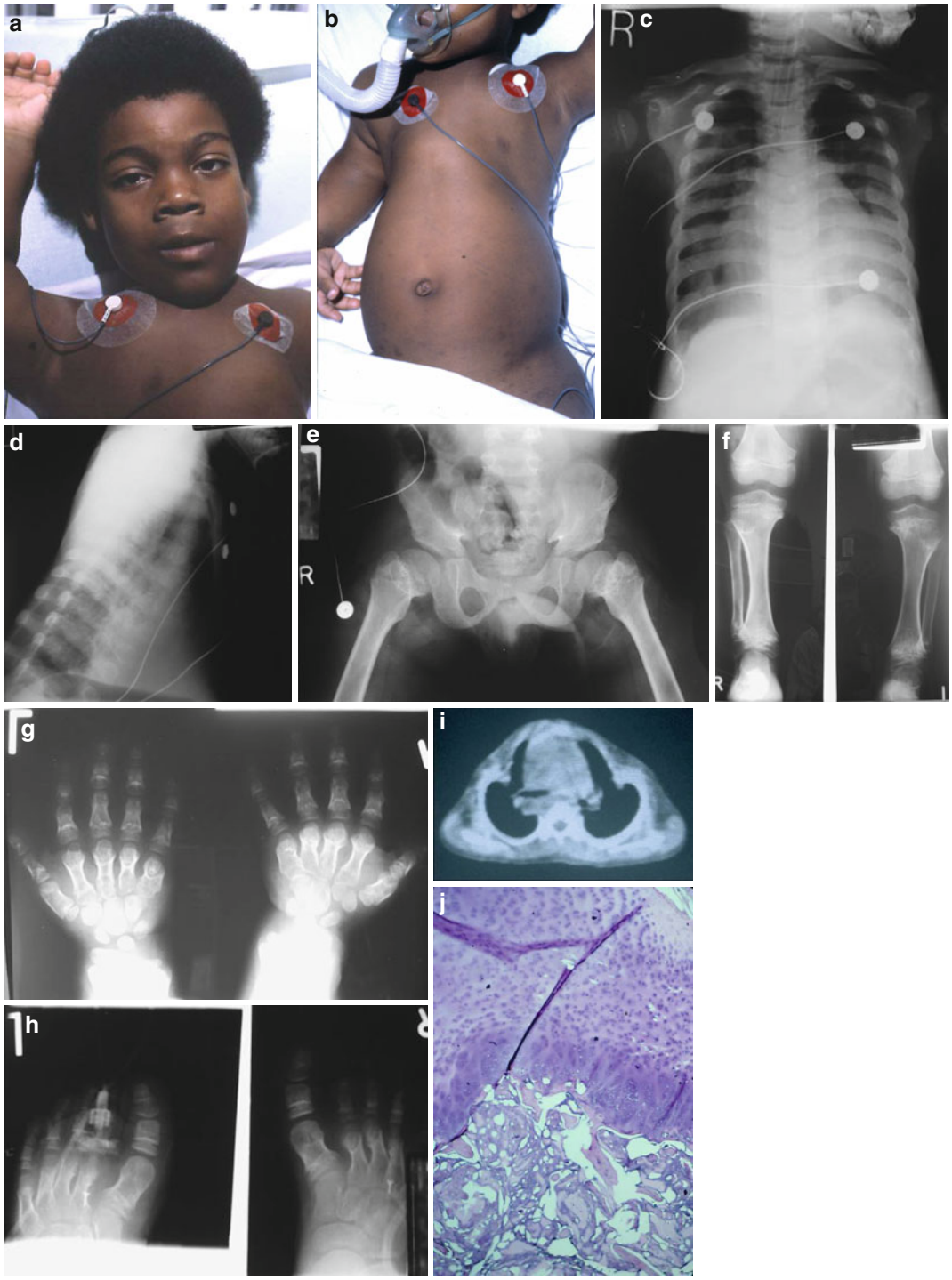

Fig. 4 (**a–j**) A 7-year-old boy with asphyxiating thoracic dystrophy showing a narrow thorax and short limbs. He had dwarfism, postaxial polydactyly, and respiratory distress since birth. Radiographs showed handlebar clavicles, short horizontal ribs, oblique superior acetabular margins, shortened tubular bones, shortened phalanges especially the middle and distal phalanges, and *cone-shaped* epiphyses. CT of the chest showed a narrow thorax, shortened ribs, and lung hypoplasia. Histology of the ribs showed that resting chondrocytes were widely separated by abundant cartilaginous matrix. Histology of a rib physeal growth zone shows greatly reduced number of chondrocytes. In some areas, they are completely nonexistent

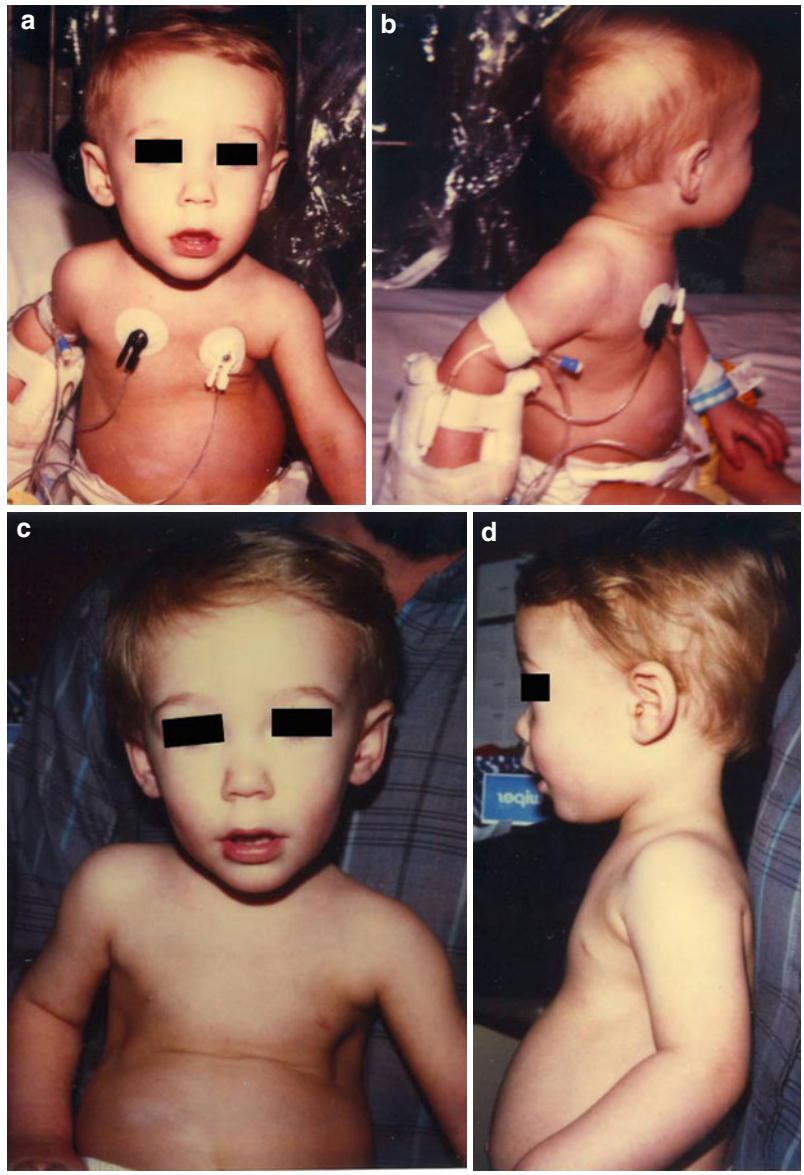

Fig. 5 (**a–d**) A boy with type II asphyxiating thoracic dystrophy at 7 months and 15 months

Ataxia-Telangiectasia

Ataxia-telangiectasia (A-T) is a rare hereditary disorder characterized by progressive cerebellar ataxia, conjunctival telangiectasias, recurrent sinopulmonary infections, radiosensitivity, and a predisposition to malignancy. It is the most common cause of progressive cerebellar ataxia in childhood. The prevalence is estimated to be 1 in 40,000–1 in 100,000 live births.

Synonyms and Related Disorders

Louis–Bar syndrome

Genetics/Basic Defects

1. Inheritance
   a. Autosomal recessive
   b. Genetic heterogeneity in at least five complementation groups (A–E)
2. Cause
   a. Mutations in the ataxia-telangiectasia mutated gene (*ATM*) which is mapped to 11q22.3
   b. Affected individuals completely lack functional ATM protein
   c. A high prevalence of specific *ATM* mutations in certain ethnic groups (Amish, Mennonite, Costa Rican, Polish, British, Italian, Turkish, Iranian, Israeli) with a founder effect, resulting in a small number of mutations that accounts for the majority of disease-causing mutant alleles
3. Pathophysiology
   a. Basic defect: abnormal sensitivity of A-T cells to x-rays and certain radiomimetic chemicals, leading to chromosome and chromatid breaks. However, sensitivity of A-T cells to ultraviolet irradiation is normal.
   b. Random distribution of breakpoints
   c. Nonrandom chromosome rearrangements selectively affect chromosomes 7 and 14 at sites that are concerned with T-cell receptors and heavy-chain immunoglobulin coding and with the development of hematologic malignancies
   d. Mechanisms responsible for neurologic disease, thymus aplasia, telangiectasias, growth retardation, and impaired organ mutation
      i. Have not been elucidated
      ii. Most likely linked to accelerated telomere loss
4. Range of mutations in the *ATM* gene (Taylor and Byrd 2005)
   a. ATM protein truncating mutations
   b. *ATM* missense mutations
   c. *ATM* splice site mutations
   d. *ATM* founder mutations
   e. New *ATM* mutations
5. Genotype–phenotype correlations (Gatti 2010)
   a. 576ins137nt mutation
      i. Somewhat slower rate of neurological deterioration

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ii. Later onset of symptoms
iii. Intermediate radiosensitivity
iv. Little or no cancer risk
b. 8494C>T mutation
i. Milder phenotype
ii. Longer life span

Clinical Features

1. CNS manifestations (Regueiro et al. 2000)
a. Functional neurologic abnormalities rare in infancy
b. Cerebellar ataxia
i. A presenting symptom
ii. Slowly progressive
iii. Truncal ataxia preceding appendicular ataxia and peripheral incoordination
iv. Swaying of the head and trunk while standing and sitting: early sign of ataxia
c. Diminished or absent deep reflexes by school age
d. Hypotonia
e. Dystonia and progressive spinal muscular atrophy affecting hands and feet in affected young adults, resulting in extension contractures
f. Dysarthric speech
g. Flexor plantar response
h. Choreoathetosis in almost all patients
i. Myoclonic jerking and intention tremors in about 25% of patients
j. Drooling
k. Oculomotor apraxia (total or partial loss of the ability to perform coordinated movement or manipulate objects in the absence of motor or sensory impairment) affecting reading (eye tracking) and writing (affected by 7–8 years of age)
l. Intellectual function generally preserved
2. Telangiectasias (dilated small blood vessels)
a. Ocular conjunctiva: most frequently observed
b. Other sites: nose, ears, behind the knees, antecubital fossae, suprasternal notch, dorsum of the hands and feet, and hard and soft palate
c. Usually noticed during 3–6 years of age, i.e., a few years after ataxia
3. Immunodeficiency
a. Frequent sinopulmonary infections
i. Mucopurulent rhinitis, retropharyngeal discharge, otitis media, and sinusitis
ii. Bronchitis and pneumonia
iii. Progress to chronic lung disease: bronchiectasis, pulmonary fibrosis, respiratory insufficiency
b. A small embryonic-like thymus
c. Problems associated with defects in humoral and cellular immunity
i. T-cell deficiency in about 30% of patients
ii. Severe immunodeficiency in about 10% of patients
iii. IgA deficiency
d. Most frequent cause of death in adolescence: bronchiectasis complicated by pneumonitis
4. Malignancy
a. The second most frequent cause of death
b. Eventual malignancy during lifetime in 38% of patients
c. Malignancy of hematologic origin most common (85% of patients)
i. Predominance of malignant lymphomas, usually of B-cell type
ii. Acute lymphocytic leukemia of T-cell origin in younger patients
iii. T-cell prolymphocytic leukemia in older patients
d. Other neoplasms
i. Breast cancer, even in female relatives who do not have ataxia telangiectasia
ii. Gastric cancer
iii. Melanoma
iv. Leiomyoma
v. Sarcoma
5. Ectodermal changes
a. Appearance of premature aging
i. Diffuse graying of the hair
ii. Atrophic and hidebound facial skin
iii. Inelastic ears
iv. Facial wasting
b. Frequent pigmentary changes: hyper-/hypopigmentation with cutaneous atrophy and telangiectasia
c. Partial albinism
d. Vitiligo
e. Café-au-lait spots
f. Seborrheic dermatitis
6. Endocrine manifestations
a. Occasional female hypogonadism associated with ovarian hypoplasia or dysplasia

   b. Male hypogonadism with delayed puberty and characteristic high-pitched voice
7. Clubbing: Observed in 40% of Costa Rican patients not correlated with chronic lung disease, humoral immunodeficiency, or with a particular mutation
8. Other features
   a. Mild postnatal growth retardation
   b. Hypersensitivity to ionizing radiation
   c. Wheelchair-bound by 10 years of age
9. A-T shares similar clinical symptoms and cellular characteristics with two other syndromes: A-T-like disorder (ATLD) and Nijmegen-breakage syndrome (NBS) (Lavin 2008)
   a. Defective protein
      i. A-T: ATM
      ii. ATLD: MRE 11
      iii. NBS: NBS1
   b. Appearance of symptoms
      i. A-T: infancy
      ii. ATLD: first decade
      iii. NBS: infancy
   c. Progression
      i. A-T: rapid
      ii. ATLD: slow
      iii. NBS: rapid
   d. Neurological defect
      i. A-T: cerebellar atrophy
      ii. ATLD: cerebellar atrophy
      iii. NBS: microencephaly
   e. Oculomotor apraxia
      i. A-T: present
      ii. ATLD: present
      iii. NBS: absent
   f. Immunodeficiency
      i. A-T: present
      ii. ATLD: absent
      iii. NBS: present
   g. Telangiectasia
      i. A-T: present
      ii. ATLD: absent
      iii. NBS: absent
   h. Alpha-fetoprotein
      i. A-T: high
      ii. ATLD: normal
      iii. NBS: normal
   i. Growth defect
      i. A-T: absent
      ii. ATLD: absent
      iii. NBS: present
   j. Radiosensitivity
      i. A-T: marked
      ii. ATLD: present
      iii. NBS: present
   k. Cell-cycle checkpoint defect
      i. A-T: present
      ii. ATLD: present
      iii. NBS: present
   l. DNA-repair defect
      i. A-T: present
      ii. ATLD: questionable
      iii. NBS: present
   m. Chromosomal instability
      i. A-T: present
      ii. ATLD: present
      iii. NBS: present
   n. Cancer predisposition
      i. A-T: present
      ii. ATLD: absent
      iii. NBS: present

Diagnostic Investigations

1. Immune workup: presence of significant humoral and cellular immune defects in most patients (Gatti 2010; Regueiro et al. 2000)
   a. Thymic hypoplasia
   b. Low numbers of circulating T-cells
   c. Functional impairment of T-cell-mediated immunity
   d. Selective deficiencies of IgA, IgE, IgG_2, and IgG_4
   e. Low or absent serum levels of IgA in 60% of patients
   f. Low or absent serum levels of IgG2 in 80% of patients
   g. Hyper IgM in approximately 1% of patients, sometimes associated with myeloma-like gammopathy, lymphadenopathy, hepatosplenomegaly, and lymphocytic interstitial pneumonitis
   h. Poor in vivo response to pneumococcal polysaccharides (Sanal et al. 1999)
   i. Immunoblotting for ATM protein (Gatti 2010)
      i. Severely depleted intracellular ATM protein in most patients with A-T
         a) About 90% have no detectable ATM protein

   b) About 10% have trace amounts of ATM protein
   c) About 1% have a normal amount of ATM protein that lacks ATM serine/threonine kinase activity (so-called kinase-dead)
  ii. The most sensitive and specific clinical test, to date, for establishing a diagnosis of A-T
  iii. Small amounts of ATM protein: occasionally associated with a milder prognosis, although there are many exceptions to this and the association needs further validation
2. Increased serum levels of alpha-fetoprotein (AFP) levels in over 90% of older children with A-T
3. Increased plasma levels of carcinoembryonic antigen
4. Colony survival assay by in vitro testing for radiosensitivity on lymphoblastoid cell line to measure the colony survival fraction after 1 Gy of in vitro radiation: sensitivity and specificity exceeding 95% but takes 2–3 months to complete
5. Western blot analysis to detect ATM protein in lysates of a lymphoblastoid cell line
6. DNA-based mutation analysis of the *ATM* gene available clinically
   a. Sequence analysis of the *ATM* coding region
   b. Deletion/duplication analysis
   c. Targeted mutation analysis
   d. Linkage analysis/ethnic haplotype analysis to identify carriers among family members at risk if direct DNA testing fails to identify two disease-causing mutations in the index case
7. Chromosome analysis to identify genetic instability, a hallmark of the A-T phenotype
   a. Types of spontaneous in vitro chromosome aberrations, frequent in both lymphoid and non-lymphoid cells
      i. Chromosome breaks
      ii. Acentric fragments
      iii. Dicentric chromosomes
      iv. Structural arrangements
      v. Telomeric fusions
      vi. An increased rate of telomeric shortening (Metcalfe et al. 1996)
      vii. Aneuploidy
   b. A-T lymphocytes
      i. Increased chromosome breaks. Common breakage points include 7p14, 7q35, 14q12, 14qter, 2p11, 2p12, and 22q11-q12
      ii. Clonal rearrangements involving abnormalities of chromosome 14, especially tandem duplication of 14q at 14q11-q12 and characteristic t(7;14)
   c. Non-lymphoid cells: break points randomly distributed
8. Radiography
   a. Decreased or absent adenoidal tissue in the nasopharynx
   b. Small or absent thymic shadow
   c. Decreased mediastinal lymphoid tissue
   d. Pulmonary changes similar to those seen in cystic fibrosis
9. EEG and nerve conduction velocities
   a. Frequently normal in children
   b. Showing denervation on EEG and reduced nerve conduction in the late stage of the disease, especially in sensory fibers
10. Electrooculography
   a. Shows characteristic oculomotor abnormality of A-T
   b. Differentiates A-T from Friedreich ataxia
11. MRI of the brain
   a. A small cerebellum
   b. Widened sulci
   c. Enlargement of the fourth ventricle
12. Histology
   a. Degeneration of Purkinje and granule cells in the cerebellum: the major pathological marker of A-T in the CNS
   b. Late degenerative gliovascular nodules in the white matter
   c. Lesions of the basal ganglia observed only occasionally
   d. Degeneration of spinal tracts and anterior horn cells often present in late stages
   e. Nucleocytomegaly, a feature of several cell types throughout the body

Genetic Counseling

1. Recurrence risk: counseling according to autosomal recessive inheritance
   a. Patient's sib
      i. A 25% recurrence risk
      ii. Two thirds of unaffected sibs are carriers.
   b. Patient's offspring: most patients with A-T do not reproduce.

2. Prenatal diagnosis
   a. Elevated maternal serum alpha-fetoprotein levels
   b. Demonstration of chromosome breaks in amniocytes
   c. Molecular genetic analysis
      i. Direct DNA mutation analysis on fetal DNA obtained from amniocentesis or CVS for pregnancies at-risk with previously identified specific disease-causing mutation
      ii. DNA-based testing with linkage analysis for at-risk family members if no specific disease-causing mutation identified
      iii. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified
3. Management
   a. No specific treatment available
   b. Antibiotics for infections
   c. Prevention of infection by regular injection of immunoglobulins in patients with antibody deficiency
   d. IV IG replacement therapy for individuals with frequent and severe infections and very low IgG levels (Nowak-Wegrzyn et al. 2004)
   e. Aggressive pulmonary hygiene for individuals with chronic bronchiectasis before the final stages of the disease (Tangsinmankong et al. 2001)
   f. Supportive therapy to minimize drooling, choreoathetosis, and ataxia; individual responses to specific medications vary (Perlman et al. 2003)
   g. Beta-adrenergic blockers may improve fine motor coordination in some cases
   h. Controversial use and doses of radiation therapy and chemotherapy
   i. Avoid bleomycin, actinomycin D, and cyclophosphamide
   j. Regular cancer surveillance of heterozygotes essential. ATM heterozygosity is a risk factor for breast and lung cancers.
   k. Desferroxamine: recently shown to increase genomic stability of A-T cells and may present a promising tool in A-T treatment
   l. Early physical therapy, occupational therapy, and speech therapy
   m. A wheelchair: usually necessary by age 10
   n. Although steroids can temporarily improve the neurologic symptoms of A-T in children, the symptoms reappear within days of their discontinuation (Gatti and Perlman 2009)

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Fig. 1 A boy with ataxia-telangiectasia showing conjunctival telangiectasis and chronic lung disease requiring oxygen support

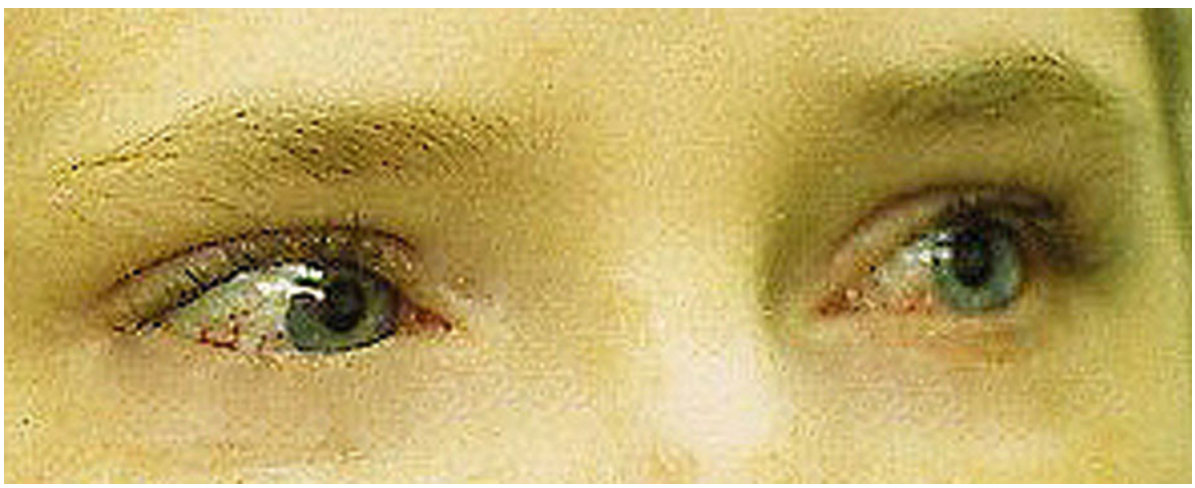

Fig. 2 A girl with ataxia-telangiectasia showing conjunctival telangiectasis and anemia

Atelosteogenesis

In 1982, Maroteaux et al. proposed the term "atelosteogenesis" for a newborn skeletal dysplasia characterized by specific patterns of aplasia/hypoplasia of humeri, femora, spine, and other skeletal elements. Atelosteogenesis encompasses a heterogeneous group of disorders with overlapping phenotypic features.

Synonyms and Related Disorders

Atelosteogenesis type I (giant cell chondrodysplasia, spondylohumerofemoral hypoplasia, boomerang dysplasia); Atelosteogenesis type II (neonatal osseous dysplasia I, De La Chapelle dysplasia); Atelosteogenesis III

Genetics/Basic Defects

1. Atelosteogenesis I (AOI)/boomerang dysplasia (BD)
   a. Inheritance: de novo autosomal dominant mutation, suggested by:
      i. Sporadic in all observed cases
      ii. No familial cases reported
   b. Previously known as spondylohumerofemoral dysplasia and giant cell chondrodysplasia
   c. Caused by mutations in filamin B (*FLNB*) gene, which also causes the following disorders:
      i. Atelosteogenesis type III
      ii. Autosomal recessive spondylocarpotarsal syndrome
      iii. Autosomal dominant Larsen syndrome
   d. A common pathogenesis suggested for atelosteogenesis type I and boomerang dysplasia
      i. Forming a spectrum of findings within the same nosologic entity with boomerang dysplasia
      ii. Similar histopathology in boomerang dysplasia
      iii. Overlapping radiologic features with boomerang dysplasia
2. Atelosteogenesis II (AOII) (Karniski 2001)
   a. Inheritance: autosomal recessive suggested by:
      i. Recurrence in the subsequent pregnancy
      ii. Parental consanguinity
   b. Synonymous with De la Chapelle dysplasia
   c. Phenotypic and radiographic overlap with atelosteogenesis I but with distinctive matrix histopathology with a major disturbance in cartilage matrix macromolecules
   d. Common pathogenetic features with disorders of sulfation of connective tissue matrix macromolecules. An overlap of phenotypic, radiographic, morphological, and cartilage histochemical features with the following conditions:
      i. Diastophic dysplasia
      ii. Achondrogenesis type IB
   e. Caused by mutated diastrophic dysplasia sulfate transporter (*DTDST*; *SLC26A2*) gene which also causes the following recessively inherited chondrodysplasias:
      i. Diastrophic dysplasia
      ii. Multiple epiphyseal dysplasia
      iii. Achondrogenesis IB

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f. The *DTDST* gene
   i. Encodes a sulfate transporter that also accepts chloride and possibly bicarbonate as substrates
   ii. Reduced sulfate transport in chondrocytes of individuals with *DTDST* mutations resulting in the under-sulfation of proteoglycans, which in turn leads to abnormal cartilage formation
g. Factors in addition to the intrinsic sulfate transport properties of the DTDST protein may influence the phenotype in individuals with *DTDST* mutations.

3. Atelosteogenesis III (AOIII)
   a. Inheritance: autosomal dominant
   b. Features overlapping with atelosteogenesis I and II but most similar to those of atelosteogenesis I
   c. Caused by mutations in *FLNB* gene
4. Genotype–phenotype correlation in a compound heterozygote (atelosteogenesis type II-diastrophic dysplasia)
   a. Atelosteogenesis type II
      i. R178X mutations of the *SLC26A2* gene
      ii. Features typical of AO II
         a) Severe and progressive cervical kyphosis
         b) V-shaped distal humerus
         c) Bowed radii
         d) Horizontal sacrum
         e) Gap between the first and second toes
   b. Diastrophic dysplasia
      i. R279W mutations of the *SLC26A2* gene
      ii. Features suggestive of diastrophic dysplasia
         a) Cystic swelling of the external ears
         b) Cervical kyphosis
         c) Rhizomelia
         d) "Hitchhiker" thumbs
         e) Bilateral talipes equinovarus
         f) Short toes
   c. Combination of a severe and a mild mutation leads to an intermediate clinical picture, representing an apparent genotype–phenotype correlation.

Clinical Features

1. Atelosteogenesis I
   a. Stillborn or neonatal death due to respiratory distress
   b. Polyhydramnios
   c. Facial dysmorphism
      i. Depressed nasal bridge
      ii. Eyelid edema
      iii. Micrognathia
      iv. Cleft soft palate
   d. Small chest
   e. Protuberant abdomen
   f. Deficient ossification of various bones
      i. Humerus
      ii. Femur
      iii. Thoracic spine
      iv. Hand bones
   g. Rhizomelic micromelic dwarfism
      i. Short and broad hands
      ii. Incurved legs
      iii. Club feet
      iv. Often dislocation of the elbows
   h. Laryngeal hypoplasia: an important role in the respiratory failure and death
2. Boomerang dysplasia
   a. Distinct facial features
      i. Horizontal palpebral fissures
      ii. Broad nasal root
      iii. Hypoplastic nasal septum
      iv. Prominent philtrum
      v. Cleft palate
   b. Small chest
   c. Protuberant abdomen
   d. Marked rhizo/mesomelic shortening of limbs
   e. Well-developed hands (broad, paddle-shaped) and feet
   f. Bowed lower limbs
   g. Calcaneo-valgus deformities
3. Atelosteogenesis II
   a. Lethal in neonatal period
      i. Pulmonary hypoplasia
      ii. Tracheobronchomalacia
      iii. Laryngeal stenosis
   b. Deficient ossification of parts of the skeleton
   c. Facial dysmorphism
      i. Midface hypoplasia
      ii. Depressed nasal bridge
      iii. Epicanthal folds
      iv. Micrognathia
      v. Cleft palate
   d. Small chest
   e. Protuberant abdomen

f. Extremities
   i. Severe rhizomelic limb shortening
   ii. Talipes
   iii. Abducted (hitch-hiked) thumbs and toes
   iv. Ulnar deviation of the fingers
   v. Gap between the first and second toes
4. Atelosteogenesis III
   a. Milder, usually nonlethal
   b. Limb anomalies
      i. Rhizomelic shortening
      ii. Clubfeet
      iii. Short broad thumbs and great toes
   c. Craniofacial abnormalities
      i. Ocular hypertelorism
      ii. A flat nasal bridge
      iii. Micrognathia
      iv. Cleft palate
   d. Small chest
   e. Protuberant abdomen
   f. Multiple dislocations of elbows, hips, and knees
   g. Respiratory and feeding difficulties secondary to laryngomalacia
   h. Apparent cause of death
      i. Respiratory complications
      ii. Cervical spine instability
   i. Long survival possible

Diagnostic Investigations

1. Atelosteogenesis I (Sillence et al. 1997)
   a. Radiography: overlapping radiological features with boomerang dysplasia
      i. Humeri: absent/geometric (AOI), absent (AOI/BD), absent (BD)
      ii. Hand phalanges: presence of distal and absent middle (AOI), hypoplastic middle (AOI/BD), presence of distal and absent proximal/middle (BD)
      iii. Femora: pointed distally (AOI), geometric (AOI/BD), absent (BD)
      iv. Tibia: bowed (AOI), hypoplastic (AOI/BD), bowed/boomerang (BD)
      v. Fibula: absent (AOI), absent (AOI/BD), absent (BD)
      vi. Spine: coronal clefts in the lumbar vertebrae (AOI), coronal clefts in the vertebrae, and uniform lack of ossification of the centra of the vertebral bodies (BD)
      vii. Pelvis: hypoplasia of the ischiopubis (AOI), lack of ossification of ischiopubis (BD), flared ilia with hypoplasia of the inferior one third (AOI, BD), producing a keyhole shape
      viii. Foot: lack of ossification of the calcaneal centers (AOI, BD)
      ix. Ribs: 10–13 pairs (BD)
   b. Histopathology
      i. Uniformly abnormal
      ii. Lack of ossification
      iii. Nonhomogeneous cell distribution with hypocellular and acellular areas
      iv. Occasional multinucleated giant chondrocytes in the relatively acellular areas of resting cartilage (alternatively named "giant cell chondrodysplasia")
      v. Disorganized growth plate in some cases
      vi. Similar histopathology in boomerang dysplasia
2. Boomerang dysplasia
   a. Radiography
      i. Triangular, boomerang-shaped long bones, diagnostic of the syndrome
      ii. Missing some tubular bone ossification centers
      iii. Ossified fingers and toes from the periphery
      iv. Characteristic shaped pelvis
      v. Retarded ossification of the spine, especially cervical and thoracic spine
      vi. Coronal clefts in the lower thoracic and lumbar spine
   b. Histopathology
      i. Chondrocytes in the resting cartilage are irregularly reduced in number with focal acellularity. Multinucleated giant chondrocytes have been noted.
      ii. The physeal growth zones are markedly retarded and disorganized.
3. Atelosteogenesis II (Bonafe et al. 2009)
   a. Radiography
      i. Normal size skull with disproportionately short skeleton
      ii. Spine
         a) Platyspondyly
         b) Hypodysplastic vertebrae
         c) Cervical kyphosis

d) Ossification of the upper thoracic vertebrae and coronal clefts of the lumbar and lower thoracic vertebrae may be incomplete

iii. Pelvis
a) Hypoplastic/flared ilia
b) Flat/horizontal acetabula with a spicule at the medial border of the acetabula
c) Often unossified pubic bones

iv. Long bones
a) Shortened with metaphyseal flaring
b) Distal humerus: sometimes bifid or V-shaped, sometimes pointed and hypoplastic
c) Femur: distally rounded, clubbed distally
d) Tibia: bowed/hypoplastic
e) Fibula: hypoplastic
f) Radius: typically bowed

v. Hands
a) Hitchhiker thumbs
b) Ulnar deviation of the fingers
c) Hand phalanges: irregular size and shape
d) Gap between the first and second toe
e) Hypoplasia of the first metacarpal bone

b. Histopathology
i. Irregularly distributed resting cartilage chondrocytes
ii. Attenuation of cartilage matrix with concentric matrix condensation rings around degenerating chondrocytes
iii. Shortened proliferative and hypertrophic zones
iv. Histopathology of cartilage essentially similar to that of diastrophic dysplasia and achondrogenesis IB reflecting the paucity of sulfated proteoglycans in cartilage matrix

c. Mutation analysis (mutation detection rate about 60%) and sequence analysis (mutation detection rate 90%) of *DTDST* (*SLC26A2*) gene: Mutations in the *DTDST* gene can be found in more than 90% of patients with radiologic and histologic features compatible with the diagnosis of atelosteogenesis II.

d. Carrier testing for AOII
i. Carrier testing available to at-risk family members once the mutation of the *DTDST* gene has been identified in the proband
ii. For the partner of a heterozygous individual. The partners can be screened for the four most common pathogenic alleles, R279W, IVS1 + 2T > C, delV340, and R178X. When these four alleles are excluded, the risk of carrying *DTDST* mutation is reduced from the general risk of 1:100 to about 1:300

4. Atelosteogenesis III
a. Radiography
i. Humeri: pointed distally
ii. Hand phalanges: tombstone-shaped proximal phalanges, widened distal phalanges
iii. Femora: pointed distally
iv. Tibia: short
v. Fibula: absent
vi. Spine: coronal clefts in the lumbar vertebrae, severe thoracolumbar kyphosis with an S-shaped cervical spine in lateral profile
vii. Pelvis: hypoplastic ischiopubis, banana-shaped pubic rami

b. Histopathology: hypocellularity without clustering, acellular areas, or "giant cells"

Genetic Counseling

1. Recurrence risk
a. AOI
i. Patient's sib: low
ii. Patient's offspring: a lethal entity not surviving to reproduce

b. AOII
i. Patient's sib: 25%
ii. Patient's offspring: a lethal entity not surviving to reproduce

c. AOIII
i. Patient's sib: low
ii. Patient's offspring: 50%

2. Prenatal diagnosis
a. Fetal ultrasonography
i. Short limbs (micromelia)
ii. Abnormal facial profile (depressed nasal base, micrognathia, apparent hypertelorism)
iii. Absence of ossification in the humerus, radius, ulna, and cervical and upper thoracic vertebral bodies
iv. Coronal clefts in the ossified vertebral bodies
v. Talipes equinovarus

b. 3D helical computed tomography (Cordier et al. 2008)
i. Not dependent on amniotic fluid volume, fetal position, and not limited at specific fetal parts

ii. Theoretical fetal exposure to radioactivity similar to that of conventional fetal radiological examination
iii. Identifies more characteristic findings than 3D ultrasonography due to its advantage of being able to image the entire skeleton and its possibilities of rereading

c. Fetal MRI using an ultrafast sequence
i. Dysmorphic features
ii. Pulmonary hypoplasia
iii. A large cysterna magna

d. Prenatal diagnosis by analysis of DNA extracted from fetal cells obtained by CVS or amniocentesis or preimplantation genetic diagnosis: Mutation analysis of *DTDST* gene for pregnancy at risk is possible for AOII for families in which the disease-causing mutations have been identified

3. Management
a. AOI and AOII: supportive measures for these two lethal conditions
b. AOIII
i. Ventilatory support and tracheostomy often necessary for respiratory distress due to laryngotracheomalacia
ii. Treat recurrent respiratory tract infections
iii. Cleft palate repair
iv. Conductive hearing loss evaluation and management
v. Orthopedic care for club feet and joint dislocations

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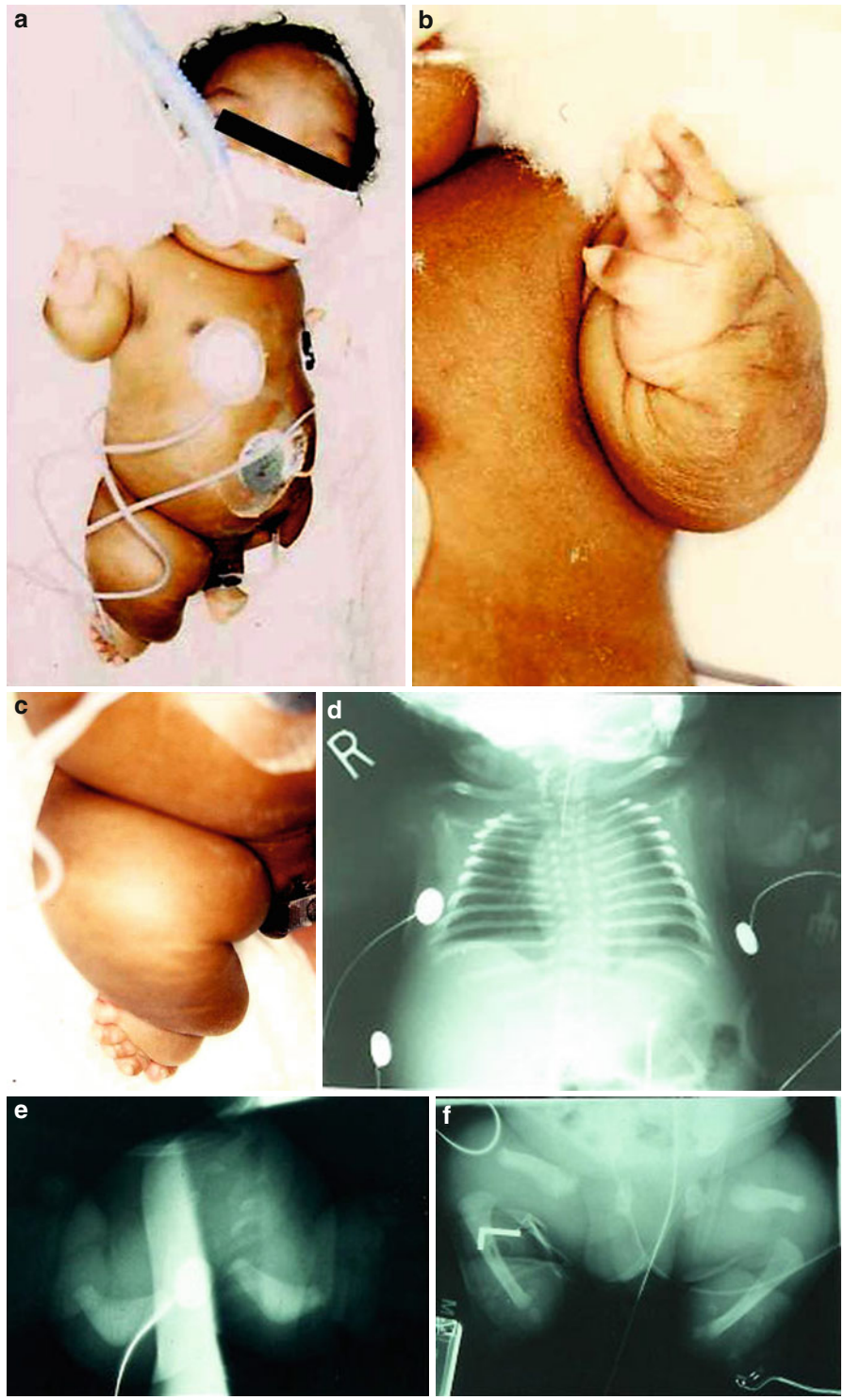

Fig. 1 (**a**–**f**) A male infant with atelosteogenesis I/boomerang dysplasia. Prenatal ultrasound showed polyhydramnios and a short limb dwarf. The infant died at 57 days. He showed relatively large head, hypertelorism, depressed nasal bridge, midfacial hypoplasia, micrognathia, cleft palate, short neck, relatively narrow chest, protuberant abdomen, severe "rhizomelic" micromelia, absent elbow joints, genu varus, and talipes equinovarus. Radiographic features included unossified vertebrae (T6–T9), single boomerang-like long bone (between acromion and wrist), short tapered femora, short bowed tibiae, absent fibulae, calcified distal phalanges, non-ossified carpals, metacarpals, and proximal phalanges, and irregularly ossified tarsals and metatarsals. Histopathology of the cartilage showed disorganized physeal growth zones and irregular areas of hypocellularity in the resting cartilage. Multinucleated giant chondrocytes were not observed

Autism

Autism is a pervasive developmental disorder, defined by impairments in social and communication function, and repetitive and stereotyped behavioral patterns. It occurs in approximately 7–40 out of 10,000 persons.

Autism spectrum disorders (ASDs) represent a heterogeneous group of neurodevelopmental disorders, including autism, Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified, and is characterized by social and communication deficits accompanied by repetitive and stereotype behaviors, with onset before 3 years of age (American Psychiatric Association 1994; DiCicco-Bloom et al. 2006; Caglayan 2010).

Synonyms and Related Disorders

Autistic disorder; Autism spectrum disorders (autism, Asperger syndrome, childhood disintegrative disorder, pervasive developmental disorder)

Genetics/Basic Defects

1. Secondary autism (nongenetic and genetic conditions associated with autism): accounts for a small minority of individuals with autism (<10%) in population-based studies (Miles et al. 2005; Muhle et al. 2004)
   a. Obstetric complications including uterine bleeding, despite absence of demonstrable causal relationship in many studies
   b. Intrauterine exposure to teratogenic drugs in a few affected children
      i. Thalidomide
      ii. Valproate
   c. Elevated cord blood levels of following substances
      i. Neuropeptides substance P
      ii. Vasoactive intestinal peptide
      iii. Pituitary adenylate cyclase-activating polypeptide
      iv. Calcitonin gene-related peptide
      v. Neurotrophin nerve growth factor
   d. Various epidemiologic data
      i. Cerebral palsy (a static motor deficit of brain origin present from early life): present in 2.1–2.9% of individuals with autism and mental retardation
      ii. Congenital rubella infection: present in 0.75% of cases
      iii. Other pre- and postnatal infections (e.g., Hemophilus influenza and cytomegalovirus): may cause autism when they significantly damage the immature brain
      iv. No association between autism and inflammatory bowel disease or with a live MMR vaccination
      v. Epilepsy with the highest association with autism: reported in up to a third of individuals with an autistic spectrum disorder by adulthood
      vi. Behavioral symptoms of autism: frequent in tuberous sclerosis complex and fragile X syndrome but account for only a minority of the total cases of autism
   e. Genetic causes associated with autism
      i. Cytogenetically visible chromosomal abnormalities (~5%)
         a) Angelman syndrome (more commonly associated with autism than Prader–Willi syndrome) can result from the loss or

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mutations of the maternally derived *UBE3A* or the *ATP10C* gene in 15q11-q13 region

b) Chromosomal duplication in the Prader–Willi/Angelman region of proximal 15q in about 3% of individuals with autism: more commonly a supernumerary isodicentric 15q chromosome detectable by routine cytogenetic studies or less commonly an interstitial duplication of the region detected by FISH analysis of the *SNRPN* gene

c) Other chromosome abnormalities in 3–5% of individuals with autism

d) A subtelomeric deletion detected by FISH telomere studies in 10% of unselected patients with autism

e) Down syndrome: Autism was found in at least 7% in one study in children with Down syndrome

f) Turner syndrome: known to have specific cognitive and behavioral deficits that overlap with but are also distinct from those found in children with idiopathic autism (Caglayan 2010)

g) Inv dup(15) or idic(15) syndrome: characterized by early central hypotonia, developmental delay and intellectual disability, epilepsy, and autistic behavior with no facial dysmorphic features (Battaglia 2008)

ii. Copy number variants (CNVs) (Miles et al. 2010): Array comparative genomic hybridization (aCGH):

a) Steadily replacing high-resolution chromosome analysis and FISH in the evaluation of children with autism

b) Designed to test for known deletion/duplication syndromes on the entire genome plus assessment of subtelomeric regions

c) Currently, aCGH identifies clinically relevant de novo genomic imbalances in 7–10% of individuals with autism of unknown cause (Sebat et al. 2007; Christian et al. 2008; Kumar et al. 2008; Marshall et al. 2008; Weiss et al. 2008)

d) Examples of CNVs associated with autism: 16p11.2 deletion syndrome in approximately 1% of individuals with autism (Marshall et al. 2008) and 15q13.3 deletion syndrome associated with mental retardation, epilepsy, and ASDs (Ben Shachar et al. 2009; Miller et al. 2009; Pagnamenta et al. 2009)

iii. Single gene causes of autism in which neurologic findings are associated with ASDs (~5%)

a) Fragile X syndrome found in a few percent of children with autism: At least 50% of children with fragile X syndrome have autistic behaviors, including avoidance of eye contact, language delays, repetitive behaviors, sleep disturbances, tantrums, self-injurious behaviors, hyperactivity, impulsiveness, inattention and sound sensitivities

b) Rett syndrome: Children affected with both autism and Rett syndrome (almost universally female sex) have a period of normal development, followed by loss of language with stereotypic hand movements (hand-wringing behavior)

c) Tuberous sclerosis complex: Mentally retarded individuals with tuberous sclerosis complex frequently have autism (almost 50% in some studies)

d) Neurofibromatosis type 1: much less frequently associated with autism than is tuberous sclerosis and fragile X syndrome

e) Duchenne muscular dystrophy: An unexpectedly large proportion of boys with Duchenne muscular dystrophy have autistic spectrum

f) Sotos syndrome: A number of affected individuals diagnosed to have ASDs or autistic features

g) Joubert syndrome: a few affected children diagnosed with autism

h) Other macrocephalic conditions with overgrowth (Simpson-Golabi-Behel syndrome, Beckwith-Wiedemann syndrome)

i) Autism and macrocephaly or autism with no other clinical features: reported to have germline *PTEN* mutations (Herman et al. 2007)

j) Timothy syndrome (an autosomal dominant disorder characterized by lethal cardiac arrhythmias, congenital heart

disease, webbing of fingers and toes, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism) (Splawski et al. 2004)
k) Williams syndrome: Individuals with Williams syndrome show an unusually strong interest in people, including strangers, warm and engaging, and highly empathetic toward others versus profound impairments in social functioning, including difficulties interacting with others, attending to people, and decoding nonverbal cures, and impairments in social emotional reciprocity (Caglayan 2010)
l) Smith–Magenis syndrome: Autistic-type behaviors reported in many affected individuals (Dykens et al. 1997)
m) Smith-Lemli-Opitz syndrome: ~75% of affected children met the criteria for some variants of ASDs (Sikora et al. 2006)
n) Cohen syndrome (an autosomal recessive connective tissue disorder caused by *COH1* gene mutations): autistic features may be relatively common (Karpf et al. 2004)
o) Duchenne muscular dystrophy: 3.1% of patients with ASDs (Hendriksen and Vles 2008)

iv. Metabolic cause associated with autism
a) Mitochondrial cytopathies: 7% of patients with ASDs (Oliveira et al. 2005)
b) Untreated phenylketonuria: an autism frequency of 2.7–5.6% in affected individuals (Baieli et al. 2003; Steiner et al. 2003)
c) Sanfilippo syndrome: prominent behavioral disturbance in affected individuals (Neufeld and Muenzer 2001)
d) Adenylosuccinate lyase deficiency: autistic features in about one-third of patients (Spiegel et al. 2006)

2. Idiopathic autism (inherited autism of unknown cause)
a. Family studies indicates genetics play the major causative role in most individuals with "idiopathic" autism (90–95%)
b. Epidemiologic studies
i. A prevalence of 5–10 cases of classic autism per 10,000 (3–6 per 1,000 if the entire spectrum of autism is included)
ii. A male-to-female ratio of 3:1
a) The preponderance of males suggests an X-linked disorder
b) Linkage to the X chromosome suggested by recent genome-wide screens, although the data are inconsistent
c) Male-to-male transmission of autism in multiplex families (families with more than a single affected family member) ruled out X-linkage in these families
d) No significant associations of autism to Y chromosome based on Y haplotype analysis, although Y chromo some abnormalities have been documented
c. Classification of idiopathic autism
i. Essential autism
a) Defined by the absence of physical abnormalities
b) Seen in about 70% of children with idiopathic autism
c) Associated with better outcome overall
d) More likely a male
e) A higher sibling recurrence risk
ii. Complex autism
a) Defined by the presence of dysmorphic features (microcephaly and/or a structural brain malformation)
b) Seen in about 30% of children with idiopathic autism
c) Associated with a poorer prognosis
d) A lower male-to-female ratio
e) A lower sibling recurrence risk
d. Evidence suggesting genetic basis of autism without a diagnosable cause
i. 25% rate of recurrence in siblings of affected individuals from family studies: much greater than the prevalence rate in the general population
ii. Greater than 60% rate of concordance for classic autism in monozygotic twins, compared with no concordance found between dizygotic twins
e. The identity and the number of genes involved in autistic disorders: remained unknown
i. Multigenic
a) Similar autistic phenotypes may arise from different genes or gene combinations in different families (single-mutation genetic heterogeneity)

b) Example: tuberous sclerosis caused by *TSC1* on chromosome 9q in some families and *TSC2* on 16p in others

ii. Polygenic
   a) Several synergistically acting genes in an affected individual's genome may be required to produce the full autistic phenotype
   b) Lowering of a theoretical threshold by certain sets of genes acting in concert to allow the development of autism, either by themselves or given the right set of environmental or immunologic modifiers
   c) Other related developmental disorders in family members presumed to have inherited some of the susceptibility genes found in the affected family member or to have the same set of susceptibility genes without exposure to the same environmental "trigger factors" for autism

3. Search for candidate genes
   a. Cytogenetics: scrutinize the region involved in visible breakpoints, translocations, duplications, inversions, and deletions for the presence of genes that potentially may be involved in the pathogenesis of autistic spectrum disorders
   b. Whole genome search: microsatellite markers screening in multiplex family uncovers specific chromosomal regions that affected individuals inherit more often than predicted by chance
4. Genes for a monogenic hereditable form of autism (Caglayan 2010; Lintas and Persico 2009)
   a. Neuroligins (*NLGN3*, *NLGN4*) (located at Xq13 and Xq22.33, respectively): gene mutations noted in 1% of individuals with ASDs (Jamain et al. 2003; Lintas and Persico 2009)
   b. *Shanks3* gene (located at 22q13.3): mutations cause ASDs with phenotype characterized mainly by severe verbal and social deficits (Moessner et al. 2007; Aneja and Tierney 2008)
   c. Neurexin 1 gene (*NRXN1*) (located at 2q32): mutations identified in individuals with autism (Yan et al. 2008)
   d. Methyl-CpG-binding protein 2 gene (*MeCP2*) (located at Xq28): de novo mutations occur in 80% of female patients with Rett syndrome
   e. The homeobox A1 gene (*HOXA1*) (located at 7p15.3): autism noted in some patients (Bosley-Salih-Alorainy syndrome) (Herman et al. 2007)
   f. The phosphatase and tensin homologue gene (*PTEN*) (located at 10q23): reported in individuals with macrocephaly and autism (Butler et al. 2005; Herman et al. 2007; Buxbaum et al. 2007)

Clinical Features

1. Early signs of infants with autism (Miles et al. 2005)
   a. Do not care to be held or cuddled
   b. Do not reach out to be picked up
   c. Often "colicky" and hard to console
   d. Typically quieting more readily when left alone
   e. Avoid and fail to initiate eye contact
   f. Stare into space
   g. Sleep disturbances
   h. Usually do not come to medical attention until after the 2nd year when language delays are evident
2. Natural history
   a. Onset of autism: prior to age three
   b. Gradual onset in most children with autism
   c. "Regressive" onset in about 30% of children with autism
      i. Initially begin to talk
      ii. Then often precipitously lose language and become distant
      iii. Refuse to make eye contact within a matter of days and no longer respond to his or her name
      iv. Repetitive movements may develop immediately or by 3 or 4 years of age
   d. About 25% of children who fit diagnostic criteria for autism at age 2 or 3 years
      i. Subsequently begin to talk and communicate
      ii. Blend to varying degrees into the regular school population by 6 or 7 years
   e. Remaining 75% of children with autism continue to have a life-long disability requiring intensive parental, school, and societal support
   f. Fewer than 5% of children with autism completely recover
3. Mental retardation by nonverbal IQ testing in 50–70% of children with autism

4. Seizures develop in about 25% of children with autism
5. Idiopathic autism
   a. About 30% of children have complex autism, defined by presence of the following features
      i. Dysmorphic features
      ii. Microcephaly
      iii. Structural brain malformation
   b. About 70% of children have essential autism, defined by absence of physical abnormalities
6. Behavioral impairments
   a. Impairments in social interaction: separates individuals with autism from individuals around them
      i. Unable to "read" other people, ignoring them and often strenuously avoiding eye contact
      ii. Do not comfort others or seek comfort and do not share interests with others
      iii. Usually prefers to be by himself, engaging in his own, often repetitive, activities at home
      iv. Fail to develop friendships with peers and siblings
      v. Demonstrate a marked deficit in imitating other's actions, which may impede the development of interpersonal synchrony, communication, symbolic play, and the learning of new behaviors
   b. Impairments in communication
      i. Fail to develop reciprocal communication either by speech, gestures, or facial expression in most children with autism
      ii. Fail to use eye gaze to communicate and direct attention in young children
      iii. Display stereotypic speech that may involve echolalia or unusual inflections and intonations when children with autism learn to talk
   c. Repetitive and stereotypic behaviors
      i. Staring or rocking
      ii. Toddlers may have motor "stereotypies"
         a) Movements of fingers
         b) Twirling strings
         c) Flicking pages of books
         d) Licking
      iii. Repetitive whole-body movements
         a) Spinning
         b) Running back and forth
      iv. Complex repetitive movements may last for hours
      v. Develop elaborate rituals in which the order of events, the exact words, and the arrangement of objects must be followed
   d. Other symptoms
      i. Hyper- and hyposensitivities to sensory stimulation of all types (e.g., visual, auditory, tactile, and pain)
      ii. Odd behaviors around foods and their presentation
      iii. Abnormal sleep patterns
      iv. Tantrums and/or self-injurious and aggressive behaviors brought on by a change in routine, an offending touch, or no apparent reason
      v. Impaired motor development with toe walking early in life and general clumsiness
      vi. Total disregard for danger, resulting in high risk of early death, most commonly from drowning
7. Diagnostic criteria for autistic disorder (adapted from DSM-IV) (American Psychiatric Association 1994)
   a. Presence of a total of >6 of the following areas
      i. Qualitative impairment in social interaction (at least two of the following areas)
         a) Marked impairment in the use of multiple nonverbal behaviors, such as eye-to-eye gaze, facial expression body postures, and gestures, to regulate social interaction
         b) Failure to develop peer relationships appropriate to developmental level
         c) Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by lack of showing, bringing, or pointing out objects of interest)
         d) Lack of social or emotional reciprocity
      ii. Qualitative impairment in communication (at least one of the following area)
         a) Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
         b) Marked impairment in the ability to initiate or sustain a conversation with others in individuals with adequate speech
         c) Stereotyped and repetitive use of language, or idiosyncratic language

d) Lack of varied, spontaneous make-believe, or social imitative play appropriate to developmental level

iii. Restrictive repetitive and stereotypic patterns of behavior, interests, and activities (at least one of the following area)

a) Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus

b) Apparently inflexible adherence to specific nonfunctional routines or rituals

c) Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)

d) Persistent preoccupation with parts of objects

b. Delays or abnormal functioning with onset prior to age 3 years (at least one of the following area)

i. Social interaction

ii. Language as used in social communication

iii. Symbolic or imaginative play

c. The disturbance is not better accounted for by Rett syndrome or childhood disintegrative disorder

8. Differential diagnosis with other pervasive developmental disorders

a. Asperger disorder (Asperger 1944; Frith 1991; Miles et al. 2010)

i. A variant of autism typically occurring in high-functioning individuals without mental retardation

ii. Whether Asperger syndrome is the expression of the high end of the autism spectrum or a discrete genetic entity is unclear

iii. Language development

a) Develops better than classic autism

b) Problems with the semantic and pragmatic use of language

iv. Requires all other DSM-IV diagnostic criteria for autism

v. Other characteristics

a) Misdiagnosed early on and in adulthood as odd or eccentric

b) Generally loners

c) Uncomfortable in groups

d) Unable to empathize with others

e) Does not chat

f) Follow a literal interpretation of speech with no understanding of idioms or jokes

g) Maintain a sameness in routine, follow strict rules

h) Have an encompassing preoccupation with one domain, such as the weather or computers

i) Speech may be pedantic or repetitive with odd intonations

j) Clumsiness: common

k) IQ must be within the normal range to qualify for the diagnosis

b. Childhood disintegrative disorder (Heller syndrome)

i. Behavioral, cognitive, and language regression between ages 2 and 10 years after entirely normal early development

ii. Lose previously acquired language, social, and play skills

iii. Cognitive skills usually impaired significantly

iv. The condition may resemble autism in clinical presentation but differs from autism in the pattern of onset, course, and outcome

v. No longer considered one of the pervasive developmental disorders

c. Pervasive developmental disorder, not otherwise specified (PDD-NOS)

i. Onset after age 3 years

ii. Children with autistic symptoms who do not meet full criteria in all three diagnostic domains can be diagnosed with PDD-NOS

a) Includes children with milder symptoms of all three autism diagnostic criteria and those meeting full criteria for autism in two of the three domains

b) Used as an initial or tentative diagnosis for younger children or before diagnostic evaluations are completed

Diagnostic Investigations

1. Cytogenetic studies and molecular genetic analyses (Filipek et al. 2000; Miles et al. 2010)

a. High-resolution or multi-FISH telomere chromosome studies

i. Chromosomal abnormality involving the proximal long arm of chromosome 15

(15q11-q13) observed in more than 1% of autistic individuals. Duplication is usually maternally derived, with one or two extra copies of the area roughly corresponding to the typical Angelman syndrome/Prader–Willi syndrome deletion region:
  a) Pseudodicentric 15 (inverted duplication 15)
  b) Atypical marker chromosomes
ii. Other chromosome abnormality: Cytogenetic abnormalities have been found on virtually every chromosome in individuals with autism

b. aCGH
i. Has replaced high-resolution chromosome analysis as the test of choice for the evaluation of any child with an autism spectrum disorder
ii. Cytogenetic analysis, in addition to aCGH, is recommended when the family history suggests transmission of a balanced chromosome rearrangement

c. Molecular genetic testing (*FMR1*) for full mutations and premutations for fragile X syndrome: unlikely positive in the presence of high-functioning autism

2. Metabolic studies: positive in probably less than 5% of children with autism
a. Metabolic evaluation
i. Quantitative plasma amino acids
ii. Quantitative urine organic acids
iii. Purines, creatine, and guanidinoacetate in the urine
iv. Serum concentration of lactate, pyruvate, creatine kinase, and uric acid

b. Increased serum serotonin in about one-third of individuals with autistic disorder
c. Toxicologic studies
d. Review of child's newborn screening test results
e. Further studies are needed to determine the prevalence of mitochondrial respiratory chain disorders in autism, especially those with recurrent setbacks, hypotonia, and failure to thrive

3. Electrophysiologic studies: epileptiform EEG abnormalities in autistic children with a history of regression and seizures

4. Neuroimaging (MRI) of the brain
a. Indicated when the history and physical examination or neurologic examination suggests a localized lesion, tuberous sclerosis complex, Joubert syndrome, or an early environmental insult
b. Its routine use is controversial because of the expense and need for sedation or anesthesia by an anesthesiologist

Genetic Counseling

1. Recurrence risk
a. Patient's sib
i. Secondary autism: The recurrence risk is based on information relevant to the primary diagnosis. For example,
  a) Supernumerary isodicentric 15q chromosome: no increased recurrence risk since it is a de novo occurrence
  b) Duplication of proximal 15q: an increased recurrence risk since it may result from segregation of a parental chromosome translocation or a maternally derived interstitial 15q duplication
ii. Idiopathic autism
  a) The empiric aggregate risk to sibs of individuals with autism of unknown cause varies across studies but is generally considered to range from 5% to 10% for autism and 10% to 15% for milder symptoms, including language, social, and psychiatric disorders (Bolton et al. 1994; Lauritsen et al. 2005; Miles et al. 2005; Landa 2008; Selkirk et al. 2009)
  b) For families with $\geq$2 children: the recurrence risk approaches 35% (Ritvo et al. 1989)
iii. Essential autism (Miles et al. 2005)
  a) For male sibs (brothers) of a proband with essential autism: a 7% of risk for autism and an additional 7% risk for milder autism spectrum symptoms
  b) For female sibs (sisters) of a proband with essential autism: a 1% risk for autism and an unknown risk for a milder autism spectrum disorder
iv. Complex autism (Miles et al. 2005): the sib recurrence risk of a proband with complex autism
  a) One percentage for autism
  b) An additional 2% for a milder autism spectrum disorder

b. Patient's offspring: no available data

2. Prenatal diagnosis: may be available for the specific etiology for families at risk of having a child with a chromosomal disorder, copy number variant, or a single gene disorder
3. Management
   a. General goals of treatment
      i. Improve language and social skills
      ii. Decrease stereotypic and disruptive behaviors
      iii. Support parents and families in their adjustment and to educate their children
      iv. Foster independence
   b. Early intervention programs focused on developing the following areas:
      i. Language
      ii. Cognitive and imitation skills
      iii. Social responsiveness
      iv. Appropriate behavior
   c. Behavior modification programs (Prater 2002)
      i. Structure the environment
      ii. Provide consistent responses to behaviors
      iii. Reward a desired behavior (positive reinforcement)
      iv. No reward for undesirable behavior (negative reinforcement)
      v. Apply an adverse stimulus to deter an unwanted response (punishment)
      vi. Reinforcing closer and closer approximations to the desired behavior (shaping)
   d. School-aged children with autism (Bennetto and Rogers 2001)
      i. Need a curriculum that is tailored to individual strengths and needs
      ii. Effective education programs
         a) Well-structured, systematic teaching routines
         b) Consistency and repetition
         c) Concrete and functional learning objectives
   e. Adolescents and adults with autism (Bennetto and Rogers 2001)
      i. Need specific help in vocations and avocations in adult life
      ii. Social skills groups
      iii. Recreational activities
      iv. Individual psychotherapy
      v. Vocational coaching and assistance
   f. Medications: No medications are autism-specific
      i. Antidepressants: Selective serotonin reuptake inhibitors with some success in treating preoccupations, ritualized behaviors, and mood disorders and anxiety
      ii. Stimulant medications: little or no clinical improvement to decrease the activity levels and to improve the attention span of some children
      iii. Antipsychotic medications: New atypical antipsychotic medications may be useful in treating aggressive and hyperactive behavior with fewer side effects
      iv. Anticonvulsant medications: used to treat individuals with autism who suffer from seizures and may be effective in decreasing aggressive behavior and episodic behavioral outbursts, particularly in children with seizure disorder
   g. Treatments for core symptoms of autism spectrum disorders (Levy et al. 2009)
      i. Socialization
         a) Educational curricula (Myers 2009)
         b) Communication and language (Paul 2008): didactic and intensive training, and Milieu teaching
         c) Social-skills training (Seida et al. 2009)
         d) Behavioral treatment (Rogers and Vismara 2008): discrete trial instruction, pivotal response training, and relationship development intervention
      ii. Communication
         a) Communication intervention (Paul 2008): within a comprehensive program (e.g., pivotal response training, or other center), social pragmatics approach, and parent training
         b) Augmentative and assistive communication (Schlosser and Wendt 2008): picture exchange communication system, sign language, and assistive technology (e.g., vocal output devices)
         c) Behavioral (e.g., play, reciprocal communication) (Ospina et al. 2008): Floor time/developmental, individual differences, relationship-based approach, applied verbal behavior
         d) Educational (Myers 2009)
      iii. Behavior
         a) Behavioral intervention (Ospina et al. 2008): discrete trial instruction, and

other comprehensive programs using applied behavior analysis
b) Psychopharmacology (King and Bostic 2006): Selective serotonin reuptake inhibitors, anticonvulsants, atypical antipsychotics, α-2 agonists

h. Complementary and alternative medical treatments (Hess et al. 2008)
i. Biological
a) Supplements – e.g., vitamin B6 or magnesium ion, dimethyl glycine, and cod-liver oil
b) Anti-infectives – e.g., antibiotics, antifungals, and antivirals
c) Immunoglobulins
d) Off-label drugs – e.g., secretin
e) Chelation medications
f) Gastrointestinal medications
g) Elimination or special diets – e.g., gluten free or casein free
h) Hyperbaric oxygen administration
ii. Non-biological
a) Auditory integration training
b) Chiropractic therapy
c) Craniosacral manipulation
d) Facilitated communication
e) Massage and qigong
f) Interactive metronome
g) Reiki
h) Transcranial stimulation
i) Yoga

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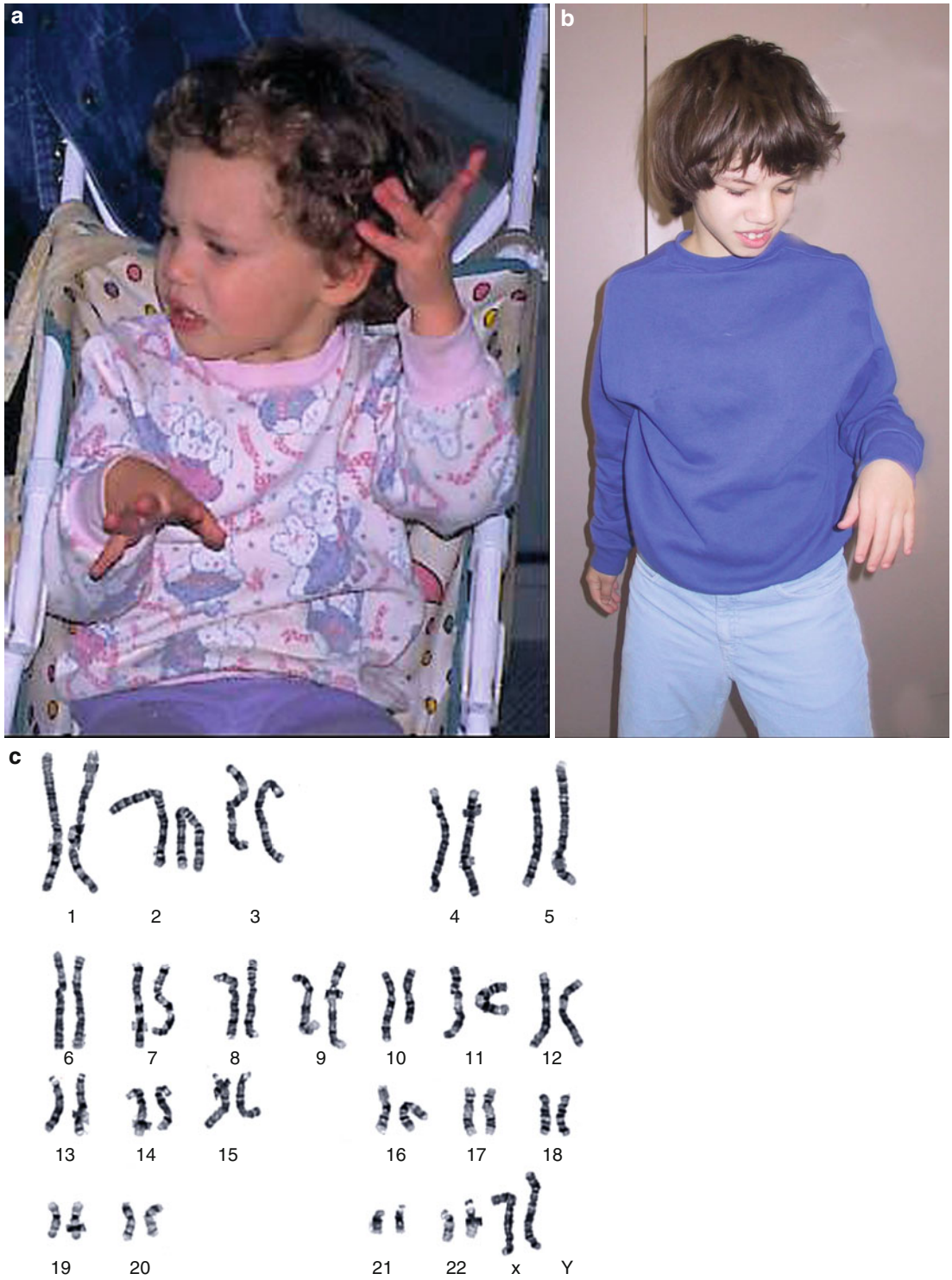

Fig. 1 (**a**–**c**) A girl (at 4 years and 10 years) with autism. Her chromosome study showed a balanced translocation between the short arm of chromosome 3 and the long arm of the chromosome 10 [t(5;10)(p13;q21)] (karyotype shown). Her parents had normal chromosomes

Fig. 2 A 11-year-old girl with autism. During infancy, she did not pay attention to people or environment and often staring into space. She had echolalia and smiled without reason. She walked in time, but had reported spinning, flapping, and rocking

Bannayan–Riley–Ruvalcaba Syndrome

In 1960, Riley and Smith described a mother and her four children with macrocephaly and pseudopapilledema due to a mutation in a single autosomal gene. In 1971, Bannayan described a 3-year-old girl with macrocephaly and numerous subcutaneous lesions ranging from lipolymphangio-hemangiomas to vascular hamartomas. This syndrome was felt to be related to the one reported earlier by Riley and Smith since both lipomatosis and hemangiomatosis are hamartomatous malformations. In 1980, Ruvalcaba, Myhre, and Smith described two patients with macrocephaly, mental retardation, pigmented spotting of the glans penis and shaft, and multiple polyps of the gastrointestinal tract. The cases described by Bannayan, Riley, Ruvalcaba, Myhre, and Smith were later known as the Bannayan–Riley–Ruvalcaba syndrome (BRRS) when Gorlin and colleagues in 1992 coined the term based on evidence of overlap of these syndromes, and later would be linked to mutations in the *PTEN* gene, which also causes Cowden syndrome (CS).

Currently, BRRS and CS are considered to be a single entity, with a phenotypic spectrum caused by mutations of the *PTEN* gene, referred to as the *PTEN* hamartoma tumor syndrome.

Synonyms and Related Disorders

PTEN hamartoma tumor syndrome

Genetics/Basic Defects

1. *PTEN* (Phosphatase and Tensin homolog deleted on chromosome 10), a tumor suppressor gene on 10q23.3, has been identified as the susceptibility gene for two hamartoma syndromes, BRRS and CS. Although distinct phenotypically, these two disorders display partial clinical overlap.
2. *PTEN* encodes a dual specificity phosphatase with homology to the focal adhesion molecules tensin and auxilin
3. Germline mutations in the *PTEN* are found in approximately 85% of individuals with classic Cowden Syndrome and in 65% of individuals with BRRS and in other disorders (20%) (Proteus syndrome, Proteus-like syndrome) which are collectively referred to as the "*PTEN* hamartoma tumor syndrome" (PHTS)
4. These phenotypically diverse disorders share several overlapping clinical features and a common genetic etiology, which has led to their gene based classification of PHTS (Marsh et al. 1998, 1999). The broad, apparently difficult to predict, clinical manifestations of PHTS mandate thorough and meticulous phenomic analysis to ensure recognition and then proper diagnosis of patients who are at risk of developing neoplasia (Orloff and Eng 2008)

Clinical Features

1. Clinical feature: Review (Gorlin et al. 1992)
   a. Macrocephaly with a normal ventricular system is common to all BRRS patients
   b. Downslanting of the palpebral fissures (60%)
   c. Strabismus or amblyopia (15%)
   d. Schwalbe lines (35%)
   e. Birth weight above the mean and body length above the 97th percentile in most cases

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f. Hypotonia, mild mental retardation, gross motor delay, and speech delay (50%)
   i. Motor delay is, for the most part, transient, and improves with time
   ii. Irreversible myopathic disease in 60% of patients
   iii. Speckling of the glans penis and shaft, cutaneous angiolipomas, lymphangiomyomas, angiokeratomas, joint hyperextensibility, pectus excavatum, scoliosis, and accelerated growth of the metacarpals and of the first and second phalanges (50%)
g. Subcutaneous lipomas (75%)
h. Hemangiomas and cafe´ au lait spots of the trunk and lower extremities (10%)
i. Hamartomatous polyps (45%): limited to the ileum and colon leading to rectal bleeding and intussusception

2. Several clinical features common to CS (Marsh et al. 1999)
   a. Hashimoto's thyroiditis
   b. Vascular malformations
   c. Mental retardation
   d. Main differential features with BRRS
      i. Pigmented macules of the glans penis and shaft, and delayed motor development: seen in BRRS but not seen in CS patients
      ii. Lipomatosis common in BRRS: rarely seen in patients with CS
3. No agreed international criteria for the diagnosis of BRRS exist
   a. Criteria of diagnosis by Marsh et al. (1999) with at least following four features
      i. Macrocephaly
      ii. Lipomatosis
      iii. Hemangiomas
      iv. Speckled penis in males
   b. Criteria by Parisi et al. (2001) with at least two of the following three features
      i. Macrocephaly
      ii. Hamartomas (including at least one lipoma, hemangioma or intestinal polyp)
      iii. Penile macules in males
4. Differential diagnosis
   a. Cowden syndrome
      i. A complex disorder with malignant and benign (hamartomatous) lesions affecting derivatives of all three germ cell layers, affecting the breast, thyroid, uterus, brain, and mucocutaneous tissues
      ii. The lifetime risk for breast cancer: estimated to be 25–50%, with an average age of diagnosis between 38 and 46 years old
      iii. The risk for thyroid cancer (typically follicular, but occasionally papillary) is approximately 10%, while the risk for endometrial cancer, although not well established, has been estimated to be 5–10%
      iv. Associated with germline mutations in *PTEN* (80% in Cowden syndrome probands ascertained by the strict operational diagnostic criteria for Cowden syndrome)
   b. Proteus syndrome and Proteus-like syndrome
      i. A highly variable disorder involving congenital malformations, hamartomatous overgrowth of multiple tissues, connective tissue and epidermal nevi, and hyperostoses which affect patients in a mosaic pattern
      ii. Consensus diagnostic criteria available (Biesecker et al. 1999)
      iii. While initially thought to be unrelated to Cowden syndrome or Bannayan–Riley–Ruvalcaba syndrome, at least two independent reports have identified germline *PTEN* mutations in approximately 20% of patients with Proteus syndrome
      iv. Furthermore, approximately 50% of patients with a Proteus-like syndrome (with significant features of Proteus syndrome, but not meeting diagnostic criteria) were also found to have germline *PTEN* mutations (Zhou et al. 2001)
      v. Thus, at least a subset of Proteus syndrome and Proteus syndrome-like conditions are allelic to Cowden syndrome and Bannayan–Riley–Ruvalcaba syndrome, and are part of the *PTEN* hamartoma tumor syndrome spectrum
   c. Juvenile polyposis syndrome (JPS)
      i. An autosomal dominant disorder
      ii. Characterized by predisposition for hamartomatous polyps in the gastrointestinal tract, specifically in the stomach, small intestine, colon, and rectum
      iii. Untreated polyps lead to bleeding and anemia

iv. Malignant transformation can occur though most juvenile polyps are benign
v. Approximately 20% of individuals with JPS have mutations in the *MADH4* gene and approximately another 20% of individuals with JPS have mutations in the *BMPR1A* gene (Howe et al. 1998, 2001)

d. Peutz–Jeghers syndrome (PJS)
i. An autosomal dominant disorder
ii. Characterized by the association of gastrointestinal polyposis and mucocutaneous pigmentation
iii. Characteristics of polyps
a) Most prevalent in the small intestine but also occur in the stomach and large bowel
b) Often symptomatic with intussusception and rectal bleeding
c) The pigmentation of the perioral region is pathognomonic, particularly if it crosses the vermilion border
d) Hyperpigmented macules on the fingers are also common
e) Molecular genetic testing of *STK11/LKB1* reveals disease-causing mutations in approximately 70% of individuals who have a positive family history and 20–70% of individuals who have no family history of PJS.

Diagnostic Investigations

1. Imaging studies to define extent of the neoplasms
2. *PTEN* molecular genetic diagnosis by full sequencing available on clinical basis
   a. Diagnosis of PHTS made only when a *PTEN* mutation is identified
   b. Detectable *PTEN* gene mutation
      i. 60% of individuals meeting the diagnostic criteria of BRRS
      ii. 80% of individuals meeting the diagnostic criteria for CS
      iii. Preliminary data available suggest that up to 50% of individuals with a Proteus-like syndrome and up to 20% of individuals with Proteus syndrome have *PTEN* mutations

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. 50% if one parent is affected
      ii. Recurrent risk probably negligible if neither parent has the *PTEN* mutation found in the proband since germline mosaicism has not been reported
   b. Patient's offspring: 50%
2. Prenatal diagnosis
   a. Possible for pregnancies at increased risk by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15–18 weeks' gestation or chorionic villus sampling at approximately 10–12 weeks' gestation if the disease-causing allele of an affected family member has been identified
   b. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified in an affected family member
3. Management
   a. Cancer surveillance: the most important aspect of management of an individual with a *PTEN* mutation
      i. Annual physical examination from age 18 years
      ii. Annual urinalysis
      iii. Baseline colonoscopy at age 50 years
   b. Molecular testing of asymptomatic at-risk relatives to identify those who have a family-specific *PTEN* mutation and ensure appropriate surveillance

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Fig. 1 The patient, a 6-year-old Caucasian female, was seen for difficulty in walking. She complained significant pain in the *left* lower leg with prominent veins associated with intermittent swelling for the past 4 years. The physical examinations and various imaging studies revealed *left* lower extremity vascular malformation causing significant pain syndrome, swelling, limb dysfunction and gait disturbance and multiple lipomas. The patient was found to have a PTEN deletion which was performed at other institution. The molecular testing confirmed the clinical diagnosis of Bannayan–Riley–Ruvalcaba syndrome. The family history revealed multiple family members affected with lipomatosis (mother, maternal great aunt, and a first cousin)

Fig. 2 Note the vascular malformation affecting *left* lower extremity

Fig. 3 A lipoma noted on the *right* axillary region

Fig. 4 A lipoma noted on the scalp

Fig. 5 A diffuse lipoma noted on the *right* side of the anterior neck

Fig. 6 A lipoma noted on the back of the neck

Fig. 7 A diffuse lipoma noted on the *left* side of the back

Beckwith–Wiedemann Syndrome

The Beckwith–Wiedemann syndrome (BWS) is the most common and the best-known congenital overgrowth syndrome. It was named after Beckwith who, in 1963, described three unrelated patients with exomphalos, hyperplasia of the kidneys and pancreas, and adrenal cytomegaly. Wiedemann in 1964 reported a familial form of omphalocele with macroglossia. The incidence is estimated to be about one in 13,700 births.

Synonyms and Related Disorders

Exomphalos-macroglossia-gigantism syndrome; Wiedemann-Beckwith syndrome

Genetics/Basic Defects

1. Genetics of BWS: complex (Engel et al. 2000)
   a. Pedigree data
      i. Sporadic (85%)
      ii. Familial (15%): autosomal dominant inheritance with variable expressivity, incomplete penetrance, and preferential maternal transmission
   b. Karyotypic data
      i. Chromosome rearrangements influenced by the parent of origin (2%)
         a) Paternally derived 11p15.5 duplications exhibiting atypical clinical features as well as a significant risk of developmental delay
         b) Maternally derived translocations and inversions exhibiting typical features of Beckwith–Wiedemann syndrome
      ii. Normal karyotype (98%)
   c. Molecular data: BWS is caused by alterations in growth regulatory genes on chromosome region 11p15.5, which is subjected to genomic imprinting (an epigenetic mechanism in which gene expression is altered according to the parental origin of the allele).
2. Pathogenesis (Ferry 2010)
   a. Imprinted genes have been implicated in the pathogenesis of both familial and sporadic BWS
   b. A subgroup of BWS patients has loss of methylation at a differentially methylated region (KvDMR1) within the *KCNQ1* gene centromeric to the *IGF2* and *H19* genes
   c. Maternally expressed 11p genes
      i. *CDKN1C* (also known as $P57^{KIP2}$): a member of the cyclin-dependent kinase inhibitor family: a candidate for a maternally expressed growth inhibitory gene in BWS
         a) Germline mutations detected in >40% of familial cases
         b) Mutations infrequent (<5%) in sporadic cases
      ii. *H19*: a maternally expressed gene encoding a biologically active nontranslated mRNA that may function as a tumor suppressor. Deletion of *H19* or transposition from its usual position relative to *IGF2* disrupts normal imprinting.
      iii. *KCNQ1* (also known as *KvLQT1*): serves as an imprinting center, disruption of which could affect transcription and DNA replication through an effect on chromatin structure.
   d. Paternally expressed 11p genes
      i. *IGF2* (the gene for insulin-like growth factor-2): a paternally expressed and

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maternally imprinted embryonic growth factor. Many sporadic cases show loss of imprinting of *IGF2* resulting in biallelic expression.

ii. *KCNQ1OT1* gene (also known as *LIT1*): The unmethylated paternal allele of *KvDMR1* permits transcription of the antisense transcript *KCNQ1OT1* and silencing of the *KCNQ1* and *CDKN1C* genes (Murrell et al. 2004).

e. Effect of multiple genes: combination of increased expression of paternally expressed growth promoter genes such as *IGF2* and loss of maternally expressed growth suppressor genes in some patients with paternal uniparental disomy of 11p15

f. Uniparental disomy (mosaic paternal isodisomy) for the band 11p15.5 (10–20% of sporadic cases)

i. Two paternally derived copies of chromosome 11p15 and no maternal contribution for that chromosome region

ii. Resulting from postzygotic mitotic recombination and mosaic paternal isodisomy

iii. All patients with uniparental disomy exhibit somatic mosaicism

3. Clinical findings relevant to molecular etiology (Weksberg et al. 2010)

a. Tumor development

i. Individuals with UPD of 11p15.5 or gain of methylation at the H19. Imprinting center (IC) carry the highest risk to develop Wilms tumor or hepatoblastoma.

ii. Individuals with loss of maternal methylation at IC2 carry a lower tumor risk; as well, the tumors in this molecular subgroup do not include Wilms tumor.

iii. Individuals with mutations in *CDKN1C* seem to have the lowest risk with only a small number of cases reported. In cases with *CDKN1C* mutation, only neuroblastoma has been reported to date.

b. Hemihyperplasia in cases of BWS: Alterations have included mosaicism for UPD 11p15.5 with hemihyperplasia and or molecular alterations at IC2 or IC1.

c. Positive family history: associated with mutations in *CDKN1C* or microdeletions of IC1 and very rarely IC2

d. Omphalocele: associated with an IC2 defect or *CDKN1C* mutation

e. Developmental delay: associated with cytogenetically detectable duplications involving the paternal copy of chromosome 11p15.5

f. A severe BWS phenotype

i. This seems to be associated, at least in certain cases, with very high levels of paternal chromosome 11p15.

ii. An increased frequency of female monozygotic twins discordant for BWS has been reported. These females usually show loss of methylation at IC2.

iii. In contrast, the less frequently observed male monozygotic twins show a broad spectrum of BWS-associated molecular alterations.

g. Sterility/assisted reproductive technologies (ART)

i. This seems to be associated with an increased risk of BWS cases with loss of methylation at IC2.

ii. No specific aspect of subfertility or its treatment has been specifically associated with the increased risk of epigenetic defects associated with BWS after ART.

Clinical Features

1. Variable phenotypic expression (Shuman et al. 2010)
2. Prenatal and postnatal overgrowth (gigantism) (cardinal feature)
   a. Fetus grows at an increased rate during the latter half of pregnancy
   b. Large or above normal size baby at birth
   c. Eventual somatic gigantism in most cases
   d. Advanced bone age
   e. Hemihyperplasia or hemihypertrophy (13%)
3. Performance
   a. Development
      i. Usually normal unless there is chromosome 11p15.5 duplication or serious perinatal complications such as prematurity or uncontrolled hypoglycemia.
      ii. Mild-moderate mental retardation from undetected hypoglycemic episodes during infancy
      iii. Hypoglycemia
         a) Reported in 30–50% of babies with BWS
         b) Likely caused by islet cell hyperplasia and hyperinsulinemia
   b. Seizures in some cases

4. A recognizable facial gestalt: common but often normalizes across childhood
   a. Macroglossia (cardinal feature)
      i. Chronic alveolar hypoventilation
      ii. Anterior open bite
   b. Earlobe grooves or indented ear lesions on the posterior rim of the helix or concha
   c. Facial nevus flammeus
   d. Midfacial hypoplasia
   e. Prominent eyes with infraorbital creases
   f. Full lower face with a prominent mandible
   g. Prominent occiput
5. Abdominal wall defect
   a. Omphalocele (cardinal feature)
   b. Umbilical hernia
   c. Diastasis recti
6. Gastointestinal anomalies
   a. Malrotation anomalies
   b. Dome-shaped defect of the diaphragm
7. Visceromegaly
   a. Fetal adrenocortical cytomegaly: pathognomonic finding for BWS
   b. Hepatomegaly (frequent)
   c. Nephromegaly (frequent)
   d. Cardiomegaly that resolves spontaneously
   e. Occasional clitoromegaly
   f. Hyperplastic pancreas, bladder, uterus, and thymus
8. Neoplasms: overall risk for tumor development in children with BWS estimated at 7.5%
   a. Benign tumors
      i. Adrenal adenoma
      ii. Carcinoid tumor
      iii. Fibroadenoma
      iv. Fibrous hamartoma
      v. Ganglioneuroma
      vi. Myxoma
   b. Malignant tumors: predisposition to embryonal malignancies
      i. Wilms tumor (most frequent)
      ii. Hepatoblastoma
      iii. Adrenocortical carcinoma
      iv. Rhabdomyosarcoma
      v. Neuroblastoma
      vi. Glioblastoma
      vii. Malignant lymphoma
      viii. Pancreatoblastoma
      ix. Teratoma
   c. Clinical findings associated with higher risks of tumor development
      i. Hemihyperplasia
      ii. Nephromegaly
      iii. Nephrogenic rests
9. Additional features
   a. Polyhydramnios
   b. Prematurity
   c. Enlarged placenta
   d. Hemangioma
   e. Other renal anomalies
      i. Medullary dysplasia
      ii. Duplicated collecting system
      iii. Nephrocalcinosis
      iv. Medullary sponge kidney
      v. Cystic changes
      vi. Diverticula
10. Adult phenotype
   a. Hemihyperplasia
   b. Prominent jaw
   c. Enlarge tongue
   d. Ear creases and pits
   e. Enlarged kidneys and other abdominal organs
   f. Normal height
11. Major and minor findings associated with BWS (Weksberg et al. 2010)
   a. Major findings
      i. Abdominal wall defect: omphalocele (exomphalos) or umbilical hernia
      ii. Macroglossia
      iii. Macrosomia (traditionally defined as height and weight >97th percentile)
      iv. Anterior ear lobe creases and/or posterior helical pits (bilateral or unilateral)
      v. Visceromegaly of intra-abdominal organ(s); for example, liver, kidney(s), spleen, pancreas, and adrenal glands
      vi. Embryonal tumor in childhood
      vii. Hemihyperplasia
      viii. Cytomegaly of adrenal fetal cortex, usually diffuse and bilateral
      ix. Renal abnormalities, including medullary dysplasia and later development of medullary sponge kidney (MSK)
      x. Positive family history of BWS
      xi. Cleft palate
   b. Minor findings
      i. Pregnancy-related findings of polyhydramnios, enlarged placenta and/or thickened umbilical cord, premature onset of labor and delivery

ii. Neonatal hypoglycemia
iii. Nevus flammeus
iv. Cardiomegaly/structural cardiac anomalies/cardiomyopathy
v. Characteristic facies
vi. Diastasis recti
vii. Advanced bone age

Diagnostic Investigations

1. Transitory neonatal hypoglycemia (spontaneous regression during the first 4 months of life) (63%)
2. Neonatal polycythemia (20%)
3. Hypercholesterolemia, hyperlipidemia, hypothyroidism, thyroxine-binding globulin deficiency: rare occurrence
4. Periodic abdominal ultrasonography for organomegaly and embryonal tumors, followed by MRI or CT if indicated
5. Radiography
   a. Advanced bone age
   b. Chest radiography to rule out rare neural crest tumors such as thoracic neuroblastoma
6. Echocardiography for suspected cardiac abnormality
7. Chromosome analysis (high resolution and FISH studies)
   a. Normal chromosomes in most patients
   b. Chromosome abnormalities involving 11p15 in $\leq$1% of cases
      i. Paternally derived 11p15 duplication
      ii. Maternally derived translocations and inversions
8. Molecular analysis (Shuman 2010)
   a. Paternal uniparental disomy (UPD) of 11p15 in multiple tissues (10–20%)
      i. Restriction fragment length polymorphism (RFLP) analysis of multiple 11p15 loci
      ii. Methylation studies of multiple imprinted genes on 11p15
   b. Mutation analysis: *P57 ^{KIP2}* (5–10%) (screen for mutation by heteroduplex/SSCP analysis, followed by sequence of *P57 ^{KIP2}* exons)
   c. Molecular testing is typically not indicated for parents or other family members when UPD is found, as these cases arise through post-zygotic somatic recombination.
   d. Parental studies are recommended if genomic alterations are found, that is, karyotype abnormalities, *CDKN1C* mutations or microduplications or microdeletions of the 11p15.5 region (Weksberg et al. 2010).

Genetic Counseling

1. Recurrence risks (Shuman et al. 2010)
   a. Patient's sib: The risk to the sibs of a child with BWS depends on the genetic basis for BWS in the proband
      i. Probably a low recurrence risk in cases of negative family history, normal karyotype, and absence of identifiable molecular etiology
      ii. Up to 50% of recurrence risk in cases of positive family history and normal karyotype
      iii. Up to 50% recurrence risk in cytogenetically detected maternal 11p15 translocation or inversion
      iv. An undetermined recurrence risk in cytogenetically detected paternal 11p15 duplication
      v. A low recurrence risk in cases of paternal 11p15 uniparental disomy as this event arises from a post-zygotic somatic recombination
      vi. 50% recurrence risk if a *CDKN1C* mutation is present in a parent (usually maternally transmitted)
      vii. Four clinically relevant categories identified for approximately 85% of individuals with BWS who have a negative family history and a normal karyotype (Shuman et al. 2010):
         a) Proband with *KCNQ1OT1* hypomethylation (~50–60%): very low recurrence risk since no recurrences of loss of methylation at *KCNQ1OT1* have been reported in first–degree relatives of individuals with BWS who have this molecular lesion.
         b) Proband with paternal uniparental disomy for 11p15 (~10–20%): the recurrence risk is empirically very low because the UPD appears to arise from a post-zygotic somatic recombination.
         c) Proband with a *CDKN1C* mutation (~510%): Both parents should be tested for mutations. Several instances of

transmission of *CDKN1C* mutations from clinically unaffected mothers to affected offspring have been reported as well as two instances of paternal transmission from clinically unaffected fathers. The recurrence risk for such parents may be as high as 50%.

d) Proband with no identifiable primary etiology (~13–15%): The risk to members in these families is unknown but empirically low.

b. Patient's offspring (Shuman et al. 2010)
   i. Negative family history (10–20% of individuals with BWS and no known family history of BWS have paternal uniparental disomy of 11p15) and normal karyotype (5–10% of all individuals with BWS with a normal karyotype have identifiable mutations in *CDKN1C)*: ~85% of individuals with BWS
      a) *KCNQ1OT1* hypomethylation: a low recurrence risk
      b) Uniparental disomy for 11p15: likely a very low risk
      c) Identified *CDKN1C* mutation: The risk to offspring of a female with a *CDKN1C* mutation is 50%; the risk to offspring of a male with a *CDKN1C* mutation is <50%, but too few cases have been reported to generate a risk figure
   ii. Positive family history and normal karyotype: ~10–15% of individuals with BWS
      a) ~50% if transmitting parent is female
      b) <50% if transmitting parent is male
   iii. Monozygous twins (<1% of individuals with BWS): theoretically low

2. Prenatal diagnosis
   a. Indications (Weksberg et al. 2010)
      i. Families having a child with severe manifestations of BWS
      ii. If a cytogenetic or genomic abnormality (e.g., microdeletion, *CDKN1C* mutation) has been identified, prenatal testing may be indicated by CVS or amniocentesis. If such abnormalities are *de novo*, gonadal mosaicism remains a possibility. Epigenetic analysis of amniocytes can be undertaken by methylation-sensitive multiplex ligation probe analysis (MS-MLPA).
      iii. Families, for whom UPD or methylation alterations have been detected in the absence of a transmissible genomic alteration, may also wish to consider prenatal diagnostic testing even though the recurrence risk would be very low. Of note, a recent follow-up study of apparently isolated fetal omphalocele reported BWS in 20% of cases based on clinical or molecular findings (Wilkins-Haug et al. 2009).
   b. Maternal serum alpha fetoprotein screening: may be elevated in a fetus with omphalocele
   c. Prenatal Ultrasonography
      i. Fetal overgrowth (macrosomia)
      ii. Polyhydramnios
      iii. Enlarged placenta
      iv. A long umbilical cord
      v. Macroglossia
      vi. Cleft palate
      vii. Distended abdomen
      viii. Abdominal wall defects
      ix. Organomegaly
      x. Renal anomalies
      xi. Cardiac anomalies
   d. Cytogenetic studies
      i. Possible if a cytogenetic abnormality has been identified in the proband and one parent
      ii. To identify translocations, inversions, and duplications involving 11p15
   e. Molecular analysis
      i. Uniparental disomy
      ii. Mutation analysis of *CDKN1C*, provided the mutation has been documented in the previously affected child

3. Management
   a. Early detection and close monitoring for hypoglycemia to reduce the risk of central nervous system complications
   b. Partial tongue resection for cosmetic purpose and to relieve severe airway obstruction
   c. Surgical risks related to hypoglycemia or difficulty in intubation secondary to macroglossia
   d. Management of abdominal wall defects, gastrointestinal malformations, and renal anomalies
   e. Orthopedic follow-up of hemihyperplasia
   f. Management of structural renal abnormalities
   g. Management of embryonal neoplasms

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Fig. 1 (**a**–**e**) Five infants with Beckwith–Wiedemann syndrome showing hemangioma, macroglossia, and umbilical hernia

Fig. 2 (**a**, **b**) An infant with Beckwith–Wiedemann syndrome showing macroglossia, ear crease, and umbilical hernia

Fig. 3 An infant with Beckwith–Wiedemann syndrome and a large omphalocele requiring surgical intervention

Fig. 4 An infant with Beckwith–Wiedemann syndrome prior to partial glossectomy

Fig. 5 A young adult with Beckwith–Wiedemann syndrome showing macroglossia and post-surgical status of umbilical and inguinal hernia repairs

Fig. 6 (**a**, **b**) A 2-month-old infant with macroglossia and posterior ear creases, suspected of having Beckwith–Wiedemann syndrome clinically. Southern blot analysis was utilized to detect abnormal methylation in the imprinting center DMR2, which is located within the BWS critical region on chromosome 1p15. The DNA probe LIT1 was used for the analysis. Hypomethylation of LIT1 was detected. The methylation index was 0.21 (Reference range: 0.40–0.58). The results are consistent with a diagnosis of Beckwith–Wiedemann syndrome

Behcet Disease

In 1937, Behçet first described three patients with oral and genital ulceration and hypopyon. It is most common in the Middle and Far East with a prevalence of 7–8 per 100,000 people, whereas in the United States the prevalence is estimated at 4 per 1,000,000 people.

Synonyms and Related Disorders

Behcet syndrome

Genetics/Basic Defect

1. A complex multisystem inflammatory disease of unknown cause
2. Considered a relapsing and remitting vasculitis of the small- to medium-sized vessels with following protean manifestations:
   a. Aphthous stomatitis
   b. Genital ulceration
   c. Uveitis
   d. Synovitis
   e. Gastrointestinal lesions
   f. Cutaneous lesions
   g. Central nervous system lesions
   h. Cardiac lesions
   i. Vessel lesions
3. Immunopathogenic aspects of Behcet disease (Direskeneli 2001; Krause and Weinberger 2008)
   a. Neutrophil activation
   b. Cellular and humoral immunity
   c. Antigenic stimuli
      i. Herpes simplex virus
      ii. Streptococci and superantigens
      iii. Heat shock proteins (65 kDa, αβ-crystallin)
   d. Genetic predisposition to HLA-B51 and antigen presentation
   e. Retinal-S antigen and HLA-B51 as autoantigens
   f. Vascular disease and antiendothelial cell antibodies
   g. Severity and sex: more severe in men
   h. Tumor necrosis factor-α-1031C allele: associated with disease susceptibility
   i. Polymorphisms in interleukin-10 and CD28 genes: also associated with Behcet disease
   j. Association with endothelial nitric oxide synthase gene polymorphism: ethnic related

Clinical Features

1. Highly variable clinical course with recurrences and remissions
2. Recurrent attacks of oral, genital, ocular, and skin lesions
   a. Oral aphthous ulcers
      i. Keystones to diagnosis of Behcet disease according to the classification criteria
      ii. Often an initial presenting sign
      iii. Occurring on the buccal mucosa, tongue, gingiva, and the soft palate area
      iv. Minor aphthous ulcers: superficial with a diameter of 2–6 mm, appearing as multiple lesions, and developing within

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1–2 days. They heal without scarring within 7–10 days and recur at various frequencies.
v. Major aphthous ulcers: deeper and painful lesions leaving scars after healing
vi. Herpetiform aphthous ulcers: numerous lesions grouped as small ulcers

b. Genital ulcers
i. Women: located on the vulva, vagina, and cervix uteri
ii. Men: located on the prepuce and scrotum
iii. Lesions resembling the oral aphthae but tend to be deeper and leaving scars
iv. Differential diagnosis from other genital ulcers (herpes simplex, syphilis, tropical ulcers, and skin infestations)

c. Ocular lesions (70–85%)
i. Generally follow the genital and oral ulceration by a few years
ii. Characterized by severe vasculitis with arterial and venous occlusions
iii. Hypopyon (presence of leukocytes in the anterior chamber of the eye)
iv. Uveitis
v. Hemorrhagic and exudative retinal lesions (retinitis)
vi. Marked vitritis
vii. Choroiditis
viii. Bilateral nongranulomatous inflammation of the iris and ciliary body
ix. Intermittent blurring of vision and loss of vision

d. Skin lesions
i. Pustular vasculitic cutaneous lesions: may evolve as lesions of small vessel necrotizing vasculitis from a neutrophilic vascular reaction to a lymphocytic perivascular reaction
ii. Erythema nodosum-like lesions: usually occurring on the lower extremities but can be seen on the arms, neck, and face
iii. Pseudofolliculitis
iv. Papulopastular lesions: neutrophil-induced, vessel-based reaction
v. Acneiform nodules

3. Articular manifestations
a. Recurrent seronegative arthritis
i. Common findings
ii. A non-specific synovitis
b. Monoarthritis
c. Polyarthritis

4. Gastrointestinal manifestations
a. Ulcerative lesions most frequently occurring in the terminal ileum, caecum, stomach, and intestine
b. Symptoms
i. Abdominal pain
ii. Diarrhea
iii. Melena
iv. Perforation

5. CNS manifestations (about 1% of patients)
a. Headaches
b. Meningitis
c. Meningoencephalitis
d. Cranial nerve palsies
e. Peripheral nerve involvement with vasculitis
f. Cerebellar ataxia
g. Hemiplegia
h. Benign intracranial hypertension
i. Neurologic deficits
j. Cerebral aneurysm
k. Cerebral vasculitis and ischaemic stroke: unusual
l. Personality changes and depression
m. Dementia
n. Hearing and vestibular disturbances

6. Pulmonary manifestations
a. Tracheobronchial ulcerations
b. Pleurisy
c. Embolism
d. Pulmonary arterial aneurysms
e. Pneumonitis
f. Fibrosis

7. Renal involvement: rare
a. Glomerulonephritis
b. Systemic amyloidosis

8. Cardiac manifestations
a. Intracardiac thrombosis
b. Myocardial infarction
c. Pericarditis
d. Endocarditis

9. Vascular manifestations
a. Superficial thrombophlebitis
b. Deep thrombophlebitis
c. Small vessel vasculitis
d. Aneurysm

10. Criteria for clinical diagnosis of Behcet disease, proposed by O'Duffy and Goldstein in 1976, require the presence of recurrent oral or genital aphtha along with two additional systemic findings

for diagnosis and only one for the diagnosis of the incomplete form:
   a. Criteria
      i. Aphthous stomatitis
      ii. Aphthous genital ulceration
      iii. Uveitis
      iv. Cutaneous "pustular" vasculitis
      v. Synovitis
      vi. Meningoencephalitis
   b. Diagnosis: At least three criteria present, one being recurrent aphthous ulceration
   c. Incomplete form: Two criteria present, one being recurrent aphthous ulceration
   d. Exclusion
      i. Inflammatory bowel disease
      ii. Systemic lupus erythematosus
      iii. Reiter's disease
      iv. Herpetic infections
11. The International Study Group criteria were published in 1990 to include positive Pathergy test as one of the criteria to establish the diagnosis of Behcet disease (Ghate and Jorizzo 1999):
   a. Recurrent oral ulceration: minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred at least three times in one 12-month period
   b. *Plus 2 of the following criteria* (findings applicable only in absence of other clinical explanations)
      i. Recurrent genital ulceration: aphthous ulceration or scarring observed by physician or patient
      ii. Eye lesions: Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
      iii. Skin lesions: erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by physician in post-adolescent patients not receiving corticosteroid treatment
      iv. Pathergy test (a non-specific pustule that is an inflammatory reaction to needle pricks in approximately 40% of patients, especially during the exacerbation period): Pathergy test is positive when pricking a sterile needle into the patient's forearm results in an aseptic erythematous nodule or pustule that is more than 2 mm in diameter at 24–48 h.

Diagnostic Investigations

1. Positive skin pathergy test
2. Laboratory findings (Önder and Gürer 2001)
   a. Acute-phase response
      i. Raised erythrocyte sedimentation rate
      ii. Increased serum levels of C-reactive protein
      iii. Elevated plasma complement components, such as C3, C4, C9, and factor B
   b. Disease exacerbations
      i. Elevated IgG, IgA, and IgM
      ii. Elevated C-reactive protein
      iii. Elevated 2-globulin
   c. Interleukin (IL)-8 as a serological marker
3. HLA typing
4. Fluorescein angiography, color Doppler imaging and fundoscopic examination to detect retinal features
5. CT scan (Ceylan et al. 2010)
   a. Effectively demonstrates vascular system involvement that is the main cause of mortality in these patients
   b. Also effective in detecting mediastinal, pleural, and pulmonary parenchymal findings related to the disease
6. MRI and CT scan to detect the neurologic lesions
7. Histopathological features
   a. Pathergy lesions
      i. Leucocytoclastic vasculitis
      ii. Neutrophilic vascular reaction
      iii. Polymorphonuclear leucocyte infiltration
   b. Erythema nodosum-like lesions
      i. Neutrophilic vascular reaction or vasculitis in the dermis and subcutaneous tissue
      ii. Perivascular lymphocytic dermal inflammation
   c. Common histopathological lesions in all organ systems
      i. Vasculitis
      ii. Thrombosis
      iii. Perivascular infiltrates of lymphomononuclear cells
      iv. Neutrophilic vascular reaction
   d. Early cutaneous lesions: neutrophilic vascular reaction or leucocytoclastic vasculitis
   e. Late cutaneous lesions: lymphocytic perivasculitis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: not increased
2. Prenatal diagnosis: no prenatal diagnosis reported
3. Management (Alpsoy and Akman 2009)
   a. Mucocutaneous lesions
      i. Topical corticosteroids: useful for oral and genital ulcers
      ii. Colchicine
         a) Beneficial effects on the mucocutaneous symptoms, presumably by inhibiting neutrophil function
         b) The first choice for treatment of genital ulcers and/or erythema nodosum, especially in female patients
         c) Combination with benzathine penicillin: for patients who are ineffective with colchicine alone, or a male patient, or in the presence of oral ulcers with or without other mucocutaneous lesions
      iii. Treatment with thalidomide: effective for oral and genital ulcers and pseudofolliculitis
      iv. Dapson, zinc sulfate, and rebamipide: can be other choices
      v. Immunosuppressive agents, such as azathioprine and cyclosporine, and biologicals, such as IFN and anti-TNF-α agents: to control the patients with severe mucocutaneous disease or unresponsive to the respected treatments
      vi. Systemic corticosteroids: prescribed for erythema nodosum that is refractory to treatment with colchicine
   b. Ocular lesions
      i. Require special attention and aggressive treatment because of its highest morbidity
      ii. About 25% of patients eventually develop blindness despite therapeutic intervention
      iii. Topical mydriatic agents and corticosteroid drops: given for acute attacks of anterior uveitis
      iv. Colchicine: prescribed to prevent both anterior and posterior uveitis because of its high degree of efficacy and relatively low toxicity
      v. Topical injection of corticosteroids, with systemic administration in some cases: used for acute attacks of posterior uveitis
      vi. Cytotoxic agents (azathioprine, chlorambucil, and cyclophosphamide): help prevent ocular attacks in approximately 50–75% of patients
      vii. Cyclosporine: beneficial in 70–80% of patients with ocular lesions that have been refractory to the conventional therapies
      viii. Subcutaneous human recombinant interferon alpha: an effective and fairly well tolerated therapy for Behcet disease
      ix. Systemic corticosteroids: generally given in acute attacks of posterior uveitis, panuveitis, and retinal vasculitis
      x. Results from therapies: improved vision and decreased pain, saving the individual a potential enucleation
   c. Arthritis
      i. Nonsteroidal anti-inflammatory drugs and colchicine: the first choice and are effective for most cases of arthritis
      ii. Additional use of benzathine penicillin: the next step
      iii. Low dose corticosteroids and azathioprine: used in patients whose arthritis is resistant to treatment with nonsteroidal anti-inflammatory drugs, colchicine, or sulfasalazine
      iv. Interferon alfa: also highly effective
   d. Gastrointestinal lesions
      i. Sulfasalazine, corticosteroids, and azathioprine: the principal drugs
      ii. Anti-TNF-α treatments, especially infliximab: a new and effective alternative
      iii. Bowel rest: obligatory in patients with an acute abdomen and bleeding
      iv. Surgery: considered for patients with bowel perforation and intractable bleeding
   e. CNS lesions
      i. High doses of corticosteroids
      ii. Supplemented with cytotoxic agents
   f. Large-vessel lesions
      i. Treated with a combination of corticosteroids and cytotoxic agents
      ii. Anticoagulants and antiplatelet agents: used for deep venous thrombosis
      iii. Surgery for refractory large-vessel disease

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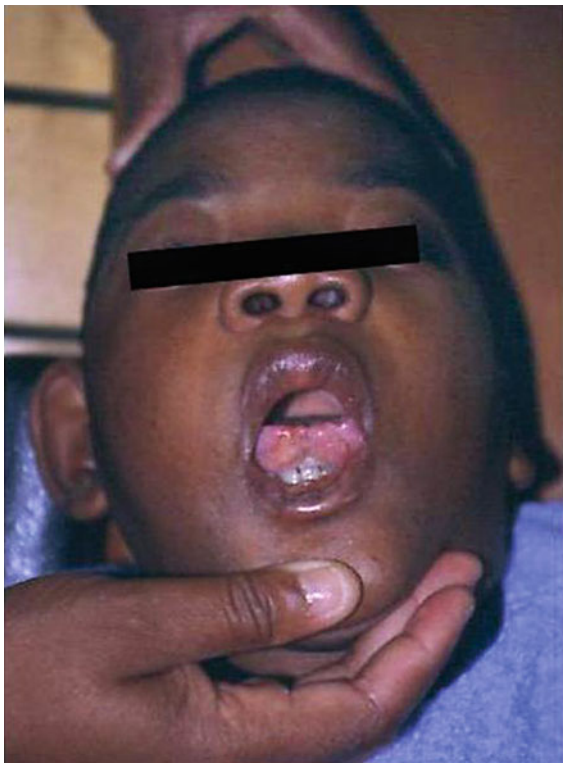

Fig. 1 Aphthae on the tongue, buccal mucosa, and gums of a child with Behcet disease

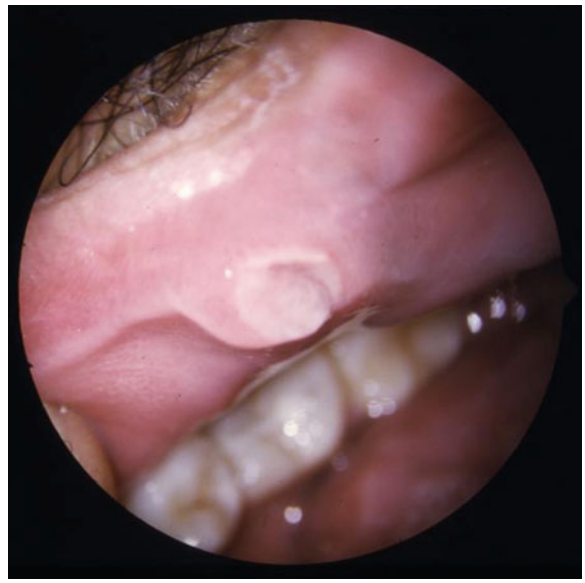

Fig. 3 A large aphthous ulcer on mucosal membrane of the lower lip of a patient with acute exacerbation of Behcet disease

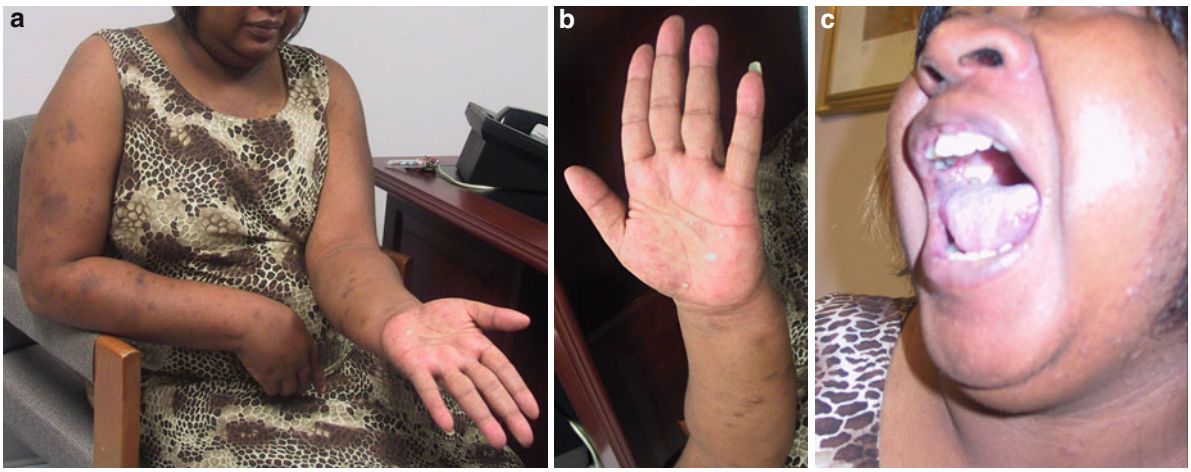

Fig. 2 (**a–c**) A female patient with Behcet disease showing generalized scars from blisters on the buccal mucosa, trunk, arms, legs, and palms

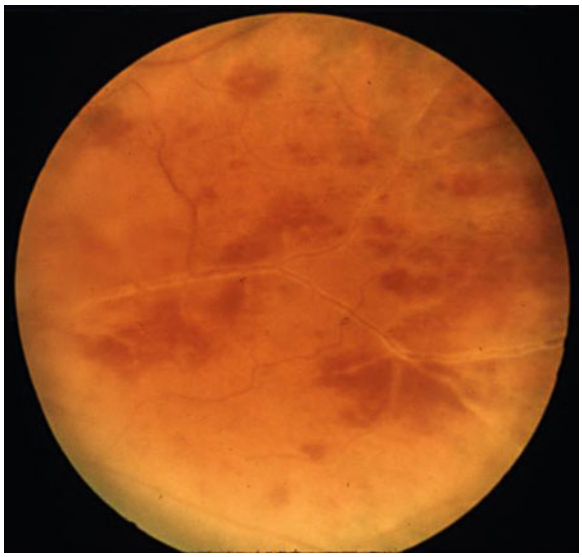

Fig. 4 Occluded retinal vessels and retinal hemorrhage with arterial and venous occlusive vasculitis in a patient with Behcet disease

Biotinidase Deficiency

In 1971, Compartz and colleagues first described multiple carboxylase deficiency responsive to biotin administration. Wolf and colleagues further characterized the infantile form of multiple carboxylase deficiency as biotinidase deficiency (BTD) in 1981.

Based on the results of worldwide screening of biotinidase deficiency (Wolf 1991), the incidence of the disorder is one in 137,401 for profound biotinidase deficiency, one in 109,921 for partial biotinidase deficiency, and one in 61,067 for the combined incidence of profound and partial biotinidase deficiency. Carrier frequency in the general population is approximately one in 120.

Synonyms and Related Disorders

Juvenile-onset multiple carboxylase deficiency; Late-onset multiple carboxylase defciency

Genetics/Basic Defects

1. An autosomal recessive disorder affecting the endogenous recycling and release of biotin (vitamin H) from dietary protein: consecutive biotin depletion resulting in low activities of biotin-dependent carboxylases and urinary excretion of organic acids characteristic of multiple carboxylase deficiency
2. Classification of biotinidase deficiency according to residual enzyme activity (Baumgartner and Suormala 1997; Wolf 2001)
   a. Profound biotinidase deficiency (residual activity $<10\%$ of mean normal value)
   b. Partial biotinidase deficiency (residual activity 10–30% of mean control value)
3. Caused by complete or partial absence of the enzyme biotinidase
4. The gene that encodes biotinidase is mapped at 3p25.

Clinical Features

1. Natural history (Wolf 2011)
   a. Individuals with biotinidase deficiency, diagnosed by newborn screening, who are treated with biotin before developing symptoms: develop normally
   b. Individuals with biotinidase deficiency who have recurrent symptoms and metabolic compromise prior to biotin treatment: develop neurologic problems
2. Untreated profound biotinidase deficiency
   a. Symptoms usually develop between ages 1 week and 10 years
   b. Clinical features, also observed in children with many other inherited metabolic disorders, include:
      i. Seizures
      ii. Hypotonia
      iii. Developmental delay
      iv. Breathing abnormalities
         a) Hyperventilation
         b) Laryngeal stridor
         c) Apnea
   c. More specific features
      i. Sensorineural hearing loss
      ii. Optic atrophy

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iii. Cutaneous symptoms
  a) Eczematous skin rash
  b) Alopecia
iv. Conjunctivities
v. Chronic and possibly lethal fungal infections (e.g., candidiasis)
vi. Ataxia

d. Symptoms encountered by older children and adolescents
i. Limb weakness
ii. Rare spastic paraparesis
iii. Scotomata

3. Children with untreated partial biotinidase deficiency: usually have mild symptoms which occur only when the child is stressed (e.g., prolonged infection, illness, fasting)

Diagnostic Investigations

1. New born screening (Wolf 2011)
   a. Utilizes a small amount of blood obtained from a heel prick for a colorimetric test for biotinidase activity (Heard et al. 1984; Wolf et al. 1985a; Heard et al. 1986; Wolf 1991)
   b. Detect virtually 100% of affected infants
   c. False positive test results in:
      i. Premature infants
      ii. Samples placed in plastic prior to sufficient drying
   d. Measure biotinidase activity in serum/plasma in infants whose initial screening tests are abnormal
2. Other laboratory findings
   a. Decreased or low normal plasma biotin concentrations in individuals with profound biotinidase deficiency
   b. In most individuals
      i. Metabolic ketolactic acidosis
      ii. Organic aciduria
      iii. Metabolic ketoacidosis
   c. Specific tests
      i. Biotinidase levels: Carriers (heterozygotes) usually have serum enzyme activity levels intermediate between those of affected and those of normal individuals (Wolf et al. 1983)
      ii. Serum ammonia
      iii. Urine organic acids
      iv. Plasma amino acids
      v. Urine ketones
      vi. Blood gas
      vii. Serum chemistries
      viii. Carnitine, and acylcarnitine profiles
3. Imaging studies: MRI of the brain (Desai et al. 2008)
   a. Cerebral edema
   b. Low attenuation of white matter signal
   c. Cerebral atrophy
   d. Compensatory ventricular enlargement
4. Other tests
   a. Ophthalmologic testing
      i. Dilated funduscopy to detect optic atrophy
      ii. Visual field testing and visual evoked potentials to detect degree of optic nerve injury
   b. Audiologic testing
      i. To detect hearing deficits in symptomatic children which can be persistent after treatment
      ii. Brainstem auditory evoked potentials to delineate the abnormality in younger children or in developmentally delayed patients
   c. EEG for seizure activities
5. Molecular Genetic testing: clinically available
   a. Targeted mutation analysis
      i. Real-time PCR of DNA from the blood spot of a newborn screen card can be used to identify a panel of common *BTD* mutations (p.Cys33PhefsX36, p.Gln456His, p.Arg538Cys, p.Asp444His), and p.[Ala171Thr;Asp444His].
      ii. These five mutations that cause profound biotinidase deficiency comprise approximately 60% of the abnormal alleles found in symptomatic individuals and in children identified by newborn screening.
   b. Sequence analysis
      i. Direct sequencing of *BTD* and its intron/exon junctions is available clinically.
      ii. Almost all individuals with partial biotinidase deficiency have the mutation p.Asp444His in one allele of *BTD* in combination with a mutation for profound deficiency in the other allele.
   c. Deletion/duplication analysis: Although deletion testing is offered clinically, no large deletions have been reported in *BTD*.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is also a carrier
2. Prenatal diagnosis possible for pregnancies at increased risk
   a. Biochemical testing (measurement of biotinidase enzyme activity in cultured amniotic fluid cells and in amniotic fluid obtained by amniocentesis) (Secor McVoy et al. 1984; Chalmers et al. 1994)
   b. Molecular genetic testing (analysis of DNA extracted from fetal cells obtained by amniocentesis or CVS), provided both disease-causing alleles of an affected family member have been identified
   c. Request for prenatal diagnosis or preimplantation genetic diagnosis is not common since biotinidase deficiency can be treated and does not affect intellect.
3. Management
   a. Biotin treatment with supplementation with oral biotin in free form
      i. Children with biotinidase deficiency identified by newborn screening: remain asymptomatic with compliance to lifelong biotin therapy
      ii. Effective in preventing symptoms (Möslinger et al. 2001; Weber et al. 2004)
      iii. Compliance with biotin therapy: improves symptoms in symptomatic individuals
   b. Medical care for developmental delay, hypotonia, spasticity, and bulbar dysfunction

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Fig. 1 A 11-month-old girl with biotinidase deficiency (0.41 nmol/mL/min) (normal, 3.66–9.21) detected by newborn screening. Her growth and development have been normal with oral biotin supplementation

Fig. 3 A 12-week-old infant boy was found to have a borderline biotinidase activity by newborn screening. DNA analysis showed a heterozygous D444H mutation and, therefore, he is a carrier

Fig. 2 A 26-month-old boy was found to have partial biotinidase deficiency by newborn screening with a biotin level of 6.3 (normal: >16). DNA analysis showed 1 copy of D444H mutation and 1 copy of G68:d7i3 mutations. His growth and developmental have been normal with oral biotin supplementation

Bladder Exstrophy

Bladder exstrophy is a rare developmental anomaly occurring as an isolated defect in about 1/25,000–1/40,000 births (Cacciari et al. 1999).

Synonyms and Related Disorders

Bladder exstrophy and epispadias complex

Genetics/Basic Defects

1. Genetics
   a. Usually an isolated defect
   b. Microduplications at 22q11.21: associated with non-syndromic classic bladder exstrophy (Draaken et al. 2010)
   c. Microduplication at 22q11.2: reported in two patients with bladder exstrophy and hearing impairment (Lundin et al. 2010)
2. Basic defects (Ives et al. 1980)
   a. Probably failure of fusion of the secondary mesoderm (from the primitive streak) in the midline of the anterior abdominal wall, with subsequent rupture of the thin wall consisting only of ectoderm and endoderm
   b. Early rupture (fifth week) resulting in exstrophy of the cloaca, later rupture (7th week) resulting in exstrophy of the bladder

Clinical Features

1. Classical bladder exstrophy (Ben-Chaim et al. 1996)
   a. Diagnosis easily made at birth
   b. Occupy 60% of the patients with the exstrophy-epispadias complex
   c. Bladder plate protruding just beneath the umbilical cord
   d. Posterior bladder wall is exposed through a midline abdominal wall defect
   e. Inferiorly displaced umbilicus located close to the superior margin of the exstrophic bladder
   f. Rectus muscles divergent on either side of the bladder
      i. Leading to the separated pubic bones
      ii. Separation of the pubic bones caused by an outward rotation of the innominate bones and eversion of the pubic rami
   g. Male patients
      i. A short epispadiac phallus with a dorsal urethral plate
         a) Caused by separation of the pubic bones
         b) Possibly caused by a true deficiency of corporeal tissue
      ii. A splayed glans
      iii. Dorsal chordee
   h. Female patients
      i. Genital defect analogous to the male but more easily reconstructed
      ii. Separated mons pubis (both hemiclitori and labia) (split clitoris and exstrophic vagina)
      iii. Predisposing to uterine prolapse, especially after pregnancy and delivery, secondary to pelvic floor defect
   i. Urinary tract abnormalities
      i. Generally normal upper urinary tract
      ii. Occasional abnormalities
         a) Unilateral renal agenesis

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b) Horseshoe kidney
c) Hydronephrosis
d) Other renal anomalies

j. Internal genitalia: usually normal
k. Fertility and childbearing
i. Documented in both sexes but less common in the males
ii. C-section advised to avoid injury to continence mechanism
iii. Postpartum uterine prolapse common because of aggravation of preexisting abnormal pelvic support
l. Inguinal hernias
i. Incidence: very common
a) 56–82% in boys
b) 11–15% in girls
ii. Incidence of bowel incarceration below 1 year of age: 10–53%
iii. Causes
a) Large internal and external inguinal rings
b) Lack of obliquity of the inguinal canal
m. Anus
i. Anteriorly placed
ii. Fecal continence adversely affected by the divergence of the pelvic musculature
n. Rectal prolapse
i. Virtually always disappears after bladder closure or cystectomy
ii. Represents an indication for surgical management of the exstrophied bladder
o. Spinal abnormalities (6.7%) (Cadeddu et al. 1997)
i. Myelomeningocele
ii. Lipomeningocele
iii. Scimitar sacrum
iv. Posterior laminal defects
v. Vertebral fusion
vi. Hemivertebrae
p. Malignancies
i. Rare late complication of bladder exstrophy, especially in untreated patients whose bladders are left exstrophic for many years
ii. Types of malignancies
a) Adenocarcinoma: the most common type, arising from the precursor cystitis glandularis, a consequence of chronic irritation and inflammation of exposed bladder mucosa
b) Squamous cell carcinoma and rhabdomyosarcoma
c) Adenocarcinoma developing adjacent to the ureterointestinal anastomoses in patients with urinary diversions that mix the urinary and fecal streams
d) The risk of developing colon adenocarcinoma is increased 7,000-fold after ureterosigmoidostomy among patients younger than 25 years of age than the general population
q. Behavioral, social, and school competency problems observed in 70% of adolescents and 33% of school aged children
r. 70% of parents express concern about the children's sexual function or sexual disfigurement
s. Consider all patients with exstrophy-epispadias complex to be latex-sensitive

2. Variants of exstrophy (Cerniglia et al. 1989)
a. Pseudo-exstrophy (exstrophic abdominal wall defect without bladder exstrophy)
b. Duplicate exstrophy
c. Superior vesical fistula and fissure
d. Covered exstrophy and visceral sequestration

Diagnostic Investigations

1. General assessment
2. Cardiopulmonary assessment
3. Renal ultrasound for baseline examination of the kidneys since increased bladder pressure after bladder closure can lead to hydronephrosis and upper urinary tract deterioration (Yerkes 2009)
4. Voiding cystourethrogram (Yerkes 2009)
a. To rule out bilateral vesicoureteral reflux which is present in nearly all patients with classic bladder exstrophy
b. Performed in early childhood to assess bladder capacity in preparation for continence reconstruction

Genetic Counseling

1. Recurrence risk (Ben-Chaim et al. 1996)
a. Patient's sib: The risk of recurrence of exstrophy or epispadias in a given family is 1 of 275 births

   b. Patient's offspring: The risk of a parent with exstrophy producing a child with exstrophy or epispadias is up to 1 of 70 or 500 times the risk of the general population
2. Prenatal diagnosis possible by ultrasonography
   a. Absence of bladder filling in the presence of normal kidneys (bladder never demonstrated on the ultrasound) (71%)
   b. A protuberance on the lower abdomen representing the exstrophied bladder (47%)
   c. A diminutive penis with anteriorly displaced scrotum (57% of the males)
   d. A low-set umbilical insertion (29%)
   e. Abnormal widening of the iliac crests (18%)
   f. Separation of the pubic rami
   g. Difficulty in ascertaining the sex of the fetus
3. Management
   a. Supportive management
      i. Ligate umbilical cord with suture to avoid bladder mucosal damage by an umbilical clamp
      ii. Protect bladder
         a) With clear plastic wrap
         b) Irrigate the bladder surface with sterile saline each time diaper is changed and the wrap replaced
      iii. Initiate prophylactic antibiotics
   b. Goals of the reconstruction of bladder exstrophy (Grady et al. 1999)
      i. Preservation of the kidney function
      ii. Creation of urinary continence
      iii. Reduction in the urinary tract infections
      iv. Creation of functionally and cosmetically acceptable external genitalia
   c. Initial bladder closure
      i. Closure of the pelvic ring
         a) Important for the initial closure
         b) Important for the eventual attainment of urinary continence
      ii. Pelvic osteotomy
         a) Two main approaches: posterior iliac osteotomy and the anterior innominate osteotomy
         b) Reduce the tension on the suture lines to help securing the bladder closure
         c) To restore the pelvic anatomy and thus increase the chances of eventual continence and reduce the likelihood of uterine prolapse
   d. Epispadias repair
      i. Usually performed at 2–3 years of age before the continence procedure
      ii. Contributing significantly to the development of bladder capacity
      iii. Goals
         a) Reconstruction of the urethra and glans penis
         b) Encourage the potential of penile length
         c) Correction of the dorsal chordee
         d) Achieving adequate skin coverage
      iv. Penis is generally reconstructible to cosmetically and functionally acceptable form, despite a short phallus
   e. Bladder neck reconstruction
      i. Usually performed at age of 4–5 years (when toilet training is possible)
      ii. Require anti-reflux procedure since all exstrophy patients have vesicoureteral reflux
      iii. Complete urinary drainage achieved with ureteral stents and suprapubic cystostomy tubes
   f. Ureteral reimplantation
   g. Bladder augmentation and continent diversion for patients who have failed bladder neck reconstruction and have an inadequate bladder capacity
   h. Alternatives for exstrophy reconstruction
      i. For patients with very small bladder plates or hydronephrosis
      ii. Ureterosigmoidostomies
         a) Allow children to achieve continence
         b) Protect upper urinary tracts
         c) Potential complications: recurrent acute and chronic pyelonephritis, urolithiasis, hyperchloremic hypokalemic metabolic acidosis, ureteral obstruction and the late development of colonic malignancy
   i. Repair of inguinal hernias at the time of primary closure of bladder exstrophy

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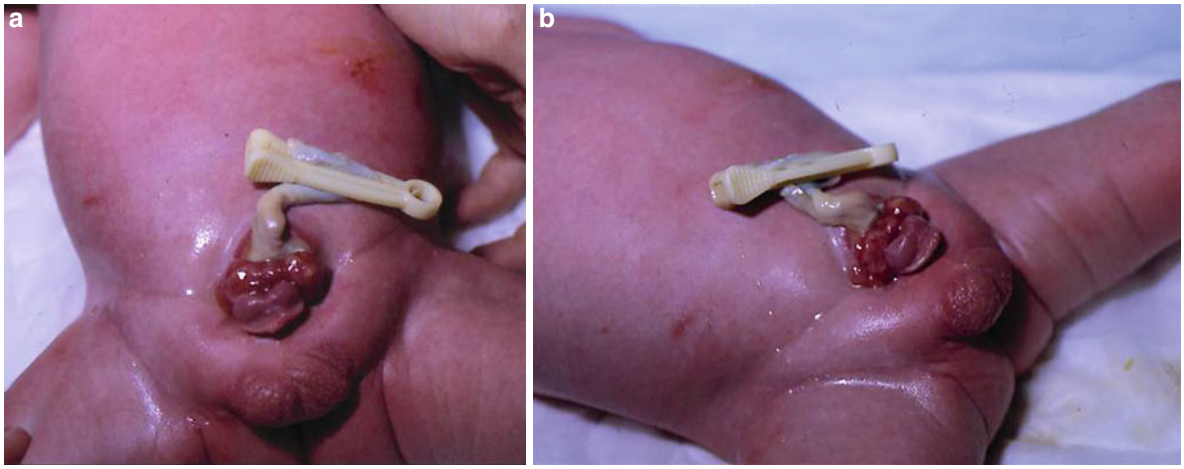

Fig. 1 (**a**, **b**) A newborn male with classic bladder exstrophy showing low insertion of the umbilical cord, a bulging mass of exstrophic bladder, and grossly abnormal external genitalia

Blepharophimosis, Ptosis, and Epicanthus Inversus Syndrome

In 1921, Komoto reported the first case, known today as blepharophimosis-ptosis-epicanthus inversus syndrome (BPES), with the triad of wide set eyes, ectropion, excessive brow hair, and hypoplasia of the caruncle and the relatives with similar phenotypic features. Later that year, Dimitry described a family with above triad and traced the pedigree of "blepharophimosis syndrome," apparently transmitted in an autosomal dominant manner for the first time. In 1971, Kohn added telecanthus to the triad of this syndrome.

Synonyms and Related Disorders

BPES with Duane retraction syndrome; BPES with/without ovarian failure

Genetics/Basic Defects

1. An autosomal dominant disorder
   a. No known affected family members in about one quarter of cases
      i. New mutation cases
      ii. Minimal expression in affected relatives
   b. A significant number of patients with no identifiable family history of BPES
2. BPES gene *FOXL2*
   a. Mapped to chromosome 3q22–23
   b. Recently mutation of *FOXL2* has been described as a cause of BPES
3. Two forms of BPES
   a. BPES type I
      i. Characterized by hypogonadism and infertility in affected females
      ii. Complete penetrance
      iii. Transmission by males as fertility in affected females is reduced
   b. BPES type II
      i. Not associated with female infertility
      ii. Incomplete penetrance
      iii. Transmission occurs in both males and females
4. *FOXL2* encodes for a transcription factor that is expressed predominantly in the developing eyelid and in the ovary.
5. Mutations of *FOXL2*: detected in patients with both type I and type II BPES
6. Genotype–phenotype correlation
   a. BPES type I: predicted to be the result of a truncated protein either lacking or containing the forkhead domain
   b. BPES type II: predicted to be the result of duplications, within or downstream of the forkhead domain, or other mutations resulting in an extended protein
7. MRI studies of BPES type I patients demonstrate the possible role of *FOX2* in the differentiation of the superior levator muscle of the eyelid.

Clinical Features

1. Clinical triad
   a. Blepharophimosis (profound small and narrow horizontal palpebral fissure): morphologically defined as reduction of both the horizontal and vertical dimensions of the palpebral fissure
   b. Ptosis of the eyelids: severe, bilateral, and symmetric

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   c. Epicanthus inversus (a small skinfold which arises in the lower lids and runs upward)
2. Other ocular associations
   a. Patients often assume a chin up, head tilt backward position to clear their visual axis.
   b. Patients often present with raised arched eyebrows because of recruitment of frontalis muscle to compensate for ptosis and visual field defect.
   c. Associated with telecanthus (normal interpupillary distance with abnormally wide intercanthal distance)
   d. Abnormalities of the eyelid margin and lacrimal drainage apparatus
   e. A high incidence of amblyopia
   f. Strabismus
   g. Microphthalmos
   h. Optic disc colobomas
3. Non-ocular associations
   a. Infertility in women with type I BPES due to premature ovarian failure which is defined as the onset of menopause before the age of 40 years
      i. Normal menarche followed by oligomenorrhea and later amenorrhea in most women with BPES type I
      ii. Fertile in early reproductive years
      iii. Soon leading to either ovarian resistance to gonadotrophins or true premature ovarian failure
      iv. Usually with normal secondary sexual characteristics
   b. Broad flat nasal bridge
   c. High-arched palate
   d. Protruding or cup-shaped ears
   e. Cardiac defects
   f. Mental retardation (controversial)
4. Natural history of BPES
   a. Epicanthal folds and telecanthus: improve significantly with time
   b. Ptosis and blepharophimosis: do not improve with time
5. Differential diagnosis
   a. Blepharophimosis
      i. As an isolated clinical finding
      ii. As part of a number of congenital syndromes
   b. Ohdo syndrome
      i. A sporadic condition
      ii. Blepharophimosis
      iii. Ptosis
      iv. Dental hypoplasia
      v. Partial deafness
      vi. Mental retardation
   c. Observed in several aneuploidies such as chromosome 3p deletion (blepharophimosis, ptosis)
   d. Fetal alcohol effects

Diagnostic Investigations

1. Diagnosis based on clinical findings which are present at birth
2. Detection of premature ovarian failure
   a. Secondary amenorrhea
   b. Endocrinologic evaluation of hypergonadotrophic hypogonadism
      i. Elevated follicle-stimulating hormone
      ii. Elevated luteinizing hormone
      iii. Decreased serum concentration of estradiol and progesterone
   c. Ultrasound studies
      i. Small hypoplastic uterus
      ii. Streak ovaries
      iii. Early on, normal presence of primordial follicle but without normal follicular development
      iv. Later on, presence of scars in place of primordial follicles when progress into true premature menopause
3. *FOXL2* mutations detectable in up to 75% of affected individuals

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Low recurrence risk when parents are not affected and do not have a *FOXL2* mutation. However, Germline mosaicism has been observed in BPES and demonstrated at the molecular level.
      ii. 50% risk if a parent is also affected
   b. Patient's offspring
      i. A 50% recurrence risk for an affected individual to have an affected offspring
      ii. Affected female individuals with type I BPES may have infertility

2. Prenatal diagnosis
   a. Available by DNA analysis from fetal cells obtained via amniocentesis (during 15–18 weeks of gestation) and chorionic villus sampling (10–12 weeks of gestation)
   b. Preimplantation genetic diagnosis may be available for families.
   c. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.
   d. These tests, however, are not commonly done for BPES.
3. Management
   a. Crucial to distinguish two types of BPES to address the infertility issues with patients and for genetic counseling of female patients of child-bearing age
   b. Endocrine and gynecologic evaluation and management recommended in affected females
      i. Hormone replacement therapy as needed
      ii. Need to address concerns of infertility such as adoption or ovum donation for premature ovarian failure
      iii. Referral to a clinical geneticist for an appropriate genetic workup and counseling
   c. Complex and requires coordination required among several specialists, including pediatric ophthalmologist, oculoplastic surgeon, pediatric endocrinologist, reproductive endocrinologist, gynecologist, and genetic counselor
   d. Treatment goals for an ophthalmologist
      i. Promote normal visual development
      ii. Improve cosmesis
      iii. Alleviate abnormal chin-up posture
   e. A comprehensive ophthalmic examination
      i. Visual acuity
      ii. Refraction
      iii. Ocular movements
   f. Diagnosis and treatment of amblyopia and strabismus crucial
   g. Ptosis repair: usually addressed after medial canthoplasty
   h. Timing of surgery for congenital ptosis: controversial
      i. Weighing the balance of early surgery to prevent amblyopia
      ii. Late surgery to allow for more reliable ptosis measurement, which provides a better surgical outcome

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Fig. 1 A father and a daughter. Both have blepharophimosis, ptosis, and epicanthus inversus of both eyes

Fig. 2 A post-surgically repaired 15-year-old girl who had bilateral blepharophimosis, bilateral ptosis, and bilateral epicanthus inversus at birth

Body Stalk Anomaly

Body stalk anomaly, sometimes also called limb body wall complex, is a rare abdominal wall defect due to failure of the development of the body stalk. Prevalence is estimated to be 0.32 per 10,000 births.

Synonyms and Related Disorders

Limb body wall complex

Genetics/Basic Defects

1. Sporadic occurrence in most cases, although concordance in twins has been reported
2. Failure in body folding in cranial, caudal, and lateral axes during the embryonic stage of development (Hiett et al. 1992)
   a. Abnormalities of cranial folding leading to pentalogy of Cantrell consisting of the following:
      i. Cardiac abnormalities
      ii. Sternal cleft
      iii. Upper abdominal defect
      iv. Anterior diaphragmatic hernia
      v. Deficiency of the diaphragmatic pericardium
   b. Abnormalities of caudal folding leading to the following:
      i. Cloacal exstrophy
      ii. Hypogastric omphalocele
      iii. Imperforate anus
      iv. Partial colonic agenesis
      v. Agenesis of one umbilical artery
   c. Abnormalities of lateral folding leading to midline omphalocele
   d. Abnormalities of folding along all three axes resulting in a body stalk anomaly
      i. Failure to obliterate the extraembryonic cavity that continues to communicate with the intraembryonic cavity
      ii. Creation of a large ventral wall defect that is covered by an amnioperitoneal membrane which contains the abdominal viscera and inserts directly into the chorionic plate
      iii. The fetus appearing to be directly attached to the placenta as the umbilical cord is significantly shortened or absent
      iv. Frequent kyphoscoliosis due to limited truncal flexion
3. Possible causes of the anomaly (Becker et al. 2000):
   a. Early amnion rupture before obliteration of the extraembryonic coelom
   b. Abnormal splitting of the embryo at the fourth gestational week
   c. Disturbance of the blood flow due to vascular rupture, as described in cocaine users
   d. A special situation in monozygotic twins
   e. Maternal uniparental disomy of chromosome 16 in a fetus with body stalk anomaly suggesting placental insufficiency or imprinting effects as cause of this anomaly (Chan et al. 2000)
4. Pathogenesis (de Silva et al. 2001)
   a. The umbilical cord, derived from a small mass of mesoderm (body stalk), attaches the embryo to the wall of the blastocysts.

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   b. Abnormal development of the body stalk resulting in an absent or rudimentary umbilical cord
   c. Consequences
      i. Direct attachment of fetus to the placenta
      ii. Abdominal viscera lying in a sac outside the abdominal cavity covered by amnion

Clinical Features

1. A large anterior abdominal wall defect with a large omphalocele
   a. Outside the abdominal cavity containing thoracic and/or abdominal organs
   b. Covered by amnion
   c. Appears continuous with (adherent to) the placental membranes
2. Absent, rudimentary, or extremely short umbilical cord. A severe type of short umbilical cord syndrome may be a variant of the body stalk anomaly.
3. Two-vessel cord
4. Severe kyphoscoliosis
5. Placenta directly attached to the amnioperitoneal sac
6. Extensive associated anomalies (Giacoia 1992)
   a. Hypoplasia of the lungs
   b. Anal atresia (imperforate anus)
   c. Agenesis of the colon
   d. Intestinal atresia
   e. Exstrophy of the cloaca
   f. Vaginal atresia
   g. Agenesis of uterus and gonads
   h. Absence of external genitalia
   i. Hypoplastic kidneys
   j. Absence of diaphragm
   k. Diaphragmatic hernia
   l. Spina bifida
   m. Dysplastic thorax
   n. Occasional coexistence of the syndrome with limb malformations (mostly lower extremities) and amniotic bands
7. Fetal death caused by abruptio placentae
8. Live-born infant die shortly afterward

Diagnostic Investigations

1. Radiography to document skeletal anomalies
2. Cytogenetic analysis
   a. No specific anomaly
   b. Placental karyotyping: report of a case with placental trisomy 16 and maternal uniparental disomy (UPD)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: not surviving to reproductive age
2. Prenatal diagnosis
   a. High maternal serum alpha fetoprotein
   b. Ultrasonography
      i. Can be diagnosed as early as the first trimester by transvaginal sonography
      ii. A large abdominal anterior wall defect with abdominal organs in a sac outside the abdominal cavity in apparent continuity with (adherent to) the placental membranes
      iii. An extremely short or absent umbilical cord
      iv. Severe kyphoscoliosis
      v. Polyhydramnios
      vi. Oligohydramnios
      vii. Two-vessel cord
      viii. Sonographic signs alone expect an unequivocal poor prognosis
   c. Amniocentesis
      i. Elevated amniotic fluid alpha feto-protein level
      ii. Abnormal acetylcholinesterase
      iii. Normal chromosomes
3. Management: newborn with the body stalk anomaly, uniformly fatal

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Fig. 1 An extremely premature neonate with body stalk anomaly. Short umbilical cord (7.5 cm with 5 cm fused with placenta) and a large amnioperitoneal sac between the abdomen and the placenta are evident. The sac was filled with internal viscera. In addition, there were anal and urethral atresia, rectovesical fistula, left renal agenesis, lumbosacral meningomyelocele, severe scoliosis, and lumbosacral hypoplasia

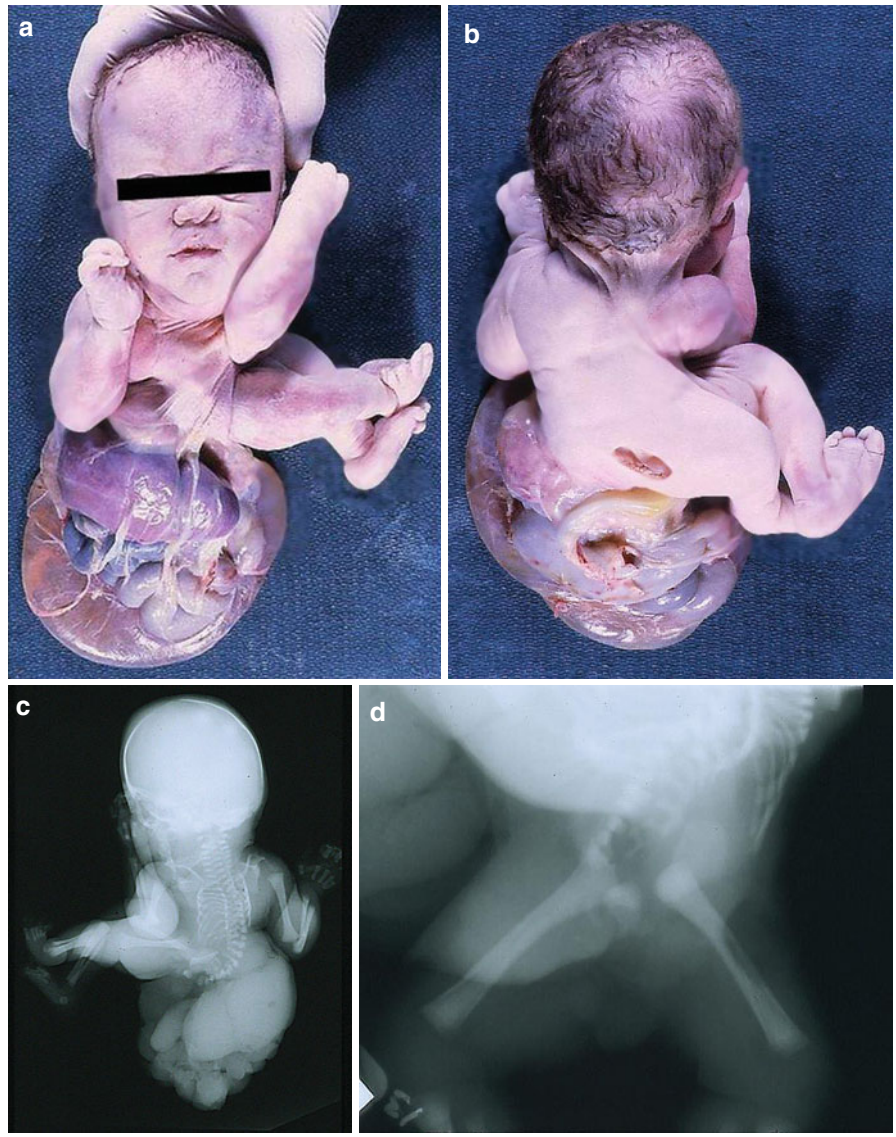

Fig. 2 (**a**–**d**) An infant with body stalk anomaly showing Potter facies, severe kyphoscoliosis, and a large amnioperitoneal sac outside the body. The sac contained abdominal organs. The umbilical cord was absent. Limb and vertebral defects illustrated in the radiographs

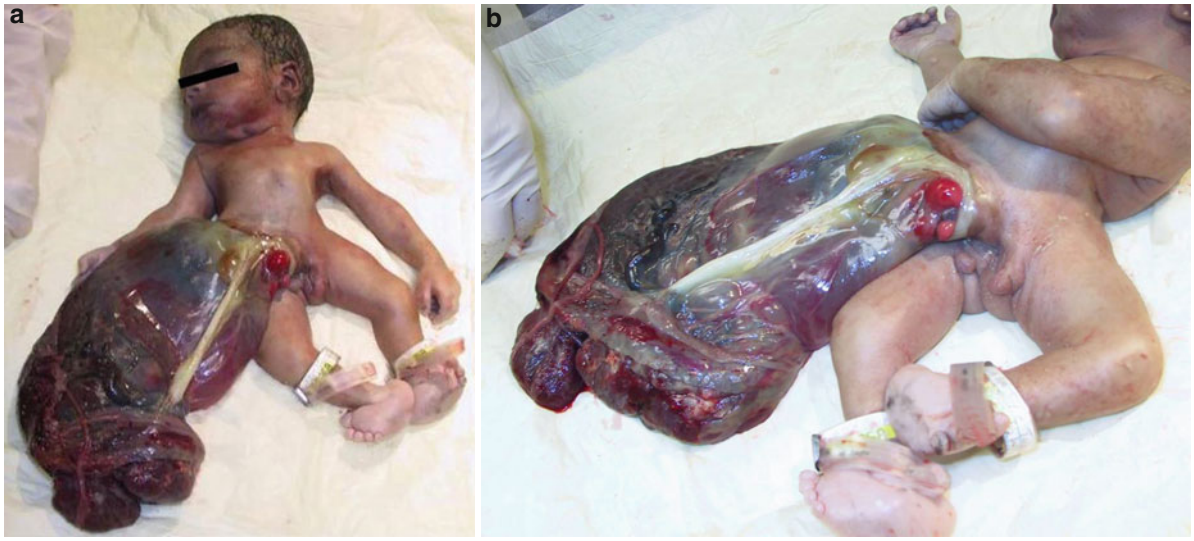

Fig. 3 (**a**, **b**) Another infant with body stalk anomaly showing anterior abdominal wall defect with a large sac containing abdominal organs, exstrophy of the bladder, and clubfeet

Brachydactyly

Brachydactyly, a general term for short digit, refers to disproportionately short fingers and toes and forms part of the group of limb malformations characterized by bone dysostosis. Dysostoses refer to abnormalities of individual bones, either in isolation or in combination with various abnormally formed bones. Dysostosis are usually static and arise during blastogenesis (first 8 weeks of embryonic life) versus osteochondrodysplasias that usually present at a later stage of development, typically affect the skeleton in general, and may continue to evolve as a result of continuous gene functioning throughout life.

Brachydactyly can occur either as an isolated malformation or as a part of a complex malformation syndrome. To date, many different forms of brachydactyly have been identified. Some forms also result in short stature. In isolated brachydactyly, subtle changes elsewhere may be present. Brachydactyly may also be accompanied by other hand malformations, such as syndactyly, polydactyly, reduction defects, or symphalangism.

Synonyms and Related Disorders

Brachydactyly type A1 (Farabee type); Brachymetatarsus IV; Kirner deformity (dystelephalangy); Sugarman brachydactyly; Type 2 (Mohr-Wriedt type); Type A3 (brachydactyly-clinodactyly); Type A4 (Temtamy type); Type A5; Type B; Type C (Haws type); Type D (stub thumb); Type E

Genetics/Basic Defects

1. Isolated brachydactyly: the inheritance is mostly autosomal dominant with variable expressivity and penetrance
2. Causative gene defect identified in the majority of isolated brachydactylies and some syndromic forms of brachydactyly
3. Genomics of isolated brachydactyly
   a. Brachydactyly type A1 BDA1
      i. Caused by mutations in the Indian hedgehog (*IHH*) gene located on chromosome 2q35-36. This supports the hypothesis that *IHH* plays a pivotal role in normal human skeletogenesis.
      ii. Another locus for this phenotype, designated *BDA1B* has been identified on chromosome 5p13.3-p13.2
   b. Brachydactyly type A2 (BDA2)
      i. Caused by mutation in the human bone morphogenetic protein receptor 1B gene (*BMPR1B*) on chromosome 4q21-q20, that affects cartilage formation in a dominant-negative manner
      ii. Sparing of the fourth finger distinguishes the Mohr-Wriedt type BDA2 from BDA2 caused by mutations in *BMPR1B* and concludes that the growth and differentiation factor 5 gene (*GDF5*) on chromosome 20q11.2 is a novel BDA2 causing gene. Mutations in *GDF5* alter the receptor binding affinities and can also cause symphalangism.

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c. Brachydactyly type A3 (BDA3): no gene or locus has yet been identified.
d. Brachydactyly type A4 (BDA4) (*HOXD13*, mapped on 2q31-q32)
   i. Mutations in the homeobox containing gene (*HOXD13* on chromosome 2q31-q32) can give rise to limb malformations with variable expressivity and a wide spectrum of clinical manifestations including synpolydactyly and brachydactylies types D and E.
   ii. The term "HOXD13 limb morphopathies" for the spectrum of limb disorders caused by *HOXD13* mutations was suggested based on a link between *HOXD13* and two additional limb phenotypes – syndactyly type V and brachydactyly type A4.
e. Brachydactyly type B (BDB)
   i. Caused by heterozygous truncating mutations in the receptor kinase-like orphan receptor 2 gene (*ROR2*) on 9q22 in the majority of cases
   ii. Patients affected with the distal mutations have a more severe phenotype than those with the proximal mutations.
   iii. Homozygous *ROR2* mutations are associated with an extreme form of brachydactyly, with extensive hypoplasia of the phalanges and metacarpals/metatarsals and absence of nails. In addition, there are vertebral anomalies, brachymelia of the arms, and ventricular septal defect, making up the manifestations of the Robinow syndrome, which also has been shown to be caused by mutations in *ROR2*.
   iv. Different mutations in the bone morphogenetic protein (*BMP*) antagonist NOGGIN (*NOG*, mapped on chromosome 4q23-q24) were identified in a subset of *ROR2*-negative patients with BDB and additional occurrence of proximal symphalangism and carpal synostosis.
   v. The BDB phenotype, as well as the location and nature of the BDB mutations, suggest a specific mutational effect that cannot be explained by simple haploinsufficiency.
f. Brachydactyly type C (BDC) (*CDMP1*, mapped on 20q11.2)
   i. Caused by heterozygous mutations of cartilage-derived morphogenetic protein 1 (*CDMP1*), also known as growth/differentiation factor-5 gene (*GDF5*), resulting in loss of function
   ii. Factors other than locus heterogeneity, such as genetic modifiers and/or environmental factors, must play a role in phenotypic variability.
   iii. Non-penetrance in a mutation carrier of heterozygous mutations was identified in additional families with BDC.
   iv. A novel missense mutation was described in the prodomain of *CDMP1* indicating an important function of the prodomain for the folding, secretion, and availability of biologically active *CDMP1*.
   v. Homozygous mutations of *CDMP1* cause the Hunter-Thompson form of chondrodysplasia, a recessive condition that is characterized by severe acromesomelic limb shortness.
g. Brachydactyly type D (BDD): associated with mutations in HOXD13 (Johnson et al. 2003)
h. Brachydactyly type E (BDE) (*HOXD13*, mapped on 2q31-q32)
   i. Brachydactyly type E as an isolated abnormality has not been mapped with confidence.
   ii. The occurrence of brachydactyly type E was one feature of what appeared to be a contiguous gene syndrome due to a cytogenetically visible de novo deletion of 2q37.
   iii. Missense mutations in the homeodomain of *HOXD13* in two cases with distinctive limb phenotypes exhibiting overlap with BDD and BDE have been described.
i. Brachymetatarsus IV: no gene or locus for Kirner deformity has yet been identified.
j. Sugarman brachydactyly: no gene or locus for Kirner deformity has yet been identified.
k. Kirner deformity: no gene or locus for Kirner deformity has yet been identified.

Clinical Features

1. Types of isolated brachydactyly
   a. Brachydactyly type A: shortening is confined to middle phalanges.

i. Brachydactyly type A1 (BDA1) (Farabee type brachydactyly)
   a) Variable short or rudimentary middle phalanges of all digits which are occasionally fused with terminal phalanges
   b) Short proximal phalanges of the thumbs and big toes
   c) An autosomal dominant trait
ii. Brachydactyly type A2 (BDA2) (Mohr-Wriedt type brachydactyly)
   a) Characterized by hypoplasia/aplasia of the second middle phalanx of the index finger and sometimes little finger
   b) Characteristic triangular-shaped middle phalanx ("delta phalanx") in the index fingers and second toes
   c) Radially curved index finger in severely affected cases
   d) Malformation of the proximal phalanx of big toes resulting in fibular deviation of the distal phalanx, while all other toes have rudimentary middle phalanges causing tibial deflection of their distal phalanges
   e) An autosomal dominant trait
iii. Brachydactyly type A3 (BDA3) (brachymesophalangy V, brachydactyly-clinodactyly)
   a) Characterized by shortening of the middle phalanx of the little finger
   b) Slanting of the distal articular surface of the middle phalanx leads to radial deflection of the distal phalanx.
   c) Not always associated with clinodactyly. A single flexion crease of the little finger indicates a short or absent middle phalanx.
   d) This type should be differentiated from other types of crooked little fingers, namely, Kirner deformity and camptodactyly; in the former, there is radial bowing of the terminal phalanx due to curving of its shaft. Camptodactyly is a flexure contracture deformity of the interphalangeal joints.
   e) An autosomal dominant trait with reduced penetrance
iv. Brachydactyly type A4 (BDA4) (brachymesophalangy II and V, Temtamy type brachydactyly)
   a) Brachymesophalangy affecting mainly the second and fifth digits
   b) When the fourth digit was affected, it showed an abnormally shaped middle phalanx leading to radial deviation of the distal phalanx.
   c) The feet also showed absence of middle phalanges of the lateral four toes.
   d) Rare autosomal dominant trait
v. Brachydactyly type A5 (BDA5) (absent middle phalanges of digits 2–5 with nail dysplasia)
   a) Absence of the middle phalanges and nail dysplasia with duplicated terminal phalanx of the thumb
   b) This type can be included in type B brachydactyly.

b. Brachydactyly type B (BDB)
   i. Absence or hypoplasia of the terminal parts of the index to little fingers with complete absence of fingernails
   ii. Intact thumbs frequently showing flattening, splitting, or duplication of the distal phalanges
   iii. Less severely affected digits on the radial side of the hand compared to those on the ulnar side
   iv. Similarly but less severely affected feet
   v. Symmetric deformity
   vi. Accompanied by soft tissue syndactyly, symphalangism, carpal and/or tarsal fusions, and shortening of metacarpals and/or metatarsals
   vii. A rare hand malformation
   viii. An autosomal dominant trait with variable severity (expressivity)
c. Brachydactyly type C (BDC) (brachydactyly with hyperphalangism, Haws type brachydactyly)
   i. Characterized by brachymesophalangy of the index, middle, and little fingers and shortening of the first metacarpal
   ii. The ring finger: usually the longest digit, longer than the index finger (hyperphalangism detected on radiological examination)
   iii. The proximal phalanx of the index finger: an anomalous configuration resulting in its ulnar deflection

iv. Short metacarpals and symphalangism: occasionally present
v. The feet: either normal or show ordinary brachydactyly
vi. Inheritance: autosomal dominant with variable expressivity
vii. Presence of considerable intra- and interfamilial variation

d. Brachydactyly type D (BDD) (stub thumb)
i. Distal phalanx of the thumb alone: characteristically shortened
ii. Various degrees of thumb shortening, either unilaterally or bilaterally
iii. Base of the distal phalanx is broader than the surface of the proximal phalanx to which it articulates, and that the distal end of the bone often shows some hyperplasia.
iv. Short distal phalanx of the thumb results from early closure of its epiphyses.
v. An autosomal dominant trait with reduced penetrance

e. Brachydactyly type E (BDE)
i. Variable shortening of the metacarpals with more or less normal length of phalanges
ii. Occasional shortening of the metatarsals, resulting from hypoplastic and partially fused metacarpal epiphyses, visible on radiographs
iii. Often presence of short terminal phalanges
iv. Hyperextensibility of the hand joints: frequently a striking feature
v. Often relatively high axial triradius
vi. Mild short stature in affected individuals
vii. An isolated type E brachydactyly is inherited as an autosomal dominant trait with variable expressivity and variable involvement of the metacarpals and/or metatarsals, with frequent bilateral asymmetry.
viii. This phenotype is an example of genetic heterogeneity, because in addition to the autosomal dominant isolated type and Albright hereditary osteodystrophy, it also occurs with Turner syndrome.

f. Brachymetatarsus IV (metatarsus IV, short, toes, fourth, short)
i. Short fourth metatarsi resulting in unilateral or bilateral short fourth toes were observed in 206 persons in northeastern India with no instance of short metacarpals, distinguishing this form from BDE.
ii. An autosomal dominant trait with approximately 27% penetrance

g. Sugarman brachydactyly (brachydactyly with major proximal phalangeal shortening)
i. A new form of brachydactyly of which a conspicuous feature was a non-articulating great toe which was set dorsal and proximal to the usual position. The great toes were amputated.
ii. Very short fingers without motion at the proximal interphalangeal joints
iii. The consanguinity in the family and the presence of seven other affected members among the patient's relatives made autosomal recessive inheritance likely.

h. Kirner deformity (dystelephalangy)
i. Malformed little finger consists of radial bowing of the terminal phalanx.
ii. Tip of the little finger points toward the thenar eminence.
iii. Usually bilateral malformations
iv. An autosomal dominant trait with incomplete penetrance

2. Brachydactyly as part of a syndrome (extensive list), for example:
a. Autosomal recessive Robinow syndrome
b. Rubinstein–Taybi syndrome
c. Albright hereditary osteodystrophy
d. Brachydactyly type E with hypertension
e. du Pan syndrome

3. Prognosis
a. Strongly dependent on the nature of the brachydactyly
b. May vary from excellent to severely influencing hand function
c. Often depends on the nature of the associated anomalies if brachydactyly forms part of a syndromic entity

Diagnostic Investigations

1. Radiographic studies
a. To document brachydactyly of hands and feet
b. To document other skeletal anomalies

2. Analysis of affected family members
3. Mutation studies

Genetic Counseling

1. Recurrence risk: The nature of genetic counseling depends both on the pattern of inheritance of the type of brachydactyly present in the family and on the presence or absence of accompanying symptoms. In autosomal dominant inheritance, variability in severity and incomplete penetrance are common in several types of brachydactyly. In autosomal recessive inheritance, variability is usually smaller although variable symptoms may still be present in affected sibs.
   a. Patient's sib
      i. Autosomal dominant inheritance
         a) Recurrence risk of 50% if a parent is affected
         b) Low recurrence risk if both parents are normal
      ii. Autosomal recessive inheritance: risk of recurrence 25%
   b. Patient's offspring
      i. Autosomal dominant inheritance: a 50% risk of offspring affected
      ii. Autosomal recessive inheritance: low recurrence risk unless the spouse is affected or a carrier of brachydactyly mutation
2. Prenatal diagnosis
   a. Usually not indicated for isolated forms of brachydactyly, but may be appropriate in syndromic forms
   b. Molecular studies of chorionic villus samples at 11 weeks of gestation and by amniocentesis after the 14th week of gestation can provide antenatal diagnosis if the causative mutation in the family is known.
3. Management
   a. No specific management or treatment applicable to all forms of brachydactyly
   b. Plastic surgery
      i. Only indicated if the brachydactyly affects hand function or for cosmetic reasons
      ii. Typically not ordered
   c. Physical therapy and ergotherapy may ameliorate hand function.

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Fig. 1 A 2 years and 6 months old boy was evaluated for brachydactyly and abnormal shaped thumbs and great toes. He had hitch-hiker shaped thumbs and great toes with short fingers and toes including clinodactyly of the fifth fingers. His sister, mother, and maternal grandmother are similarly but less severely affected. The brachydactyly present in this kindred is consistent with brachydactyly type A1

Fig. 2 His great toes showed hitch-hiker shaped deformities

Fig. 3 His thumbs showed hitch-hiker shaped deformities

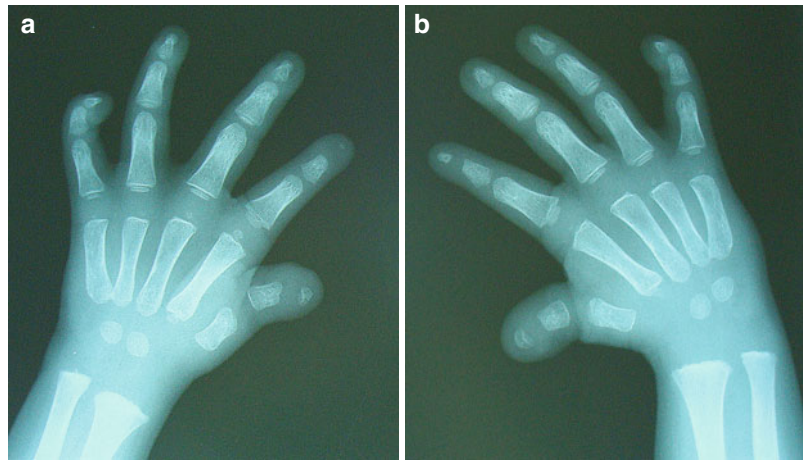

Fig. 4 (**a**, **b**) Radiographs of both hands showed short phalanges, especially short middle and distal phalanges in addition to deformities of the thumbs

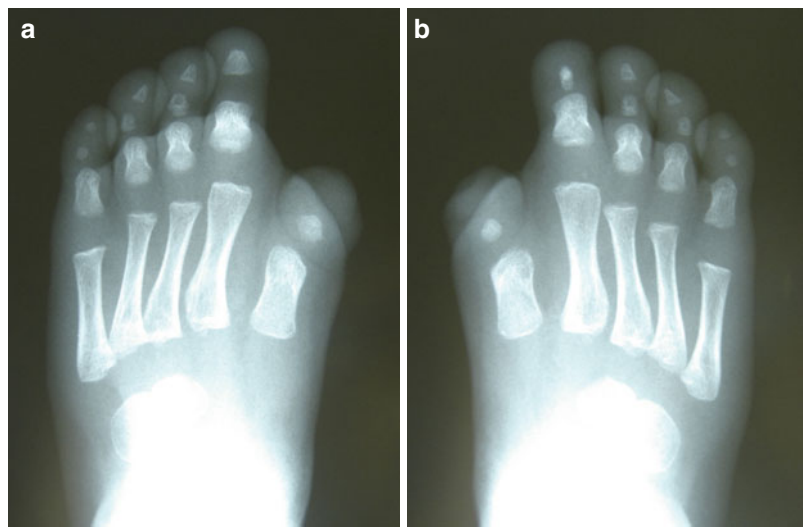

Fig. 5 (**a**, **b**) Radiographs of both feet showed short phalanges, especially middle and distal phalanges, in addition to deformities of the great toes

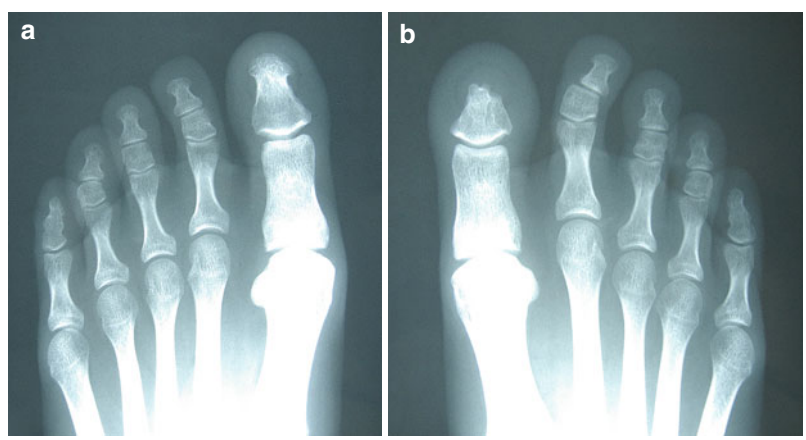

Fig. 6 (**a**, **b**) Radiographs of the feet of his mother

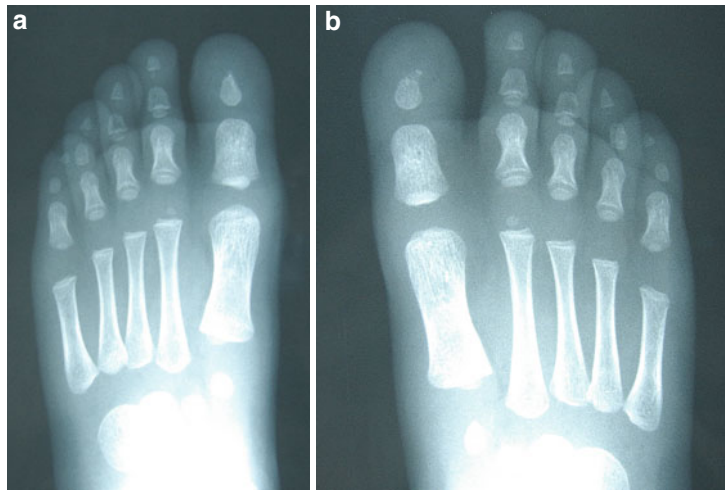

Fig. 7 (**a**, **b**) Radiographs of the feet of his sister

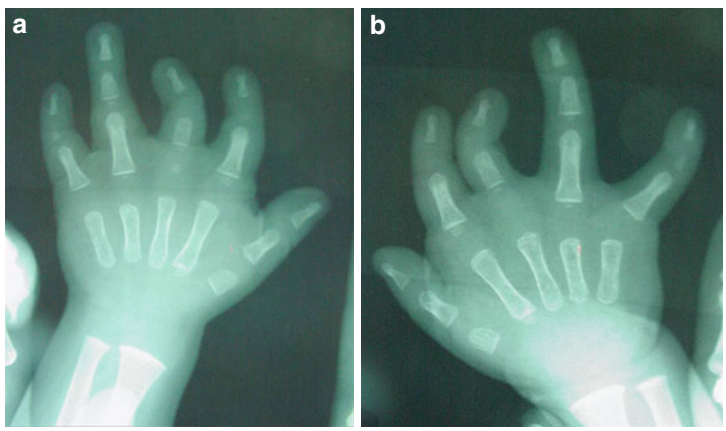

Fig. 8 (**a**, **b**) Radiographs of the hands of a 21-month-old boy, who was evaluated for hand anomalies, showed short first metacarpals, ulnar deviation of the second to third fingers with deficient ossification of the middle phalanges, relatively normal fourth finger (the longest digit and longer than the middle finger), and clinodactyly of the fifth finger with hypoplastic middle phalanges. No carpal bones were apparent. The brachydactyly in this child appears to represent brachydactyly type C

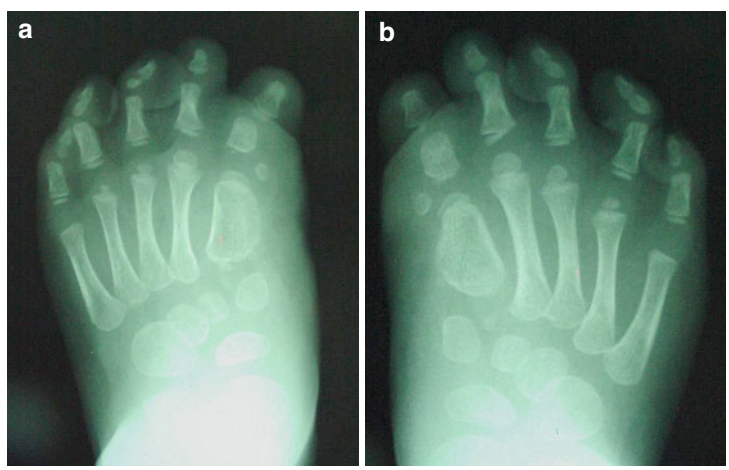

Fig. 9 (**a**, **b**) Radiographs of the feet showed abnormal shaped first metatarsals and short toes with absent or hypoplastic middle phalanges

Branchial Cleft Anomalies

Abnormal persistence of branchial apparatus remnants results in branchial anomalies.

Synonyms and Related Disorders

Branchial cyst; Branchial fistula; Branchial sinus; Branchial remnant presenting as skin tag

Genetics/Basic Defects

1. Embryology of the fetal branchial apparatus
   a. A derivative of a foregut, developed during the second fetal week
   b. Consisting of five paired pharyngeal arches, separated internally by four endodermal pouches and externally by four ectodermal clefts
2. Embryology of the branchial clefts
   a. First branchial cleft
      i. Giving rise to the Eustachian tube, tympanic cavity, and mastoid antrum
      ii. Contributing to the formation of the tympanic membrane
      iii. The only cleft to contribute to the adult structure is the external auditory canal
   b. Second, third, and fourth branchial clefts
      i. Known as the cervical sinus of His (part of an ectodermally lined depression)
      ii. Obliteration of the cervical sinus as the second and fifth branchial clefts merge
   c. Second branchial pouch
      i. Lined by ectoderm
      ii. Contributing to the palatine tonsil and tonsillar fossa
   d. Third branchial pouch: forming the following structures
      i. Inferior parathyroid gland
      ii. Thymus
      iii. Pyriform sinus
   e. Fourth branchial pouch: forming the following structures
      i. Superior parathyroid gland
      ii. Apex of the pyriform sinus
3. Pathogenesis of branchial cleft anomalies: remains controversial
   a. Arising from incomplete obliteration of the cervical sinus of His
   b. Arising from buried epithelial cell rests
4. Genetics: autosomal dominant inheritance in some families

Clinical Features

1. Manifestation of branchial cleft anomalies
   a. Cyst
      i. An epithelial-lined structure without an external opening
      ii. Most common branchial cleft anomalies (75%)
   b. Sinus
      i. A blind tract with an opening externally through the skin on the side of the neck representing persistence of a branchial groove
      ii. A blind tract with an opening internally into the foregut representing persistence of a branchial pouch
   c. Fistula
      i. A tract communicating between the skin externally (a patent abnormal canal

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opening externally on the neck surface) and the foregut internally (within the pharyngeal mucosa).
ii. Representing persistence of a branchial groove with its corresponding pouch and without branchial membrane between them.
d. Skin tag: A branchial remnant presenting in the lateral neck
e. Bilateral branchial cleft anomalies
i. Occurring in 2–3% of cases
ii. Often familial
2. First branchial cleft cyst
a. Accounting for only 5–8% of all branchial cleft defects
b. Most commonly seen in middle-aged women
c. Usually manifesting as recurrent abscesses or other inflammation (sinus tract) either around the ear or at the angle of the mandible
d. History of recurrent parotid abscesses unresponsive to antibiotics and drainage
e. Cystic drainage into the external auditory canal
i. Aural fistulas
ii. Auricular swelling
iii. Otitis
iv. Otorrhea
v. A cervical skin tag at birth
f. Occasional sinus tract extending to the hyoid bone
g. Cyst related to the parotid gland
i. Forming abscess and produce parotitis
ii. May be associated with facial nerve palsy
3. Second branchial cleft cyst
a. Most common developmental anomalies arising from the branchial apparatus
b. Cysts
i. Accounting for at least three fourths of branchial cleft anomalies
ii. Typically occurring between 10 and 40 years of age
c. Location of the cysts
i. Most commonly in the submandibular space
ii. Anywhere along a line from the oropharyngeal tonsillar fossa to the supraclavicular region of the neck
d. Signs and symptoms of second branchial cleft cyst
i. Usually appearing as painless, fluctuant masses in the lateral portion of the neck adjacent to the anteromedial border of the sternocleidomastoid muscle at the mandibular angle
ii. Enlarge slowly over time
iii. Painful and tender if secondarily infected
iv. Highly suggestive in a young patient with a history of recurrent inflammation in the region of the mandibular angle
v. Ostium usually noted at birth just above the clavicle in the anterior neck if a fistula is present
e. Fistulas and sinuses
i. Almost always present at birth
ii. With a small pinpoint external opening
iii. May go unnoticed for years if there is no drainage
iv. Symptoms consisting of continuous or intermittent mucoid drainage and recurrent attacks of inflammation that often follow mild trauma or an infection of the upper respiratory tract
v. Occasional formation of cellulitis and abscess
vi. Probing of the track producing irritation of the vagus nerve
vii. Usually unilateral
viii. Found in several members of the same family
4. Third branchial cleft cyst
a. Extremely rare
b. Most cysts located in the posterior cervical space posterior to the sternocleidomastoid muscle
c. Constituting the second most common congenital lesion of the posterior cervical space of the neck after cystic hygroma
d. Usually manifesting as a painless, fluctuant mass in the posterior triangle area of the neck
e. Mass usually distending during a viral infection of the upper respiratory tract
5. Fourth branchial cleft cyst
a. Extremely rare
b. Usually manifesting as a sinus tract rather than a cyst or fistula
c. Majority of the lesions occurring on the left side

Diagnostic Investigations

1. CT scans/MRI imagings
a. First branchial cleft cyst
i. Appearing as a cystic mass either within, superficial to, or deep to the parotid gland

ii. Variable wall thickness and enhancement: increase with recurrent infections
iii. Difficult to differentiate from other cystic mass of the parotid gland

b. Second branchial cleft cyst
i. Typically well-circumscribed, homogeneously hypoattenuated masses surrounded by a uniformly thin wall
ii. Increased mural thickness after infection
iii. "Beaked sign" (a curved rim of tissue or "beak" pointing medially between the internal and external carotid arteries) considered a pathognomonic imaging feature of a second branchial cleft cyst

c. Third branchial cleft cyst
i. Most commonly appearing as a unilocular cystic mass centered in the posterior cervical space
ii. Cyst fluid varying in signal intensity on T1-weighted images depending on the protein concentration and is typically hyperintense relative to muscle on T2-weighted images

d. Fourth branchial cleft cysts
i. Connected with the pyriform sinus
ii. Appearing similar to an external or mixed laryngocele

2. Ultrasonography
a. A fluctuant, compressible, anechoic, or hypoechoic mass
b. May have fine internal debris

3. Sinogram or fistulogram with radiopaque dye
a. To help confirming the diagnosis
b. To identify length and location of the fistulous tract
c. To identify an associated cyst

Genetic Counseling

1. Recurrence risk
a. Patient's sib
i. Not increased in de novo case
ii. 50% recurrence risk if a parent is affected with an autosomal dominant disorder

b. Patient's offspring: 50% in autosomal dominant inheritance

2. Prenatal diagnosis by ultrasonography possible by demonstrating a cystic neck mass in the fetus with differential diagnosis including hemangioma, dermoid cyst, neuroblastoma, congenital cystic hygroma, teratoma, epignathus, esophageal duplication, goiter, and laryngocele

3. Management
a. First branchial cleft cyst: complete surgical excision (only curative therapy)
b. Second and third branchial cleft cysts: surgical excision recommended because of increased frequency of secondary infection
c. Recurrence risk uncommon after surgical excision
d. Antibiotics required for treating infections or abscess

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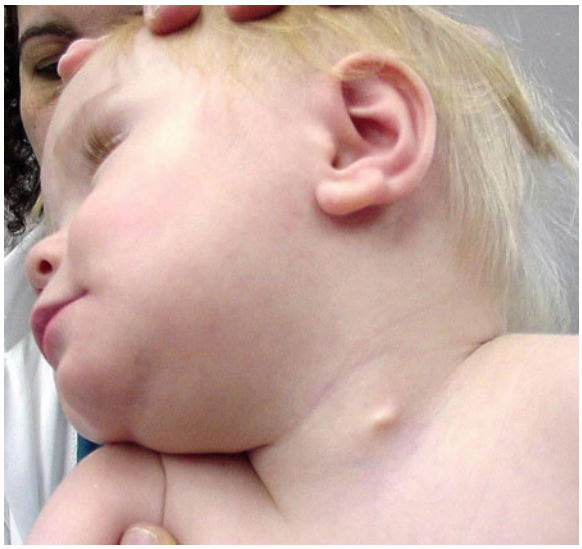

Fig. 1 A branchial cleft cyst in the left side of the neck

Calcinosis Cutis

Calcinosis cutis is a group of disorders characterized by the deposition of crystals of calcium phosphate (hydroxyapatite) in the skin in various areas of the body (Ianello et al. 1998) and can be associated with both normal and elevated calcium levels. Classically, it is divided into dystrophic, metastatic, iatrogenic, and idiopathic types.

Synonyms and Related Disorders

Calcinosis cutis (dystrophic, metastatic, iatrogenic, or idiopathic types)

Genetics/Basic Defects

1. Dystrophic calcinosis cutis (Nunley and Jones 2009)
   a. A common form of calcinosis cutis
   b. Localized or generalized
   c. Absence of calcium or phosphorus metabolic abnormalities
   d. Depositions of calcium salts: secondary to local inflammation, tissue damage, and degeneration
   e. Localized tissue damage
      i. Trauma
      ii. Burn
      iii. Inflammatory processes
         a) Acne
         b) Insect bites
      iv. Varicose veins
      v. Infections: Necrotic tissue produced by an infectious process may subsequently become calcified.
         a) Onchocerciasis
         b) Cysticercosis
         c) Histoplasmosis
         d) Cryptococcosis
         e) Intrauterine herpes simplex infection
      vi. Tumors: Benign and malignant tumors may develop calcification.
         a) Pilomatrixoma
         b) Calcifying epithelioma of Malherbe
         c) Epithelial cysts
         d) Syringomas
         e) Basal cell carcinomas
         f) Rarely in melanocytic nevi, malignant melanoma, atypical fibroxanthoma, hemangioma, pyogenic granuloma, seborrheic keratoses, neurilemomas, and trichoepitheliomas
   f. Generalized tissue damage
      i. Connective tissue diseases
         a) Dermatomyositis
         b) Scleroderma
         c) Lupus erythematosus
         d) Systemic sclerosis
         e) Calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasias (CREST) syndrome
      ii. Panniculitis
      iii. Porphyria cutanea tarda
      iv. Subcutaneous fat necrosis of the newborn
      v. Inherited disorders
         a) Ehlers–Danlos syndrome
         b) Werner syndrome
         c) Pseudoxanthoma elasticum
         d) Rothmund–Thomson syndrome
2. Metastatic calcinosis cutis
   a. Precipitation of calcium salts in normal tissue due to increased serum calcium and phosphate

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levels as a result of an underlying defect in calcium and/or phosphate metabolism
   b. Generally indicates chronic renal failure
   c. Calcification usually widespread and affects predominantly blood vessels, kidneys, lungs, and gastric mucosa
   d. Cutaneous and subcutaneous tissues may be involved: a rare complication
   e. Some of the factors involved are:
      i. Factors involved in increased serum calcium levels:
         a) Primary or secondary hyperparathyroidism
         b) Paraneoplastic hypercalcemia
         c) Albright hereditary osteodystrophy
         d) Destructive bone disease (malignancies, Paget disease)
         e) Excessive vitamin D intake
         f) Milk-alkali syndrome
         g) Sarcoidosis
         h) Chronic renal failure
         i) Calciphylaxis
      ii. Factor involved in increased serum phosphate levels: chronic renal failure
3. Iatrogenic causes: secondary to a treatment or procedure
   a. Parenteral calcium: extravasation of intravenously administered calcium chloride or calcium gluconate
   b. Parental inorganic phosphate
   c. Tumor lysis syndrome
   d. Repeated heel sticks in the newborn
   e. Prolonged use of calcium-containing electrode paste
      i. Electromyography
      ii. Electroencephalography
      iii. Brain auditory evoked potential
4. Idiopathic calcinosis cutis (Ogretmen et al. 2002)
   a. Also known as calcinosis cutis universalis
   b. Sporadic occurrence
   c. Characterized by calcium deposits in dermis, subcutis, and muscles without any metabolic disorder or tissue injury
   d. An uncommon type and may be solitary of multiple
   e. Causes
      i. Idiopathic calcinosis of scrotum/penis/vulva
      ii. "Milia-like" idiopathic calcinosis cutis with or without Down syndrome
      iii. Subepidermal calcified nodule
      iv. Tumoral calcinosis
      v. Calcinosis cutis circumscripta
      vi. Transplant-associated calcinosis

Clinical Features

1. Dystrophic calcinosis cutis (Nunley and Jones 2009)
   a. Most common type of calcinosis cutis
   b. Large and widespread deposits: termed calcinosis universalis
   c. Dystrophic calcification occurring locally and consists of only a few deposits of calcium salts termed "calcinosis circumscripta"
2. Metastatic calcinosis
   a. First manifestations
      i. Bone demineralization
      ii. Non-visceral and/or visceral calcification, mostly with mural deposits in arteries and arterioles
   b. Calcium deposition
      i. Frequently widespread
      ii. Large deposits frequently found around large joints, such as knees, elbows, and shoulders, in a symmetrical distribution
      iii. Visceral organs: deposition of calcium in the lungs, kidneys, blood vessels, and stomach occurring more frequently than deposition within the skin or muscle
      iv. Calciphylaxis: characterized by progressive vascular calcification, soft tissue necrosis, and ischemic necrosis of the skin
3. Iatrogenic calcinosis cutis
   a. Calcification generally localized at the site of an invasive procedure
   b. Diffuse deposition may occur
4. Idiopathic calcinosis cutis
   a. Uncommon
   b. Calcification deposit
      i. Most commonly localized to one general area
      ii. Observed in dermis, subcutis, and muscles without any metabolic disorder or tissue injury

Diagnostic Investigations

1. Laboratory studies (Nunley and Jones 2009)
   a. Serum calcium, inorganic phosphate, alkaline phosphatase, and albumin levels

i. Elevated serum calcium and alkaline phosphatase levels with a decrease in the inorganic phosphate level: suggestive of hyperparathyroidism
ii. An albumin value: needed to interpret the significance of hypocalcemia or hypercalcemia
iii. Serum blood urea nitrogen and creatinine concentrations: needed to measure renal function

b. Abnormal complete blood cell count with differential: suggest an underlying malignancy or lupus erythematosus
c. Abnormal plasma bicarbonate or arterial pH value: indicates the presence of a metabolic alkalosis (milk-alkali syndrome)
d. Parathyroid hormone concentration: direct measurement for hyperparathyroidism
e. Abnormal creatine kinase and aldolase value
i. Dermatomyositis
ii. Myositis
iii. Rhabdomyolysis
f. Serum amylase or lipase levels: to assess pancreatic disease
g. Antinuclear antibody testing: helpful in screening for lupus erythematosus
h. Presence of SCL-70 (topoisomerase) antibody: portends a poor prognosis for scleroderma patient
i. Vitamin D levels: to evaluate for excess vitamin D. A test of the 24-hour urinary excretion of calcium and/or inorganic phosphate may be useful.

2. Imaging studies
a. Radiographic examination: to demonstrate the extent of tissue calcification
b. Bone scintigraphy with radiolabeled phosphate compounds (technetium Tc 99m methylene diphosphonate [MDP]): to evaluate non-visceral soft tissue calcification (Bhattacharya et al. 2005)
c. CT for the identification of visceral and non-visceral calcification, particularly in assessing tumoral calcinosis
d. MRI: to evaluate characteristic patterns of calcific deposits, particularly in evaluating granulomatous foreign-body reaction in tumoral calcinosis

3. Biopsy and histopathologic examination of a cutaneous lesion
a. Observation of granules and deposits of calcium in the dermis, with or without a surrounding foreign-body giant cell reaction
b. Massive calcium deposits: may be located in the subcutaneous tissue
c. Calcium deposition: frequently found within the walls of small- and medium-sized blood vessels in areas of necrosis
d. Calcium deposition: may be confirmed on Von Kossa and alizarin red stains

Genetic Counseling

1. Recurrence risk
a. Patient's sib
i. No increase in sporadic cases
ii. Autosomal recessive: a 25% recurrence risk (e.g., Rothmund–Thomson syndrome, Ehlers–Danlos syndrome types VI–VII, familial hyperphosphatemic tumoral calcinosis)
iii. Autosomal dominant: not increased unless a parent is affected, in which case a 50% recurrence risk (e.g., pseudoxanthoma elasticum, Ehlers–Danlos syndrome types I–IV)
iv. X-linked recessive: 50% of male sibs affected if the mother is a carrier (e.g., Ehlers–Danlos syndrome type V)

b. Patient's offspring:
i. Autosomal recessive: not increased unless the spouse is also a carrier
ii. Autosomal dominant: a 50% risk
iii. X-linked recessive: all daughters of affected males will be carriers. All sons of an affected male will be normal.

2. Prenatal diagnosis: not reported
3. Management
a. Medical management: limited with variable benefit; should attempt to correct the underlying problems
i. Intralesional corticosteroids: may be beneficial because of their anti-inflammatory and inhibitory effects on fibroblast activity
ii. Probenecid and colchicines: beneficial in some individuals
iii. Magnesium or aluminum antacids: may be effective phosphate binders in patients with hyperphosphatemia but the use of these agents in patients with renal insufficiency may result in magnesium or aluminum toxicity

iv. Sodium etidronate and diphosphonates: may reduce bone turnover and inhibit the growth of ectopic hydroxyapatite crystals. Paradoxical hyperphosphatemia may result from prolonged treatment
v. Myo-inositol hexaphosphonate is a dietary substance shown to inhibit the crystallization of calcium salts in animal studies and potentially could be of benefit in humans
vi. Warfarin: has shown benefit in some individuals
vii. The use of the calcium-channel blocker diltiazem over at least 5 years has variable benefits. The therapeutic effect is believed to be the antagonism of the calcium-sodium ion pump
viii. Response to intravenous immunoglobulin in some patients with dystrophic calcification (Schanz et al. 2008)

b. Surgical removal
   i. Indications
      a) Pain
      b) Recurrent infection
      c) Ulceration
      d) Functional impairment
   ii. Initial test removal of a test site before pursuing a large excision because the surgical trauma may stimulate calcification
   iii. Recurrence common after excision
c. Electric shock wave lithotripsy
   i. Anecdotally successful in dermatomyositis-induced tissue calcification
   ii. Complete relief of associated pain although reduction in the size of the calcification is minimal

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Fig. 1 (**a–d**) A 4-year-old boy has had numerous hard nodules in his neck, arms, legs, and trunk since early infancy. The subcutaneous hard nodules were tender and began to multiply and eventually became ulcerated. Recently he complained restricted arm and leg movement

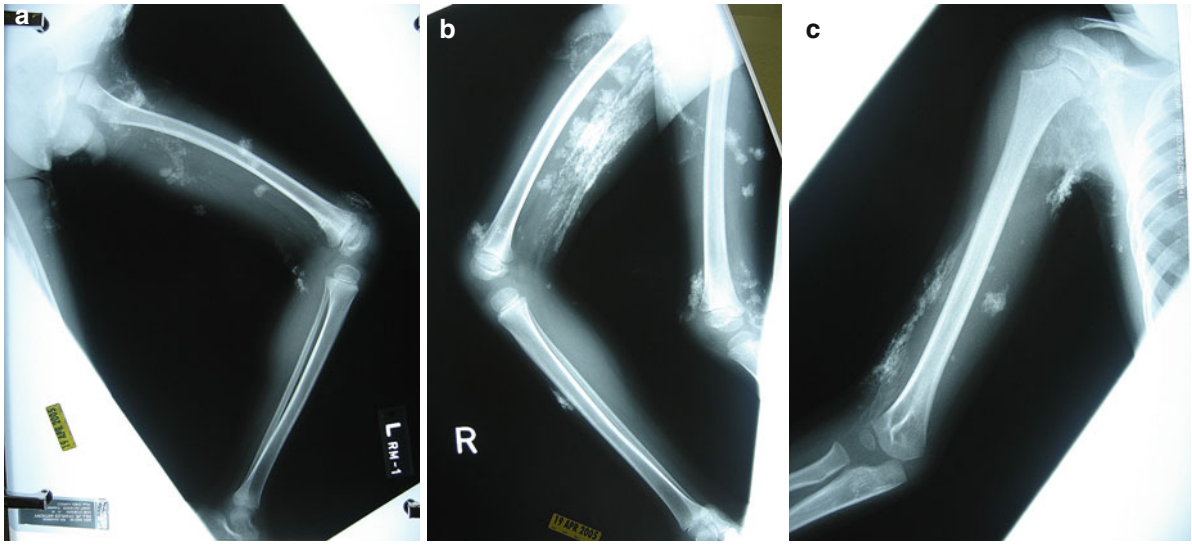

Fig. 2 (**a–c**) Radiologic studies revealed numerous subcutaneous calcifications throughout the body (only arm and legs are illustrated here). *GNAS1* gene mutation testing revealed no sequence variation

Campomelic Dysplasia

Campomelic dysplasia is a rare, often lethal congenital osteochondrodysplasias associated with skeletal malformations and sex reversal. The term "campomelia" derives from Greek, meaning bent or curved limb. Since most patients die in the neonatal period due to respiratory distress, patients with campomelic dysplasia are most often sporadic but few familial cases have been reported. The incidence of campomelic dysplasia is reported to be 0.05–0.9 per 10,000 births (Iravani et al. 2000).

Synonyms and Related Disorders

Acampomelic campomelic dysplasia; Campomelic dysplasia with autosomal sex reversal; Camptomelic dysplasia

Genetics/Basic Defects

1. Inheritance: autosomal dominant
2. Etiology (Kwok et al. 1995): can be caused by heterozygous intragenic *SOX9* mutations or chromosomal aberrations (translocations, inversions, or deletions) affecting *SOX9* or the putative enhancer region (Wada et al. 2009)
   a. Assignment of a locus *CMPD1* to 17q24.3-q25.1 was based on characterization of three independent de novo chromosome 17 translocations in campomelic dysplasia patients.
   b. XY sex reversal of two of these translocation patients placed an autosomal sex-determining locus, *SRA1*, in the same region.
   c. *SOX9*, a gene related to the mammalian Y chromosome sex-determining gene SRY, was mapped to this region and found to be near the translocation breakpoint of a sex-reversed campomelic dysplasia patient.
   d. Subsequent identification of de novo mutations in sex-reversed campomelic patients demonstrated that SOX9 is the gene responsible for both campomelic dysplasia and autosomal sex reversal.
   e. SOX9 mutations.
      i. Disrupt skeletogenesis and chondrocytic differentiation
      ii. Produce defective testicular development often resulting in sex reversal with female phenotype in chromosomal XY males
   f. Proof of *SOX9* being responsible for both campomelic dysplasia and XY sex reversal: demonstration of de novo heterozygous loss-of-function mutations within the SOX9 coding region in non-translocation campomelic dysplasia patients (Iravani et al. 2000).
   g. Isolation of the *SOX9* gene on chromosome 17q by positional cloning in combination with positional candidate information from the vicinity of breakpoints in campomelic dysplasia patients with reciprocal de novo translocations (Moyer et al. 1977).
   h. Report of a familial acampomelic dysplasia caused by an inherited deletion mapping upstream of the *SOX9* gene (Lecointre et al. 2009).

Clinical Features

1. Clinically a heterogeneous disorder (Houston et al. 1983; Iravani et al. 2000)

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a. Long-limbed variety
   i. Bent bones of normal thickness, may be slightly shortened
   ii. Rarely involves the upper limbs
b. Short-limbed variety
   i. Bent bones are short and wide
   ii. Two skull types
      a) Craniosynostotic type with cloverleaf skull
      b) Normocephalic type
c. Acampomelic campomelic dysplasia
   i. The eponymous feature "campomelia" (the bending of the long bones): not an obligatory feature of the syndrome
   ii. Absence of campomelia in about 10% of campomelic dysplasia cases

2. Prenatal history
   a. Polyhydramnios (30% of cases) in the third trimester common
   b. Growth retardation
3. Extreme hypotonia at birth
4. Characteristic craniofacial features
   a. Frequent macrodolichocephaly
   b. Cloverleaf skull
   c. Wide fontanel
   d. Short, narrow, and upslanted palpebral fissures
   e. Ocular hypertelorism
   f. Flat nasal bridge
   g. Long philtrum
   h. Micrognathia (Pierre Robin sequence)
   i. Cleft palate in two third of the cases
   j. Low-set and posteriorly rotated ears
   k. Prominent nuchal folds
   l. Hearing loss (deaf) in survivors
5. Prominent and characteristic musculoskeletal features
   a. Congenital bowed lower limbs (anterior bowing of the tibiae) with pretibial skin dimples. Pretibial dimples appear to result from the loss of subcutaneous tissue secondary to marked stretching of the skin overlying the apexes of the bony curvatures during fetal life
   b. Short limbs
   c. Short neck
   d. Pterygium coli
   e. Narrow thorax
   f. Kyphoscoliosis
   g. Talipes equinovarus
   h. Hand anomalies
      i. Brachydactyly
      ii. Clinodactyly
      iii. Camptodactyly
   i. Congenital dislocation of the hips
   j. Winging of the scapula
   k. Fewer ribs
6. Genitalia
   a. Genotypic XY males (three fourth of karyotypic males with sex reversal)
      i. External genitalia: range from an unambiguous female external genitalia to hypospadias with a bifid scrotum and an enlarged clitoris
      ii. Internal genitalia: various combinations of internal Mullerian and Wolffian duct structures
   b. Genotypic XX females: remain phenotypic female
7. CNS
   a. Mental retardation in survivors
   b. Large brain
   c. Hydrocephalus (25%)
   d. Polygyria
   e. Absent olfactory bulbs and/or tracts
   f. Dysgenesis of the corpus callosum
   g. Gross cellular disorganization, especially of cerebral peduncle, thalamus, and caudate nucleus
8. Respiratory insufficiency secondary to
   a. Robin sequence
   b. Narrow airways due to laryngotracheobronchomalacia (the most characteristic finding)
   c. Hypoplastic lungs
   d. A small bell-shaped thorax
9. Occasional abnormalities
   a. Congenital heart diseases
      i. Patent ductus arteriosus
      ii. Ventricular septal defects
      iii. Coarctation of the aorta
      iv. Tetralogy of Fallot
   b. Renal anomalies
      i. Hydronephrosis
      ii. Hydroureter
      iii. Renal hypoplasia
      iv. Renal cortical and medullary cysts
   c. Ear anomalies
      i. Hypoplastic cochlea and semicircular canals
      ii. Anomalies in incus and stapes
10. Cause of death
   a. Usually due to respiratory insufficiency

i. Primarily owing to airway and pulmonary defects, lack of laryngotracheobroanchial cartilages and hypotonia
ii. Resulting in apneic spells, atelectasis, aspiration, and pneumonia

b. A high rate of neonatal death
i. Most deaths occurring neonatally (77%)
ii. 90% of deaths before 2 years

11. Life expectancy varies depending on the severity of the phenotype
a. Young infants who survive
i. Feeding difficulties
ii. Stridor
iii. Retractions
iv. Frequent otitis media
v. Bronchitis
vi. Poor growth
b. Infants who survive several years
i. May be mentally retarded
ii. May show variable breakpoints within the vicinity of chromosome 17 (q21-q25)
iii. Oldest reported survivor: 17 years of age with an IQ of 45
c. Complications of survivors of campomelic dysplasia (Mansour et al. 2002)
i. Recurrent apnea
ii. Upper respiratory infections
iii. Progressive kyphoscoliosis
iv. Mild to moderate learning difficulties
v. Short stature
vi. Dislocation of the hips
d. Possible explanations for the survival of patients with campomelic dysplasia
i. Mosaicism of the *SOX9* mutations
ii. Chromosomal rearrangements involving chromosome 17q (q23.3-q25.1) shown to cause campomelic dysplasia without disrupting the *SOX9* gene, resulting in a milder phenotype

Diagnostic Investigations

1. Radiography (skeletal survey)
a. Affected infants
i. Tubular bones
a) Bowed femora and tibiae
b) Short fibulae
c) Radioulnar dislocation
ii. Thorax
a) Severe hypoplastic, bladeless scapulae
b) Thin short clavicles
c) Nonmineralized sternum
d) Small thoracic cage with slender and/or decreased number of ribs (usually 11 pairs)
iii. Spine
a) Abnormal cervical vertebrae
b) Kyphoscoliosis
c) Nonmineralized thoracic pedicles
iv. Pelvis
a) Dislocation of the hips
b) Narrow iliac wings
c) Poorly developed ischiopubic rami
d) Coxa vara
v. Hands and feet
a) Short first metacarpal bone
b) Talipes equinovarus
vi. Skeletal maturation
a) Delayed bone age
b) Delayed ossification of proximal tibial and distal femoral epiphysis and talus
b. Survivors
i. Hypoplastic scapulae
ii. Defective ischiopubic ossification
iii. Absent or hypoplastic patellae
iv. Spinal dysraphism
c. Considerable radiographic overlap with ischiopubic-patella syndrome
2. Hearing screening
3. Gonadal histology (Cameron et al. 1996)
a. Similar to XY gonadal dysgenesis
b. Ranging from dysplastic testicular tissue to poorly differentiated ovarian tissue with a few primordial follicles
4. Histology of growth plate: unremarkable epiphyseal resting cartilage
5. Cytogenetic analysis
a. Abnormal in about 5% of patients (Unger et al. 2008)
i. A de novo reciprocal translocation with one breakpoint in chromosome region 17q24.3-q25.1 where SOX9 is located: rarely the translocation may be familial, thus parental karyotypes should be obtained
ii. A de novo interstitial deletion of 17q
b. Identification of the sex reversal
6. Molecular analysis of *SOX9* mutation (Unger et al. 2008)

a. Sequence analysis: to detect coding regions and splice mutations (positive in about 90%)
b. Deletion analysis: to detect partial or whole-gene deletions (positive in about 5%)

Genetic Counseling

1. Recurrence risk (Unger et al. 2008)
   a. Patient's sib
      i. An affected parent (non-mosaic): a 50% risk
      ii. Not increased unless somatic or gonadal mosaicism or SOX9 deletion is present in one of the parent
         a) Unaffected mother with somatic mosaicism for the *SOX9* mutation has been reported (Wagner et al. 1994)
         b) An unaffected father of three affected children was reported to have germline, but not somatic, mosaicism (Cameron et al. 1996)
         c) A *SOX9* deletion in a mildly/minimally affected father of two affected children has been reported (Smyk et al. 2007)
      iii. Proband with an unbalanced chromosome constitution
         a) If neither parent has the chromosome rearrangement: a negligible risk
         b) If a parent has a balanced chromosome rearrangement: an increased risk, dependent on the specific chromosome rearrangement and the possibility of other variable
   b. Patient's offspring: provided the patient survives to the reproductive age
      i. A 50% risk to offspring when the proband has a non-mosaic *SOX9* mutation
      ii. Risk to offspring depends on the proband's cytogenetic abnormality involving *SOX9*
2. Prenatal diagnosis
   a. Possible by ultrasonography as early as 18 weeks of gestation.
      i. Ultrasonographic findings
         a) Symmetrical anterior bowing of femurs and tibias
         b) Hypoplastic or absent scapulae
         c) Small thorax compared to the abdomen
         d) Bilateral talipes equinovarus
         e) External genitalia not compatible with 46, XY karyotype
         f) Polyhydramnios
         g) Fetal growth retardation
         h) Large head with internal hydrocephalus
         i) Sagittal scan of the face showing a flat nasal bridge, elongated philtrum, and micrognathia
      ii. Major differential diagnosis of ultrasonographic features
         a) Osteogenesis imperfecta
         b) Hypophosphatasia
         c) Unclassifiable varieties of congenital bowing of the long bones
   b. Amniocentesis result of 46,XY with ultrasonographic finding of female external genitalia.
   c. Identification of *SOX9* mutation in the fetus: Prenatal diagnosis for pregnancies at risk as a result of a mildly affected parent or potential somatic or germline mosaicism requires prior identification of the disease-causing mutation in a previously affected child or the mildly affected parent.
3. Management
   a. Supportive medical care
   b. Orthopedic treatment of the musculoskeletal malformations to prevent additional morbidity
      i. Hip dislocation
      ii. Bracing or spinal fusion for spinal deformity
      iii. Serial casting or surgical correction for foot deformity
   c. Gonadodectomy advocated in surviving phenotypic females with Y chromosome fragments owing to the increased risk of gonadoblastoma

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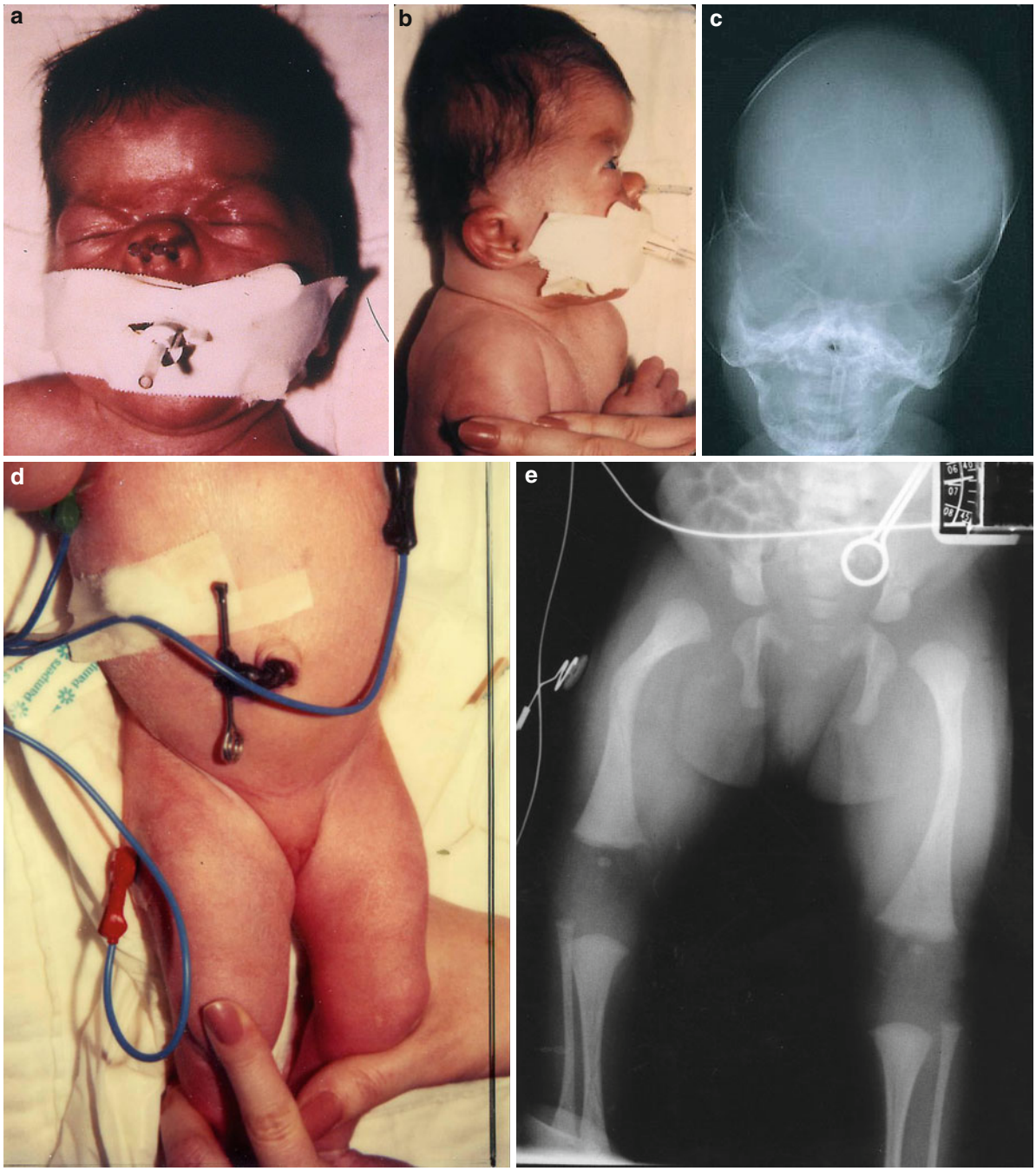

Fig. 1 (**a–e**) A neonate with campomelic dysplasia showing cloverleaf skull and bowed femurs, illustrated by radiographs

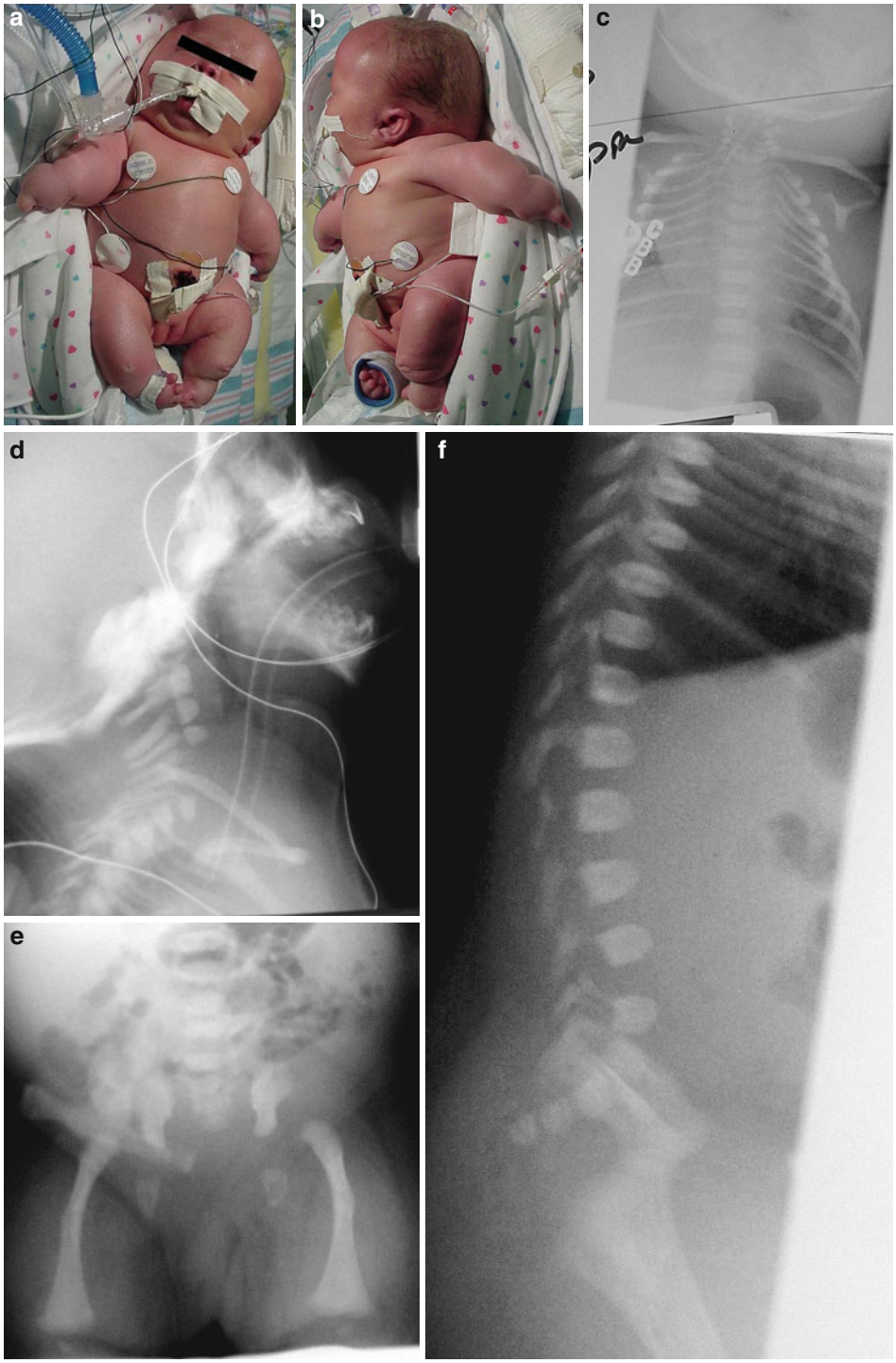

Fig. 2 (**a–f**) An infant with campomelic dysplasia showing bowing of the limbs with pretibial skin dimples, hypoplasia of cervical vertebra and scapula, 11 pairs of ribs, nonmineralized pedicles, *vertical*/*narrow* iliac wings, and bowing of femurs

Fig. 3 (**a–c**) A neonate with campomelic dysplasia showing large head, flat face, flat nasal bridge, low-set ears, micrognathia, and bowed lower legs with pretibial dimples. The radiograph showed bowing of the femora, tibia, and fibulas

Carpenter Syndrome

Carpenter in 1901 described two living siblings and one stillborn sibling with peculiar facies, acrocephaly, brachydactyly, syndactyly of the hands, and preaxial polydactyly and syndactyly of the toes. Temtamy in 1966 documented 12 additional cases (10 of which were familial) and proposed the eponymous designation "Carpenter syndrome."

Synonyms and Related Disorders

Acrocephalopolysyndactyly type II

Genetics/Basic Defects

1. An autosomal recessive inheritance: unlike other acrocephalosyndactyly syndromes or acrocephalopolysyndactyly syndrome
2. Caused by mutations in *RAB23*, a negative regulator of hedgehog signaling involved in cranial suture development (Jenkins et al. 2007)

Clinical Features

1. Craniofacial anomalies (Perlyin and Marsh 2008)
   a. Craniosynostosis (abnormal fusion of the cranial sutures): the basic abnormality of the craniofacial skeleton in Carpenter syndrome
      i. Premature closure of the sagittal, metopic, and lambdoid sutures, with coronal suture often remaining patent until the remaining sutures became synostotic (Marsh and Vannier 1995)
      ii. Pattern of craniosynostosis at birth may vary among affected siblings.
   b. Cranial configuration (Marsh and Vannier 1995)
      i. Acrocephalic
      ii. Often asymmetric
   c. Marked absence or underdevelopment of the anterior cranial fossa and bulging of the middle cranial fossa
   d. Maxillofacial manifestations (Carpenter 1901; Temtamy 1966; Der Kaloustian et al. 1972; Poole 1993; Puri et al. 1980)
      i. Brachycephaly
      ii. Flat facies with midface hypoplasia
      iii. Eyes
         a) Hyper/hypotelorism
         b) Shallow orbits
         c) Epicanthal folds
         d) Corneal opacity
         e) Microcornea
         f) Optic atrophy
      iv. Fat nasal bridge
      v. High-arched palate
      vi. Teeth
         a) Missing teeth
         b) Delayed loss of deciduous teeth
      vii. Ears
         a) Low-set/malformed ears
         b) Preauricular pits
         c) Conductive hearing loss
         d) Sensorineural hearing loss
      viii. Short muscular neck
2. Acral anomalies
   a. Polydactyly of the great toes
   b. Clinodactyly of the fingers

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c. Brachydactyly of the hands and feet
d. Syndactyly of the hands and feet
3. Neurologic findings: presence of phenotypic variability
a. Dilatation of ventricles
b. Discernible brain abnormalities
4. Growth
a. Short stature
b. Obesity
5. Other features
a. Cardiovascular defects
i. Atrial septal defect
ii. Ventricular septal defect
iii. Pulmonic stenosis
iv. Tetralogy of Fallot
v. Transposition of the great vessels
vi. Patent ductus arteriosus
b. Abdomen
i. Umbilical hernia
ii. Omphalocele
c. Genitourinary tract anomalies
i. Cryptorchidism
ii. Hydronephrosis
iii. Hydroureter
d. Other skeletal anomalies
i. Spine
a) Pilonidal dimple
b) Absent coccyx
c) Spina bifida occulta
d) Scoliosis
ii. Pelvis
a) Coxa valga
b) Decreased hip joint mobility
c) Flared ilia
iii. Limbs
a) Genu valgum
b) Lateral displacement of patellae
e. Endocrine features
i. Hypogenitalism
ii. Precocious puberty
f. Learning disability

Diagnostic Investigations

1. Radiography/CT scan of the skull
a. Craniosynostosis
i. Sagittal suture
ii. Metopic suture
iii. Lambdoidal suture
iv. Coronal suture
b. Cranial configuration: acrocephalic and often asymmetric
2. Radiography of the hands and feet
a. Polysyndactyly
b. Brachydactyly
c. Clinodactyly
3. Molecular genetic testing of *RAB23* mutations: not available clinically at present

Genetic Counseling

1. Recurrence risk
a. Patient's sib: 25%
b. Patient's offspring: not increased unless the spouse is also a carrier, in which case there is a 50% risk of having an affected offspring
2. Prenatal diagnosis: may be suspected in a pregnancy at risk with abnormal ultrasonography demonstrating abnormal craniofacial shape with polysyndactyly of the hands and feet
3. Management
a. Correction of skull malformations within the first year of infancy
b. Correction of other anomalies
i. Congenital heart defects
ii. Polysyndactyly
c. Care for eyes, vision, and hearing impairments
d. Intervention programs
i. Speech therapy
ii. Occupational therapy
e. Dietary control for obesity

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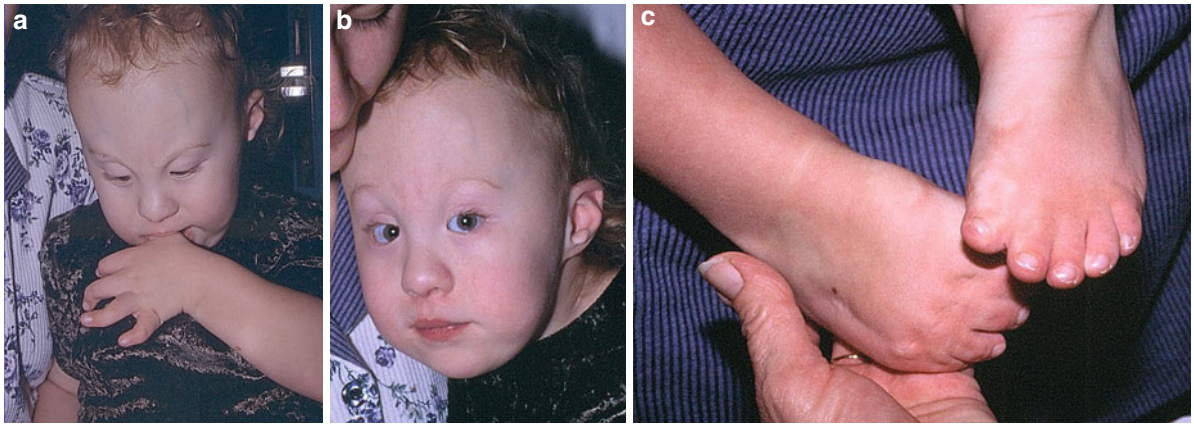

Fig. 1 (**a–c**) A two and a half year old girl had cone-shaped head, postaxial polydactyly of the hands and extra big toes of both feet (surgically excised at one month of age). The patient also had no opening of the anterior fontanel which was surgically repaired. She was noted to have brachycephaly, shallow orbits, high forehead, scanty eyebrows, lateral displacement of inner canthi, operation scars on the coronal sutures and sagittal suture, low-set malformed ears, small chin, high-arched palate, and operation scar for the umbilical hernia. Fingers and toes were abnormal with brachydactyly, clinodactyly, syndactyly, and polydactyly (surgically excised)

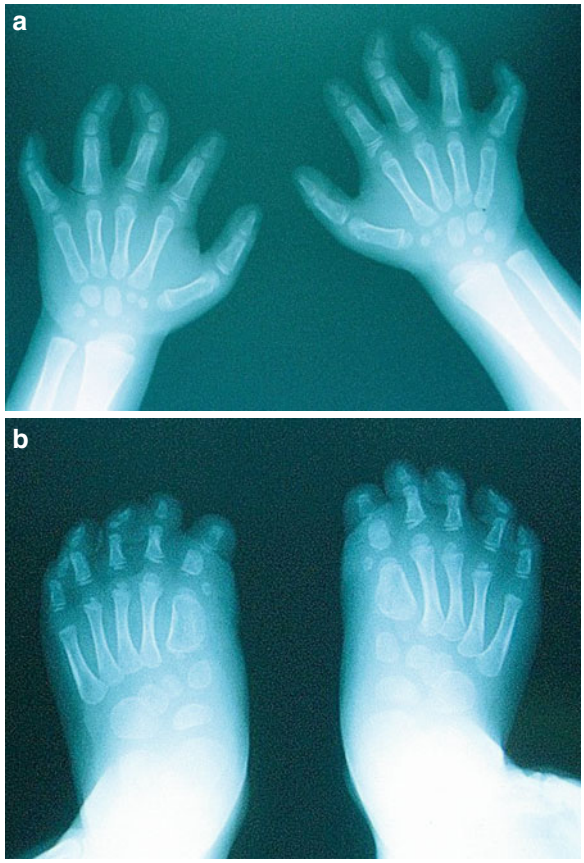

Fig. 2 (**a**, **b**) X-ray of hands and feet

Fig. 3 Patient at 10 years of age

Cat Eye Syndrome

Cat eye syndrome is a clinically recognizable congenital malformation syndrome consisting primarily of colobomas, anal anomalies, preauricular anomalies, cardiac and renal defects, and mild to moderate mental retardation. The name "cat eye" was introduced because of iris colobomas resembling the pupils of the cat.

Synonyms and Related Disorders

Schmid-Fraccaro syndrome; Chromosome 22 partial tetrasomy inv dup(22)(q11)

Genetics/Basic Defects

1. Historic background
   a. In 1965, an extra bisatellited marker chromosome was described in patients with cat eye syndrome phenotype (Schachenmann et al. 1965).
   b. Later in 1981, the marker was determined to be an inverted dicentric duplication of a part of chromosome 22 [inv dup(22)(pter → q11::q11 → pter)].
2. Molecular and cytogenetic bases
   a. Associated with the presence of three copies (trisomy) or four copies (tetrasomy) of a segment of chromosome 22q11.2, usually in the form of a bisatellited, isodicentric supernumerary chromosome (Footz et al. 2001)
   b. Formation of transient or unstable dic r(22) during early fetal development, which subsequently are lost from most cells, resulting in cat eye syndrome features
   c. The minimal common duplication required to produce features of cat eye syndrome (the cat eye syndrome critical region): defined by the dic r(22) patient, breakpoints between proximal locus ATP6E and distal locus D22S57, and covering approximately 2 Mb of 22q11.2
   d. Maternal origin of the supernumerary chromosome in cases studied
   e. Direct correlations between the extent of duplicated chromosome 22 materials and the severity of the cat eye syndrome remain difficult
   f. Human homolog of insect-derived growth factor, *CECR1*,: a candidate gene for features of cat eye syndrome
3. 22q11.2 region (Jezela-Stanek et al. 2009)
   a. Highly susceptible to chromosomal rearrangement: mediated by low-copy repeats causing nonallelic homologous recombination (Stankiewicz and Leepski 2002)
   b. A variety of clinical disorders are associated with either increased or decreased gene dosage (McDermid and Morrow 2002).
      i. Most common: DiGeorge/Velocardiofacial syndrome caused by microdeletion of 22q11.2
      ii. Other well characterized but less frequently recognized disorders
         a) Cat eye syndrome (CES) because of 22pter-q11 trisomy/tetrasomy
         b) Emanuel syndrome – the result of unbalanced 11, 22 chromosomal translocation, resulting in der (22)(22pter-22q11: 11q23-11qter) (Zakai and Emanuel 1980)

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iii. Other 22q11.2 rearrangements have been recognized recently.
  a) Microduplication 22q11.2 (Yobb et al. 2005; Kriek et al. 2006; Courtens et al. 2008)
  b) Triplication 22q11.2 (Yobb et al. 2005)
  c) Deletion of CES critical region (Kriek et al. 2006)
  d) 22q11.2 distal deletion (Ben-Shachar et al. 2008)
  e) Aberrations resulting in CES phenotype: proximal 22q duplication (Lindsay et al. 1995; Feenstra et al. 2006) or interstitial duplication 22q11 (Ensenauer et al. 2003)

Clinical Features

1. Marked phenotypic variability
2. Major features
   a. Preauricular skin tags and/or pits: most consistent features
   b. Ocular coloboma
   c. Congenital heart defect
      i. Ventricular septal defect
      ii. Total anomalous pulmonary venous connection
      iii. Atrial septal defect
      iv. Patent ductus arteriosus
      v. Pulmonary stenosis
      vi. Aortic malformation
      vii. Tricuspid atresia
      viii. Hypoplastic left heart syndrome
   d. Anorectal malformations
      i. Anal atresia or imperforate anus
      ii. Anal stenosis
      iii. Anorectal atresia
      iv. Ectopic anus
      v. Associated rectal fistulas
   e. Urogenital malformations
      i. Male external genital malformation
      ii. Renal agenesis/hypoplasia
      iii. Hydro(uretero)nephrosis
      iv. Vesicoureteral reflux
      v. Female genital malformation
      vi. Renal dysplasia or polycystic kidney
      vii. Bladder defects
      viii. Renal cystic malformation
      ix. Ectopic/horseshoe kidney
3. Minor features
   a. Craniofacial abnormalities
      i. Microcephaly
      ii. Ocular abnormalities
         a) Downslanting palpebral fissures
         b) Hypertelorism
         c) Ocular motility defect
         d) Epicanthal folds
         e) Microphthalmia
      iii. Oral abnormalities
         a) Micrognathia
         b) Cleft palate or absent uvula
      iv. Low-set or dysplastic ears
   b. Skeletal abnormalities
      i. Arm or hand deformity
      ii. Leg or foot deformity
      iii. Scoliosis or chest deformity
      iv. Vertebral anomaly
      v. Congenital dislocation of the hip
      vi. Rib or sternal anomaly
   c. Abdominal abnormalities
      i. Umbilical hernia
      ii. Malrotation of the gut
      iii. Hirschsprung or megacolon
      iv. Biliary atresia or choledochal cyst
      v. Volvulus
      vi. Meckel diverticulum
4. Neurodevelopmental outcome
   a. Growth and development
      i. Short stature
      ii. Mental development: markedly variable
         a) Normal-borderline normal
         b) Mild-moderate retardation
         c) Severe mental retardation
   b. Neurological abnormalities
      i. Dysregulation of muscle tone
      ii. Visual defect
      iii. Hearing impairment
      iv. Ventricular dilatation
      v. Abnormal slow EEG
      vi. Seizures
      vii. Spasticity
      viii. Cerebral or cerebellar atrophy
      ix. Hyperactive behavior
      x. Ataxia
      xi. Facial nerve palsy

Diagnostic Investigations

1. Chromosome analysis from blood and other tissues
   a. Conventional
   b. FISH
2. Radiography for limb defect
3. Echocardiography for congenital heart defects
4. Renal ultrasonography for renal anomalies
5. Developmental evaluation

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: a small recurrence risk because of possible presence of germline mosaicism
   b. Patient's offspring
      i. Patients with an inv dup(22): 50%
      ii. Patients with mosaic form of an inv dup(22): lower than 50%, depends on the percentage of the marker chromosomes
2. Prenatal diagnosis by amniocentesis or CVS
   a. Presence of a bisatellited, dicentric supernumerary chromosome
   b. FISH with a chromosome 22-specific cosmid probe to identify chromosome 22
3. Management
   a. Supportive
   b. Surgery
      i. Congenital heart defect
      ii. Anorectal anomalies
      iii. Urogenital anomalies
      iv. Gastrointestinal anomalies
      v. Skeletal anomalies
   c. Potential anesthetic risks (Devavaram et al. 2001)
      i. Potential difficult airway management
      ii. Congenital heart disease
      iii. Renal and hepatic dysfunction

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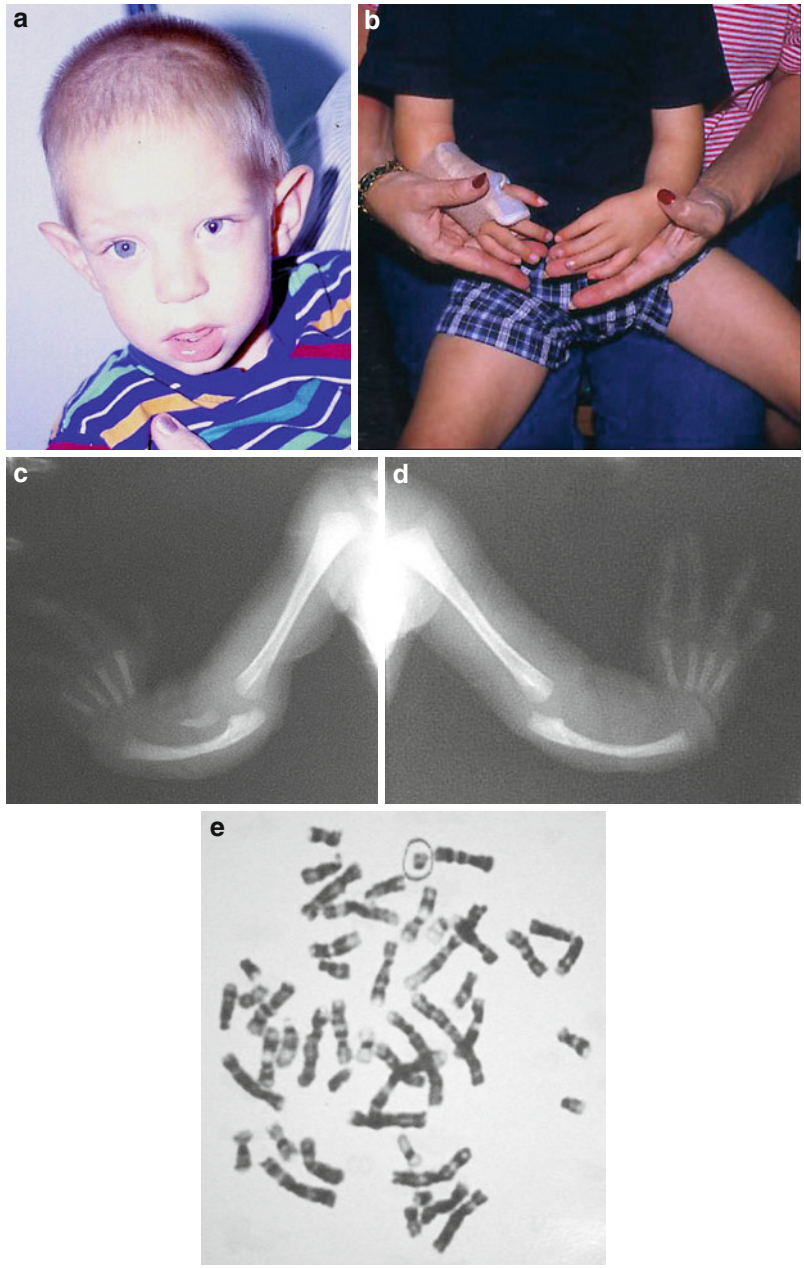

Fig. 1 (**a–e**) A boy with cat eye syndrome showing ocular coloboma and bilateral club hands with missing thumbs. The radiographs show bilateral radial aplasia/ hypoplasia with missing thumbs. The patient has a supernumerary marker chromosome 22, illustrated by the chromosome spread

Celiac Disease

Celiac disease is a gastrointestinal disorder characterized by chronic inflammation of the small intestine that can develop in genetically susceptible individuals ingesting proteins in wheat (gliadin), rye (secalin), and barley (hordein), collectively called gluten. The prevalence of celiac disease in the United States and Canada is as high as 0.5–1%, similar to earlier estimates outside North America.

Synonyms and Related Disorders

Celiac sprue; Gluten sensitive enteropathy

Genetics/Basic Defects

1. Pathogenesis
   a. Celiac disease occurs in genetically susceptible individuals who ingest gluten, a protein found in certain grains
   b. Gluten causes an abnormal T cell–mediated immune response and inflammatory injury to the mucosa of the small intestine, resulting in malabsorption of nutrients in these individuals
   c. Gliadin fraction of gluten is mainly responsible for this intestinal damage
   d. Approximately 97% of individuals with celiac disease have genetic markers on chromosome 6 called human leukocyte antigen (HLA) DQ2 and HLA DQ8, compared with 40% of the general population
   e. An individual's intolerance to gluten is lifelong and self-perpetuating because of this genetic predisposition
2. A multifactorial disorder with complex genetics (Sollid and Lie 2005)
   a. Interplay between genetic and environmental factors
      i. Gluten (consisting of the gliadin and glutenin subcomponents): a critical environmental component
      ii. Both HLA and non-HLA genes: considered to be predisposing genetic factors
      iii. HLA as a necessary but not sufficient genetic factor for celiac disease development
         a) HLA-DQ as the chief locus mediating the HLA-linked effect in celiac disease
         b) The great majority of the patients carry a variant of DQ2 (*DQA1*05*/*DQB1*02*)
         c) A minority of the patients carry DQ8 (*DQA1*03*/*DQB1*0302*)
   b. HLA molecules
      i. The role of the molecules: to bind and present peptide fragments to T cells
      ii. Different HLA molecules thus present different sets of peptides
      iii. Gluten-reactive T cells of the celiac intestinal mucosa uniquely recognize gluten peptides in the context of DQ2 and DQ8, suggesting that these HLA molecules predispose to celiac disease by preferentially presenting gluten peptides to CD4 T cells

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Clinical Features

1. Variable clinical presentations may lead to difficulty in diagnosis (Westerberg et al. 2006)
   a. Signs and symptoms in children
      i. Abdominal distention/bloating
      ii. Chronic diarrhea
      iii. Delayed puberty
      iv. Growth failure
   b. Signs and symptoms in adults
      i. Abdominal pain
      ii. Chronic diarrhea
      iii. Infertility or recurrent spontaneous abortion
      iv. Iron deficiency anemia
      v. Irritable bowel syndrome
      vi. Peripheral neuropathy
      vii. Persistent fatigue/malaise
      viii. Weight loss
   c. Associated conditions
      i. Autoimmune disorders
      ii. Dermatitis
      iii. Down syndrome
      iv. Epilepsy
      v. Idiopathic dilated cardiomyopathy
      vi. Immunoglobulin A deficiency
      vii. Immunoglobulin A nephropathy
      viii. Microscopic colitis
      ix. Osteoporosis or other bone diseases
      x. Thyroid diseases
      xi. Turner syndrome
      xii. Type I diabetes mellitus
2. Changing celiac disease pattern
   a. Less frequent so-called classic/typical celiac disease with a malabsorption syndrome in childhood. The symptomatic cases (about 10%) are considered to be the tip of the iceberg (Kaukinen et al. 2002).
   b. Increasingly common to diagnose children who have subtle or no gastrointestinal or non-gastrointestinal symptoms (Ravikumara et al. 2006)

Diagnostic Investigations

1. Initial serology tests before eliminating gluten from diet (Hill et al. 2005; Rostom et al. 2006; Westerberg et al. 2006)
   a. IgA-tissue transglutaminase (tTG) antibody and endomysial antibody (EMA) (performed to identify candidates for duodenal biopsy)
   b. Total serum IgA (performed to identify individuals with IgA deficiency).
2. Serologic tests are helpful in screening at-risk populations for celiac disease (Rashid et al. 2009)
   a. Helpful in screening at-risk populations for celiac disease, such as:
      i. First- and second-degree relatives of patients with celiac disease
      ii. Individuals with type 1 diabetes mellitus and other autoimmune endocrinopathies
      iii. Individuals with atypical symptoms
   b. Anti-deamidated gliadin-related peptide (a-DGP) antibodies IgA and IgG: detects antibodies binding synthetic deamidated gliadin-related peptides (DGPs) (Liu et al. 2007; Niveloni et al. 2007)
   c. An over-the-counter home self-testing kit for celiac disease has recently been marketed in Canada. Using a tiny blood sample obtained by a pinprick of the fingertip, the home blood test identifies the tTG antibodies present in the blood of those with celiac disease. This test is for screening only and should not replace a medical diagnosis.
3. Final diagnosis of celiac disease is based on the biopsy findings of typical histologic alterations of the small intestinal mucosa of patients eating gluten.
4. A clinical response on a gluten exclusion diet: considered to be important in diagnosis.
5. Recent recommendations also include HLA genotyping as a diagnostic adjunct (Hill et al. 2005).
   a. DQ2 heterodimer (encoded by specific *HLA-DQA1**05 alleles and specific *HLA-DQB1**02 alleles) and/or
   b. DQ8 heterodimer (encoded by specific *HLA-DQA1**03 and *HLA-DQB1**0302 alleles)
   c. Clinical molecular testing by targeted mutation analysis to determine *HLA-DQA1* and *HLA-DQB1* genotypes to detect the presence or absence of the celiac disease-associated alleles, *HLA-DQA1**0501, *HLA-DQA1**0505, *HLA-DQB1**0201, *HLA-DQB1**0202, and *HLA-DQB1**0302 (Snyder et al. 2008).
6. Informing an individual that she or he is the carrier of predisposing genes has an ethical aspect, and the possibility of a psychological impact of an HLA test

in relation to celiac disease must be considered (Sollid and Lie 2005). The presence of celiac disease predisposing HLA alleles means little, whereas the absence of the same HLA alleles makes celiac disease an improbable disorder for that patient.

Genetic Counseling

1. Recurrence risk (Snyder et al. 2008)
   a. Patient's sib
      i. The overall empiric risk for celiac disease in sibs of a proband is 7–20% if the HLA haplotype is not known (Treem 2004).
      ii. If the HLA haplotype of the parents is known, the risk to the sibs can be refined.
      iii. Sibs who share the same celiac disease-susceptibility HLA haplotype with the proband have a risk of developing celiac disease that approaches 40% (Treem 2004).
      iv. The risk to a sib of having celiac disease is estimated at 23.6% when multiple family members are affected (Gudjónsdóttir et al. 2004).
      v. If a parent of the proband has the DQ2 celiac disease-susceptibility haplotype in *cis* configuration or the DQ8 celiac disease-susceptibility HLA haplotype, the risk to each sib of inheriting the celiac disease-susceptibility HLA haplotype is 50%.
      vi. If one parent of the proband has half of the DQ2 heterodimer (*HLA-DQA1**0501 or *0505) and the other parent has half of the DQ2 heterodimer (*HLA-DQB1**0201 or *0202), the risks to sibs are as follows:
         a) Risk of inheriting both HLA haplotypes and having the full DQ2 heterodimer encoded in *trans* configuration: 25%
         b) Risk of inheriting half of the DQ2 heterodimer (*HLA-DQA1**0501 or *0505) or (*HLA-DQB1**0201 or *0202): 50%
         c) Risk of inheriting neither the *HLA-DQA1**0501 or *0505 nor the *HLA-DQB1**0201 or *0202 celiac disease-susceptibility haplotype: 25%.
   b. Patient's offspring
      i. The overall risk for celiac disease in offspring of a proband is 5–10% if the celiac disease-susceptibility HLA haplotype is not known.
      ii. The risk increases when the offspring has the DQ2 celiac disease-susceptibility HLA haplotype and/or the DQ8 celiac disease-susceptibility HLA haplotype (Treem 2004).
      iii. The risk is lower when only half of the DQ2 heterodimer (i.e., the *DQA1* sequence variant **or** the *DQB1* sequence variant, but not both) is present (Qiao et al. 2005).
      iv. Each child of an individual with the DQ2 celiac disease-susceptibility HLA haplotype or the DQ8 celiac disease-susceptibility HLA haplotype has a 50% chance of inheriting the celiac disease-susceptibility HLA haplotype.
      v. The child of a proband who has the DQ2 celiac disease-susceptibility HLA haplotype in the *trans* configuration will inherit one of the celiac disease-susceptibility HLA haplotypes from the affected parent.
      vi. Because the DQ2 or DQ8 heterodimer is found in 30–40% of the general population, testing the proband's reproductive partner is appropriate.
2. Prenatal diagnosis: While technically possible, prenatal testing of celiac disease-susceptibility HLA haplotypes does not seem relevant in this complex disorder (Snyder et al. 2008)
   a. The genetic change is common in the general population
   b. The genetic change is predisposing to, but not predictive of, celiac disease
   c. A highly effective treatment is available
3. Management
   a. Gluten-free diet
      i. Many patients cope easily.
      ii. Some patients may find that the dietary restrictions are laborious, negatively influencing their quality of life.
      iii. Requires strict adherence to a gluten-free diet for life for symptomatic and asymptomatic children with characteristic histological findings on small bowel biopsy.
      iv. Compliance with the gluten-free diet is often incomplete among celiac disease patients.
      v. When maintained on a long-term gluten-free diet (including wheat starch-based gluten-free flours), there is probably no increase in mortality, morbidity, or malignancies (Holmes et al. 1989) in patients with celiac

disease over the population in general, although there are conflicting reports whether gluten-free food completely eliminates all risks (Green et al. 2003).

b. Treat nutritional deficiencies and osteoporosis
c. A need for future alternative treatments

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Fig. 1 A 3-year-old girl was healthy until 1 year of age when she developed severe watery diarrhea and abdominal distention for approximately a year and 9 months. She was diagnosed to have gluten-induced gastroenteropathy. The diarrhea stopped immediately upon withdrawal of gluten. She has been healthy since then. Her 18-month-old brother was admitted to a local hospital at 11 days of age for 6 days including 3 days of intensive care stay for a respiratory syncytial virus bronchiolitis. He again developed RSV infection at 2 months of age. In addition, he developed severe watery diarrhea with abdominal distention which improved upon discontinuation of gluten from his diet. He has since been healthy. HLA allelic variants associated with celiac disease were detected in both siblings: DQ2 heterodimer (HLA DQA1*05/DQB1*02). These alleles are present in 96–99% of confirmed celiac disease

Cerebral Palsy

Cerebral palsy (CP) is currently considered as a clinically defined symptom complex applied to individuals with a static, nonprogressive motor impairment of early onset that is cerebral in origin. It describes a group of motor impairment syndromes secondary to genetic and acquired disorders of the developing brain. Therefore, it is not a single entity with respect to pathogenesis but rather an etiologically heterogeneous entity with multiple possible causes that result in an aberration or injury to the maturing central nervous system. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior, and/or by a seizure disorder. The prevalence is estimated between 1.5 and 2.5 per 1,000 live births.

Synonyms and Related Disorders

Ataxic-hypotonic CP; Dyskinetic CP; Mixed CP; Monoplegic/hemiplegic CP; Spastic diplegic CP; Spastic quadriplegic CP; Spastic triplegic CP

Genetics/Basic Defects

1. Components of CP classification (Bax et al. 2005)
   a. Motor abnormalities
      i. Nature and typology of the motor disorder
         a) Tonal abnormalities assessed on examination (e.g., hypertonia or hypotonia)
         b) Diagnosed movement disorders (e.g., spasticity, ataxia, dystonia, or athetosis)
      ii. Functional motor abilities: motor function in all body areas, including oromotor and speech function
   b. Associated impairments
      i. Presence or absence of associated non-motor neurodevelopmental or sensory problems
         a) Seizures
         b) Hearing or vision impairments
         c) Attentional, behavioral, communicative, and/or cognitive deficits
      ii. The extent to which impairments interact in individuals with cerebral palsy
   c. Anatomic and radiological findings
      i. Anatomic distribution (the parts of the body affected by motor impairments or limitations), e.g.,
         a) Limbs
         b) Trunk
         c) Bulbar region
      ii. Radiological findings: the neuroanatomic findings on computed tomography or magnetic resonance imaging, e.g.,
         a) Ventricular enlargement
         b) White matter loss
         c) Brain anomaly
   d. Causation and timing
      i. Clearly identified cause
         a) Usually postnatal CP (e.g., meningitis or head injury)
         b) Brain malformations
      ii. Presumed time frame during which the injury occurred, if known

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2. Etiologies: Distribution of observed diagnoses is noted by Shevell et al. (2003):
   a. Single cause
      i. Periventricular leukomalacia (13.8%)
      ii. Asphyxia (12.4%)
      iii. Cerebral dysgenesis (17.1%)
      iv. Intracranial hemorrhage (5.5%)
      v. Vascular (9.2%)
      vi. Infection (5.1%)
      vii. Atrophy (1.8%)
      viii. Toxins (1.1%)
   b. Multiple causes
      i. Periventricular leukomalacia (24.9%)
      ii. Asphyxia (21.7%)
      iii. Cerebral dysgenesis (17.1%)
      iv. Intracranial hemorrhage (12.9%)
      v. Vascular (9.7%)
      vi. Infection (6.5%)
      vii. Trauma (1.8%)
      viii. Atrophy (1.8%)
      ix. Toxins (2.2%)
3. Common etiologies of cerebral palsy (Russman and Ashwal 2004; Dodge 2008)
   a. Prenatal onset
      i. Brain malformations
      ii. Intrauterine infection such as cytomegalovirus infection
      iii. In utero stroke
      iv. Toxemia
      v. Placental abruption
   b. Perinatal onset
      i. Hypoxic–ischemic encephalopathy
      ii. Viral encephalitis
      iii. Meningitis
      iv. Kernicterus
      v. Trauma
   c. Postnatal onset
      i. Infection
      ii. Accidental head trauma
      iii. Anoxic insult
      iv. Child abuse
      v. Progressive hydrocephalus
4. Occurrence of CP phenotype has been seen in a variety of recognizable genetic syndromes including (Fisher and Russman 1974):
   a. Coffin–Lowry syndrome
   b. Cerebro-oculo-facio-skeletal syndrome
   c. Rett syndrome
   d. Angelman syndrome
   e. Hereditary spastic paraplegia
   f. Pelizaeus–Merzbacher spectrum
   g. West syndrome (infantile spasm and status dystonicus)
5. Recently described metabolic conditions associated with cerebral palsy phenotype (Schaefer 2008)
   a. Glucose transport disorders
   b. Molybdenum cofactor deficiency (sulfite oxidase deficiency)
   c. Serine biosynthesis disorder
   d. Glycine cleavage encephalopathy
   e. Creatine biosynthesis disorder
   f. Neurotransmitter disorders
   g. Nonlactic acidemia Leigh syndrome
   h. Adenylosuccinate lyase deficiency
   i. Congenital disorders of glycosylation
   j. Glutamate transporter EAAT1
   k. 2-methylbutyryl-CoA dehydrogenase deficiency
   l. Mitochondrial disorders (Fryer et al. 1994)
      i. Report of a family, affected with Leigh's encephalopathy and the mitochondrial DNA (mtDNA) mutation 8993, presented with nonspecific delayed development or cerebral palsy.
      ii. There was some correlation in this family between the disease severity and the proportion of mutant mtDNA in the blood.
      iii. This mutation appears to segregate to high levels of mutant mtDNA rapidly within pedigrees.
      iv. The mother of a severely affected child has a high risk of having further children with a high proportion of mutant mtDNA and a severe phenotype.
6. Types of cerebral palsy (Shevell et al. 2003)
   a. Spastic quadriplegic (35.5%)
   b. Spastic hemiplegic (31.3%)
   c. Spastic diplegic (18.0%)
   d. Mixed (5.5%)
   e. Ataxic–hypotonic (5.5%)
   f. Spastic monoplegic (2.7%)
   g. Dyskinetic (0.9%)
   h. Worster-Drought (also called bilateral perisylvian or opercular) syndrome (0.9%)

Clinical Features

1. Prenatal and perinatal history (Green et al. 2003)
   a. Prenatal history: potential pregnancy complications
      i. Maternal illnesses during pregnancy
      ii. Exposure to toxins (e.g., alcohol or drugs)
      iii. Prenatal care
      iv. Fetal movements
      v. History of trauma
   b. Perinatal history
      i. Gestational age at delivery
      ii. Delivery type and presentation
      iii. Length of labor
      iv. Birth weight
      v. Apgar scores
      vi. Cord gas pH
      vii. Presence of intraventricular hemorrhage
      viii. Procedures done during hospitalization
      ix. Ability to feed
      x. Degree of tone
2. Developmental history
   a. Age of attainment of developmental milestones
   b. Age-appropriate developmental function
   c. Assessment of gross motor function
      i. Head control
      ii. Trunk control
      iii. Rolling
      iv. Sitting
      v. Crawling
      vi. Standing
      vii. Cruising
      viii. Walking
   d. Assessment of fine motor function
      i. Handedness
      ii. Hand-to-mouth movements
      iii. Bimanual activities
      iv. Grasping
      v. Writing
      vi. Feeding
   e. Assessment of language ability
      i. Babbling
      ii. Size of vocabulary
      iii. Ability to string words together
      iv. Counting
      v. Naming of body parts, colors, alphabet, and comprehension
   f. Current social and personal skills
3. Other histories
   a. Nutritional status, including feeding style, ability, and content
   b. Medications and allergies
   c. Past surgeries
   d. Presence of seizures
   e. Tone and body movement patterns
   f. Bowel and bladder concerns
   g. Visual and hearing concerns
   h. General health
   i. Immunization history
   j. Positioning devices
   k. Bathing equipment
   l. Wheelchair and seating equipment
   m. Adaptive devices
   n. Communication devices
   o. Computers
   p. Environmental control units
   q. Transportation systems
   r. Educational information
      i. Early intervention programs
      ii. School environment
      iii. Special services
      iv. Individualized education plan
      v. Adaptive physical education and recreation
      vi. Vocational and vocational activities in adults
4. Criteria for diagnosis (Paneth 2008): presence of one or more of the following four types of neurologic impairment of the motor system:
   a. Spasticity
      i. Commonest neurologic abnormality
      ii. Characterized by increased muscle tone manifesting as increased resistance to stretch that is velocity dependent
      iii. Generally accompanied by hyperreflexia, which may include prolonged or sustained clonus, as well as pathologic reflexes such as an abnormal Babinski response (Sanger et al. 2003)
      iv. When spasticity affects the lower limbs:
         a) Internal rotation and adduction of the hips is often seen, leading to the typical flexed posture and pigeon-toed gait of CP

b) Spasticity of the gastrocnemius muscle in the calf leads to another characteristic finding of toe walking due to plantar flexion

b. Dyskinesia
   i. Stereotyped, involuntary movements accentuated with effort
   ii. Presence of two forms of dyskinesia
      a) Dystonia in which abnormal postures due to sustained muscle contractions are the essential feature.
      b) Choreoathetosis, in which abnormal movements predominate, consists of two related motor disorders: choreiform movements are rapid and jerky, whereas athetoid movements have a writhing quality. Athetoid CP is characteristic of children who suffered kernicterus in the neonatal period. With control of rhesus hemolytic disease, and better management of all forms of neonatal hyperbilirubinemia, this form of cerebral palsy has become very rare. Patients with the dystonic form of cerebral palsy generally have spasticity as well, whereas patients with choreoathetoid cerebral palsy often have varying tone, with hypertonia and hypotonia both found.
c. Hypotonia.
d. Ataxia.
   i. Usually presence of both truncal and gait ataxia, which can both be observed (e.g., wide-based gait) and elicited by examination (e.g., inability to accurately place finger on nose)
   ii. Intention tremor commonly seen
   iii. Fine motor skills are particularly limited
   iv. Tone is usually hypotonic in this form of cerebral palsy

5. Musculoskeletal features
   a. Hip assessment should include evaluation for contractures involving flexion, internal and external rotation, adduction, and leg length discrepancies
   b. The knee should be tested for hamstring contracture
   c. The foot and ankle should be tested for contractures and tibial torsion
   d. The back should be examined for posture, spinal curves, or asymmetries
   e. The upper extremities should be assessed for resting posture and spontaneous movement
   f. An occupational therapy evaluation of grip and fine motor coordination often is beneficial
6. Neurologic features
   a. CP is a disorder of movement resulting in a delay in the development of gross motor skills
   b. Focus on tone
      i. If movement has a velocity-dependent component, it is spastic
      ii. In addition to the deep tendon reflexes (which are often increased in spastic CP) and the Babinski, or plantar, response (which is often upgoing)
7. Spastic cerebral palsy
   a. Spasticity
      i. Definitions
         a) An increase in the physiologic resistance of muscle to passive motion
         b) Hypertonicity that increases with increased velocity of movement (or having an increased stretch reflex)
      ii. Most common of cerebral palsy (70–80% of children who have cerebral palsy are spastic) (Panteliadis 2004)
      iii. A part of the upper motor neuron syndrome characterized by:
         a) Hyperreflexia
         b) Clonus
         c) Extensor plantar responses
         d) Persistent primitive reflexes
   b. Cause: damage to the pyramidal parts of the brain
   c. Subdivision of spastic cerebral palsy: according to the area of the body involved
      i. Diplegia
         a) 50% of children with spastic cerebral palsy have diplegia (Berker and Yalçin 2008).
         b) The most common type seen in premature infants (Schaefer 2008).
         c) Greater involvement of legs than arms.
         d) Children with spastic diplegia are late in attaining all gross motor skills, but the delay in standing and walking are most notable. Generally, there is only mild functional impairment of the upper

extremity. In a prospective study, being able to sit independently at 2 years was a good predictive sign of future ambulation. Children who could not sit by age 4 did not ambulate.

ii. Quadriplegia
   a) 30% of children with spastic cerebral palsy have quadriplegia (Berker and Yalçin 2008)
   b) The only type associated with asphyxia in term infants (Schaefer 2008)
   c) All four extremities, the trunk, and muscles that control the mouth, tongue, and pharynx get affected
   d) Children with spastic quadriplegia present a much broader spectrum of disability
   e) The severity of motor involvement affects the delay in developmental milestones
   f) About one-fourth of children with spastic quadriplegia have only mild involvement, with minimal functional limitation with regard to mobility or self-care
   g) About one-half are moderately impaired
   h) These patients are unable to achieve complete independence but are able to function reasonably well
   i) About one-quarter of patients are severely involved, require total care, and are unable to ambulate
   j) Independent sitting at 2 years and suppression of obligatory reflexes are good prognostic signs for eventual ambulation

iii. Hemiplegic/monoplegia
   a) Most likely causes (focal traumatic, vascular, or infectious lesion).
   b) Not typically associated birth asphyxia (Schaefer 2008).
   c) 20% of children with cerebral palsy have hemiplegia (Berker and Yalçin 2008).
   d) One-sided (unilateral) involvement: a unilateral brain infarct with posthemorrhagic porencephaly apparent on MRI.
   e) Upper extremity generally more affected than the lower.
   f) Exhibit definite hand preference before 1 year of age, compared with most children who display handedness at about age 2.
   g) Display either an asymmetric crawl or no crawl at all.
   h) Almost all children with spastic hemiplegia do ambulate. Most become independent with activities of daily living, using some aids.
   i) Seizures, mild mental retardation, learning difficulties, and behavioral disturbances may complicate the management and integration into society.

iv. Double hemiplegic: both sides, arms > legs

d. Children with spastic syndromes, in general, often show white matter injury on imaging
e. Most closely linked to periventricular leukomalacia but may also be secondary to congenital human immunodeficiency virus, dopa-responsive dystonia, hereditary spastic paraplegia, or spinal pathology, arginase deficiency, and Sjögren–Larsson syndrome, with characteristic appearances on imaging

8. Dyskinetic cerebral palsy
   a. Dyskinetic cerebral palsy accounts for approximately 10–15% of all cases of cerebral palsy (Berker and Yalçin 2008).
   b. The most probable etiology: hyperbilirubinemia or severe anoxia that causes basal ganglia dysfunction.
   c. Choreoathetoid (hyperkinetic) and chorea: the main movement disorders seen in dyskinetic children.
   d. Dysarthria, dysphagia, and drooling accompany the movement problems.
   e. Children with dyskinetic cerebral palsy typically suffer from severe neuromuscular dysfunction. The abnormal movements are first noticed in the hands and fingers, but abnormal movements are usually noted in all extremities by 18 months of age. The writhing, involuntary movements give way to dystonia. As a result, all of their gross motor milestones are significantly delayed. Only about one-half of these children are able to walk, and they normally do not walk until after 3 years of age.

Children who are able to walk usually develop the coordination necessary to perform their activities of daily living. Those who do not walk typically require almost total care.

f. Abnormal movements that are most obvious when a patient initiates a movement. These abnormal movements are caused by inadequate regulation of muscle tone and coordination.
g. When the patient is relaxed, there is usually full range of motion with decreased tone.
h. The patient often has a "cogwheel" type resistance, without changes in the deep tendon reflexes. Tone decreases when the patient is supine, and tone may "shake loose."
i. There are two main types of dyskinetic movement.
   i. The first is dystonia, in which abnormal shifts of general muscle tone are induced by movement. These patients tend to retain abnormal posture in the same stereotyped patterns.
   ii. The second main type of dyskinetic movement is choreoathetoid, in which the initiation of movement in one extremity leads to movement of other muscle groups. These patients exhibit slowly writhing involuntary movements in combination with abrupt, irregular, jerky movements.

9. Ataxic cerebral palsy
   a. Ataxic CP is the disturbance in the coordination of voluntary movements caused by muscle dyssynergia.
   b. Usually caused by cerebellar dysfunction.
   c. Ataxia becomes apparent toward the age of 2–3 years.
   d. Generally seen in association with spastic diplegic cerebral palsy.
   e. Now often categorized in the group of dyskinetic CP.
10. Mixed cerebral palsy
   a. Ataxia and dystonia occurring together with spasticity.
   b. The damage, usually, is more global, and the patients are quadriplegic.
11. Extrapyramidal cerebral palsy syndromes
   a. Characterized by rigidity, elicited clinically by passive stretch independent of velocity or dystonia, which is often action-induced twisting or fixed postures
   b. Arm use is typically more affected than leg function
   c. Children with extrapyramidal syndromes, in general, frequently have basal ganglia abnormalities on imaging
   d. May result from genetic metabolic disorders such as glutaric aciduria type 1 (caudate/putamen), mitochondrial disorders such as Leigh syndrome (globus pallidus/caudate/putamen), kernicterus (globus pallidus), or hypoxic–ischemic encephalopathy (putamen/thalamus)
12. Associated conditions in children with cerebral palsy (Ashwal et al. 2004)
   a. Mental retardation (52%)
      i. Cognitive and neuropsychological function in children with CP are commonly impaired
      ii. In general, no absolute relation between the type of CP and severity of cognitive impairment. However, the following correlations are noted:
         a) Greater degree of mental impairment in spastic quadriplegia than in spastic hemiplegia
         b) Severity of cognitive deficits appears to correlate with motor deficits associated with spastic cerebral palsy in contrast to dyskinetic cerebral palsy where this relation is lacking
         c) Greater intellectual impairment in cerebral palsy in the presence of epilepsy, abnormal EEG, or abnormal neuroimagings
   b. Speech and language disorders (38%)
      i. Anarthric or dysarthric speech and other impairments related to oral motor dysfunction are common due to bilateral corticobulbar dysfunction (i.e., articulation disorders and impaired speech intelligibility present in 38%)
      ii. Inability to develop the linguistic skills necessary to develop more complex speech patterns due to impaired mobility which causes limited interaction with individuals in the environment
      iii. Language (as opposed to speech) deficits in CP closely related to verbal intellectual limitations associated with mental retardation

iv. Oral motor problems may lead to potential serious impacts on nutrition and growth, oral health, respiration, and self-esteem
a) Feeding difficulties
b) Swallowing dysfunction
c) Drooling

c. Ophthalmologic defects (28%)
i. Visual impairments and disorders of ocular motility are common
a) Strabismus
b) Amblyopia
c) Nystagmus
d) Optic atrophy
e) Refractive errors
ii. Visual perceptual problems more likely in those due to periventricular leukomalacia

d. Hearing impairment (12%)
i. More commonly in children with following etiologies:
a) Low birth weight
b) Kernicterus
c) Neonatal meningitis
d) Severe hypoxic–ischemic insults
ii. Greater risk in children with CP who have mental retardation or abnormal neuroimaging studies

e. Epilepsy (43%)

13. Clues to the so-called cerebral palsy of unknown etiology (Dodge 2008)
a. Family history (familial spastic paraplegia)
b. Normal deep tendon reflexes (transient toe walking)
c. Calf hypertrophy with positive Gower sign (muscular dystrophy)
d. Regression, lethargy, unusual vomiting
i. Ichthyosis (Sjögren–Larsson syndrome)
ii. Severe self-mutation (Lesch–Nyhan syndrome)
e. Recurrent stroke, cardiomyopathy, hypoglycemia (mitochondrial disorders)
f. Multiple anomalies
g. Lissencephaly (Miller–Dieker syndrome)
h. Acquired microcephaly, hand wringing (Rett syndrome)

14. Medical complications associated with cerebral palsy (Dougherty 2009)
a. Spasticity
b. Joint contractures, misalignment secondary to muscle spasticity
c. Hip dislocation
d. Osteoporosis
e. Intellectual disability (seen in 30–50% of individuals)
f. Seizures
g. Gastroeosphageal reflux
h. Dysphagia or aphagia
i. Failure to thrive/malnutrition
j. Hearing loss

15. Possible source of pain (dodge 2008)
a. Cranial
i. Increased intracranial pressure
ii. Migraines and other headaches
b. Ophthalmologic
i. Corneal abrasion
ii. Glaucoma
c. Dental
i. Abscesses
ii. Temporomandibular joint pain
d. Gastrointestinal
i. Gastroesophageal reflux
ii. Constipation
e. Musculoskeletal
i. Hip dislocation
ii. Scoliosis
f. Neuromuscular (muscle spasms)
g. Urologic
i. Urolithiasis
ii. Bladder spasms
h. Other (Decubitus ulcers)

16. Proposed diagnostic criteria of cerebral palsy (Kavčič and Vodušek 2005)
a. Possible CP
i. Mandatory inclusion criteria
a) Disorder of movement and posture manifesting as spastic diplegia, spastic hemiplegia, spastic tetraplegia, ataxia, dystonia, choreoathetosis – alone or in any combination
b) Onset early in life
c) No evidence of progression
ii. Mandatory exclusion criteria
a) Active disease that could explain the foregoing features
b) Chromosomal disorders
iii. Supportive features
a) Other signs of brain dysfunction that could be caused by the same pathological process as the foregoing disorders of

movement and posture (epilepsy, learning disorders, disorders of speech, vision or hearing)
- b) Born after multiple pregnancy
- c) Vanishing twin syndrome
- d) Intrauterine growth retardation
- e) Major antenatal placental abruption
- f) Preterm birth
- g) Acute intrapartum hypoxia
- h) Reduced fetal heart rate variability from the onset of labor
- i) Extensive chorioamnionitis
- j) Congenital coagulation disorders
- k) Autoimmune disease of the mother
- l) No child with the same/similar clinical picture in a family

b. Probable CP: Mandatory inclusion criteria:
- i. Disorder of movement and posture as in possible CP
- ii. Onset early in life
- iii. No evidence of progression or other disease that could explain the foregoing features at school age

c. Definite CP: Mandatory inclusion criteria:
- i. Disorder of movement and posture as in probable CP
- ii. Plus still no evidence of progression unrelated to aging or other disease that could explain the foregoing features at age 18 or older

17. Prognosis (Blair et al. 2001)
    a. Most persons with cerebral palsy survive to adulthood except those with profound intellectual deficit
    b. Survival strongly associated with degree of intellectual deficit
    c. Mortality declines with age during childhood
    d. Cause of death usually due to respiratory problems such as aspiration pneumonia

Diagnostic Investigations

1. EEG
    a. For features suggesting presence of epilepsy or epileptic syndrome
    b. Probably not very helpful in determining the etiology of cerebral palsy
2. Neonatal audiometric screening
3. MRI (preferred to CT scanning) (Russman and Ashwal 2004)
    a. Higher yield of suggesting an etiology and timing of insult leading to CP
    b. MRI abnormalities in children with cerebral palsy
        - i. Acquired lesions
            - a) Periventricular leukomalacia with other areas of injury
            - b) Diffuse encephalopathy (cortical/subcortical atrophy/ventriculomegaly)
            - c) Focal ischemic/hemorrhagic (e.g., infarct porencephaly)
            - d) Multicystic encephalomalacia
            - e) Trauma (at birth or later)
            - f) Infection
        - ii. Malformations
            - a) Cortical dysplasia/polymicrogyria
            - b) Schizencephaly
            - c) Pachygyria/lissencephaly
            - d) Complex brain malformation
            - e) Agenesis/hypoplasia of the corpus callosum
            - f) Arachnoid cyst
            - g) Vermian/cerebellar hypoplasia
            - h) Hydrocephalus/holoprosencephaly/hydranencephaly
        - iii. Miscellaneous or unknown
            - a) Miscellaneous etiologies
            - b) Delayed/abnormal myelination
        - iv. Normal
4. Metabolic and genetic testing (Russman and Ashwal 2004; Schaefer 2008)
    a. Features of family history that might prompt a genetics/metabolic workup
        - i. Thromboses/vascular accidents
        - ii. Mental retardation/developmental disabilities
        - iii. Seizures
        - iv. Cerebral palsy
        - v. Neuromotor disorders
        - vi. Tumors
        - vii. Neurobehavioral disorders
        - viii. Joint contractures/stiffness
        - ix. Congenital anomalies
        - x. Infertility
        - xi. Recurrent miscarriages/stillborns
        - xii. Adult-onset neurodegenerative conditions

   b. Features on medical history and physical examination prompting a genetics/metabolic workup (Schaefer 2008)
      i. Neuroregression
      ii. Seizures/change in seizure type
      iii. Late onset/acquired microcephaly
      iv. Macrocephaly
      v. Pigmentary changes
      vi. Major and minor dysmorphic features
      vii. Congenital anomalies
   c. Metabolic or genetic causes for CP to occur infrequently (0–4%; true incidence unknown)
   d. Neuroimaging studies showing 7–11% of children with cerebral palsy have a brain malformation suggest the presence of additional risk for genetic and possibly a metabolic etiology
   e. Metabolic studies
   f. High-resolution chromosome analysis
   g. Chromosome microarray analysis
5. Recognizable genetic syndromes known to be associated with a cerebral palsy phenotype
   a. MECP2 mutation study for Rett syndrome
   b. Chromosome 15 anomaly and UBE3A mutation studies for Angelman syndrome
   c. L1CAM mutation study for hereditary spastic paraplegia
   d. PLP1 mutation study for Pelizaeus–Merzbacher spectrum
   e. ARX (X-linked aristaless-related homeobox gene) mutation study for West syndrome

Genetic Counseling

1. Recurrence risk: Recurrence risk depends on the underline genetic disorders (rare) of cerebral palsy
   a. Patient's sib
      i. Recurrence risk is low in most cases caused by hypoxic or ischemic injury to the brain
      ii. Autosomal recessive: 25%
      iii. Autosomal dominant: not increased unless a parent is affected or having gonadal mosaicism
      iv. X-linked recessive disorder: 50% of male sibs affected if the mother is a carrier
      v. Mitochondrial: All sibs are at risk of being affected if the mother has the mitochondrial DNA mutation
   b. Patient's offspring
      i. Autosomal recessive: not increased
      ii. Autosomal dominant: 50%
      iii. X-linked recessive: all daughters of affected males will be carriers. All sons of an affected male will be normal.
      iv. Mitochondrial:
         a) Offspring of males with a mtDNA mutation are not at risk
         b) All offspring of females with a mtDNA mutation are at risk of inheriting the mutation
         c) A female harboring a heteroplasmic mtDNA point mutation may transmit a variable amount of mutant mtDNA to her offspring, resulting in considerable clinical variability among sibs within the same nuclear family (Poulton and Turnbull 2000; Chinnery 2006)
2. Prenatal diagnosis: not reported to date
3. Management
   a. Management strategy and rehabilitation of the child with cerebral palsy (Berker and Yalçin 2008)
      i. Support growth and nutrition
      ii. Therapy for vision
         a) Rehabilitation
         b) Glasses
         c) Surgery
      iii. Dental hygiene
      iv. Gastointestinal problems
         a) Medications for reflux
         b) Gastrostomy
         c) Antireflux surgery
      v. Therapy for motor function
         a) Physical therapy
         b) Occupational therapy
         c) Adaptive seating
         d) Bracing
         e) Wheeled motility
         f) Orthopedic surgery
         g) Sports-recreation
      vi. Oromotor therapy
         a) Chewing
         b) Swallowing
         c) Speech
      vii. Seizure prevention

viii. Spasticity and dyskinesia
  a) Medical treatment
  b) Botulinum toxin

b. Timing of rehabilitative measures
  i. Infancy
    a) Goal: supportive measures for prolonging and optimizing physical status and life
    b) Methods: nutritional support and infant stimulation and positioning
  ii. Childhood
    a) Goal: strategies to obtain maximum independent mobility
    b) Methods: medication to minimize spasticity, exercise, Botulinum toxin, bracing
  iii. Preschool
    a) Goal: maximum independent mobility
    b) Methods: minimize deformity, medication, exercise, Botulinum toxin, bracing, orthopedic surgery
  iv. Adolescence
    a) Goal: education, vocation, and integration into the community
    b) Methods: schooling, sports, psychosocial support

c. Effects of physiolotherapy (Berker and Yalçin 2008)
  i. Physiolotherapy to improve:
    a) Postural control: decreasing spasticity and contracture
    b) Muscle strength: increasing muscle elasticity and joint laxity
  ii. Range of motion
    a) Joint alignment: increasing coordination/agility
    b) Motor control: balance
    c) Muscular/cardiovascular endurance and mobility skills: transitions, use of assistive devices

d. Oral sensorimotor therapy
  i. May be effective in promoting oral motor function
  ii. Not shown to be effective in promoting oral feeding efficiency, caloric intake, weight gain, or pharyngeal motility and airway protection during feedings

e. Gastrostomy tube feeding (Rogers 2004)
  i. An important alternative nutritional source for children with cerebral palsy
  ii. Relative indications
    a) Dysphagia resulting in undernutrition
    b) Aspiration with associated respiratory disease
    c) Insufficient fluid intake and/or refusal of oral medications
    d) Excessive effort or stress during oral feedings.

f. Early intervention programs
  i. Work to optimize development
  ii. Goals: improve function and encourage independence
  iii. Improve family interaction
  iv. Provide family support
  v. Provide education in how to promote development
  vi. The Individuals with Disabilities Education Act mandates early intervention for all children 0–3 years old who demonstrate developmental delay
    a) These programs are typically multidisciplinary and may take place in centers or in the family's home.
    b) The therapists directly provide hands-on therapy to the child or educate the family on how to provide the interventions themselves.

g. Management of spasticity
  i. The management of spasticity is a large part of the treatment of children with cerebral palsy.
  ii. Daily range of motion shown to decrease muscle tone for several hours after it is done and may delay or prevent contractures.
  iii. Use of heat or cold can modify tone in the short term, but either modality is impractical for long-term use.
  iv. Casting and splinting often used as adjuncts to regular range of motion: Casting for 2–3 weeks can decrease tone and improve range of motion for several months.
  v. Cyclical use of electrical stimulation has been found to decrease upper extremity contractures and improve agonist/antagonist balance, but these affects last only for hours.
  vi. Medications.

h. Management of seizures

i. Complemental and alternative therapies (Liptak 2005)
   i. Hyperbaric oxygen (delivery of 100% oxygen)
      a) Theory/benefits: awakens dormant brain tissue surrounding the original injury
      b) Adverse effects: ear trauma, pneumothorax, fire and explosions
      c) Evidence: improvements in the treated children in uncontrolled studies, improvement in treated and controls in controlled study
      d) Comments: more evidence is required
   ii. Adeli suit (originally developed for Russian cosmonauts to counteract the adverse effects of zero gravity, including muscle atrophy and osteopenia)
      a) Theory/benefits: resistance across muscles improves strength, posture, and coordination
      b) Adverse effects: discomfort from suit, expense for intensive therapy and travel to centers that prescribe the suit
      c) Evidence: no conclusive evidence
   iii. Patterning (passively putting children through certain repeated normal motions)
      a) Theory/benefits: passively repeating steps in normal development overcome brain injuries.
      b) Adverse effects: time, energy, and expenses required
      c) Evidence: results of uncontrolled studies are inconsistent; controlled trials show no benefits
      d) Comments: not recommended
   iv. Electrical stimulation (elicits muscle contraction): more evidence required
   v. Threshold electrical stimulation
      a) Theory/benefits: increased blood flow from electrical current leads to stronger muscles
      b) Adverse effects: expense for units, generally safe
      c) Evidence: subjective improvements in some uncontrolled trials; inconclusive in controlled trials
   vi. Functional neuromuscular stimulation
      a) Theory/benefits: increased muscle contraction improves strength and function
      b) Adverse effects: expense, infection from needles, discomfort
      c) Evidence: somewhat more positive than for threshold stimulation but still inconclusive
   vii. Conductive education (interventions including promoting independent functioning using repetition and verbalization by the child)
      a) Theory/benefits: problems with motor skills are due to problems of learning. New abilities are created out of teaching
      b) Adverse effects: not known
      c) Evidence: benefit shown in uncontrolled trials, mixed results in controlled trials
      d) Comments: conductive education implemented in many different ways making generalizations from a single program difficult
   viii. Hippotherapy (equine-assisted therapy)
      a) Theory/benefits: riding a horse improves muscle tone, head and trunk control, mobility in the pelvis, and equilibrium
      b) Adverse effects: trauma from a fall, allergies
      c) Evidence: beneficial effects on body structures and functioning shown by uncontrolled and controlled trials
      d) Comments: increases social participation
   ix. Craniosacral therapy (a cranial rhythm linked with movements in the sacrum transmitted through the dura of the spinal cord by light corrective pressure applied to various points along the craniosacral axis)
      a) Theory/benefits: used to remove impediments to the flow of cerebrospinal fluid within the cranium and spinal cord
      b) Adverse effects: none known
      c) Evidence: no studies showing efficacy, some question the basis of the intervention
   x. Feldenkrais intervention method
      a) Theory/benefits: gentle change of position and directed attention to relax muscles, improve movement, posture, and functioning

b) Adverse effects: none known
c) Evidence: no studies showing efficacy

xi. Acupuncture
a) Theory/benefits: help to restore the normal flow of Qi (energy)
b) Adverse effects: forgotten needles, pain, bruising, and infection
c) Evidence: improvements in several areas shown by uncontrolled and some controlled studies
d) Comments: appears promising, but more studies needed

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Fig. 1 A 10-year-old girl with cerebral palsy secondary to anoxic encephalopathy

Fig. 2 The patient, a 14-year-old boy, was diagnosed with diplegia cerebral palsy. He was born 27 weeks gestation by C Section and was one of the fraternal twins. He had a grade IV intraventricular bleed. Birth weight was 2 lbs. 1 oz. He was in NICU for 2 months

Fig. 3 The patient, a 14-year-old boy, was diagnosed with triplegia cerebral palsy. He was born 32 weeks gestation and on the ventilator for several weeks

Cerebro-Costo-Mandibular Syndrome

Cerebro-costo-mandibular syndrome, a rare congenital syndrome, consists of severe micrognathia, often with the Pierre Robin anomaly, posterior rib-gap defects, and developmental delay (Smith et al. 1966). It is also known as "rib-gap syndrome," "rib-gap defect with micrognathia syndrome," and "Smith–Theiler–Schachenmann syndrome."

Synonyms and Related Disorders

Rib gap defects with micrognathia

Genetics/Pathogenesis

1. Cause: unknown
2. Inheritance
   a. Sporadic in majority of cases
   b. Familial occurrence in a few instances
      i. Autosomal recessive pattern
      ii. Autosomal dominant pattern
3. Pathogenesis of the rib gaps (Megier et al. 1998)
   a. Not well understood.
   b. Rib abnormality results from a lack of fusion between two mesenchymal tissues derived from the somatic mesoderm (posteriorly) and the lateral plate mesoderm (anteriorly).
   c. Defective organization of the somite results in discontinuities of the ribs.

Clinical Features

1. Variable inter- and intrafamilial expression
2. Cardinal signs
   a. Rib abnormalities
      i. Posterior rib gaps
         a) Present in almost all affected newborn infants
         b) Showing great variability in severity
         c) Disappear in time
         d) Sometimes replaced by callus or pseudo-arthroses
      ii. Segmentation defects and rudimentary rib development, fusion of most ribs to the vertebrae, and absence of any normal costovertebral articulations
      iii. Thin ribs
      iv. Agenetic ribs
   b. Micrognathia/Pierre Robin anomaly
   c. Cerebral abnormalities
      i. Microcephaly
      ii. Agenesis of the corpus callosum
      iii. Dilated lateral ventricles
      iv. Porencephalic cyst
      v. Variable degree of mental retardation probably secondary to hypoxia following respiratory distress
3. Other skeletal anomalies
   a. Vertebral anomalies including hemivertebrae
   b. Hip dislocation
   c. Subluxation of the elbows

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   d. Pectus carinatum
   e. Hypoplasia of the sternum, clavicles, and pubic rami
   f. Epiphyseal stippling
   g. Abnormal phalanges and toes
   h. Clubfoot
4. Intrauterine growth retardation
5. Postnatal growth deficiency
6. Respiratory distress
7. Feeding difficulties
8. Language delay
9. Conductive deafness
10. Palatal defect
    a. Short soft palate
    b. Cleft palate
11. Dental defects
12. Laryngeal and tracheal abnormalities
13. Pterygium coli
14. Renal anomalies
    a. Renal cysts
    b. Ectopia
15. Congenital heart defects
16. Prognosis
    a. Mental retardation often among the late survivors
    b. High mortality (40% in the first year of life, 50% in the first month of life) mostly due to respiratory insufficiency secondary to rib abnormalities and flail chest

Diagnostic Investigations

1. Radiography
   a. Rib malformations
      i. Multiple gaps consisting of fibrous or cartilaginous tissue
      ii. Thin ribs
      iii. Agenetic ribs
   b. Vertebral anomalies
   c. Other associated skeletal anomalies
   d. Micrognathia
2. Three-dimensional CT of costo-thoracic skeleton: demonstration of variable gaps in the posterior ribs and absence of ribs (Su et al. 2010)
3. Cranial ultrasonography for cerebral abnormalities
4. Histology of rib gaps: undifferentiated fibrous connective tissue and muscles, instead of cartilage and bone

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Not increased in sporadic cases and in a fresh mutation case of an autosomal dominant disorder
      ii. 25% in an autosomal recessive disorder
   b. Patient's offspring: not increased unless the patient survives and is affected with an autosomal dominant disorder in which case there is a 50% risk of having an affected child
2. Prenatal diagnosis by ultrasonography: difficult to establish
   a. Small mandible
   b. A narrow short chest
   c. Defective ribs
   d. Growth retardation
   e. Vertebral anomalies
   f. Limb anomalies
   g. Increased nuchal translucency
   h. Cystic hygroma
   i. Polyhydramnios
3. Management
   a. Treatment of respiratory distress.
   b. Nasogastric tube feeding.
   c. Tracheostomy may be required.
   d. Surgery for cleft palate.
   e. Early intervention and multidisciplinary team approach.
   f. Orthopedic care for skeletal anomalies.

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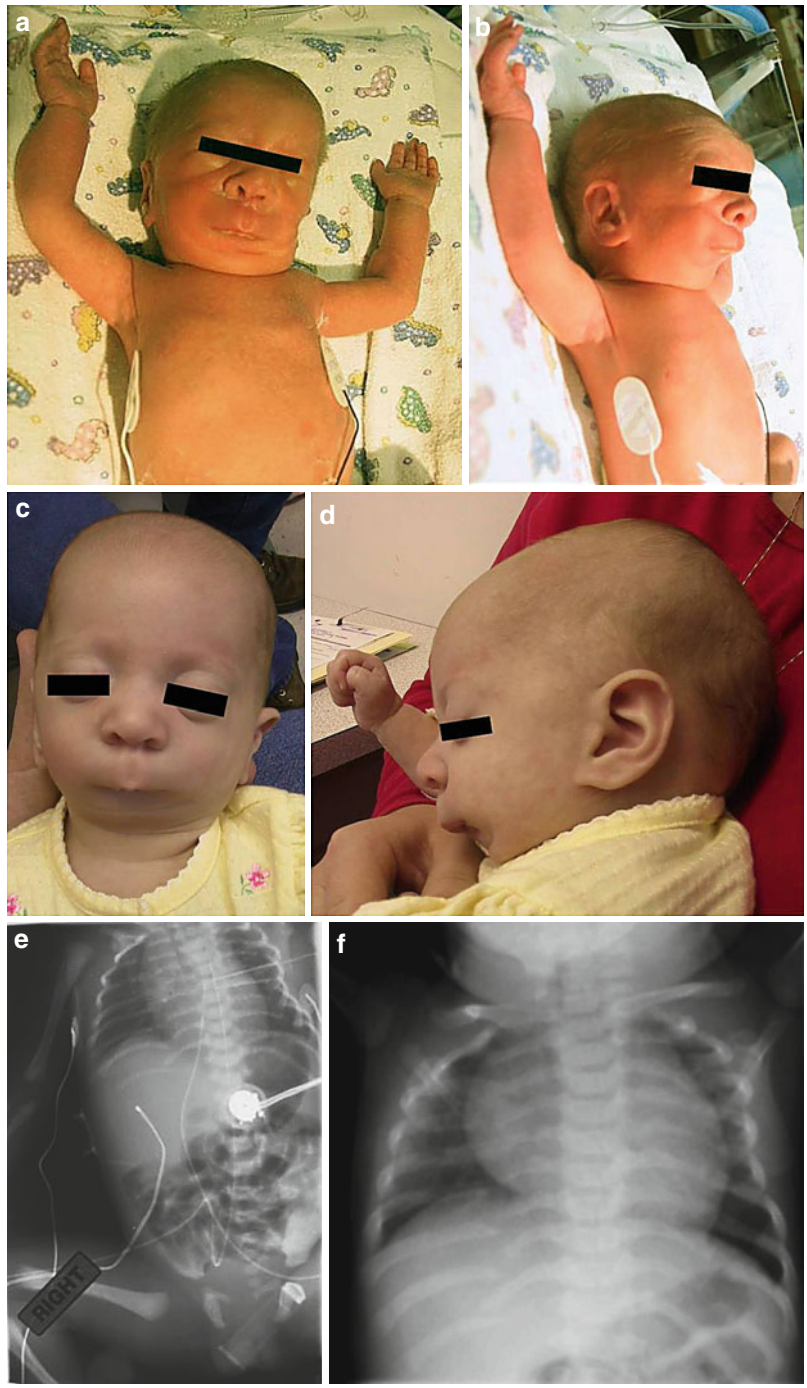

Fig. 1 (**a**–**f**) An infant with cerebro-costo-mandibular syndrome (at birth and 12 weeks of age) showing severe micro/retrognathia and malformations of the ribs with multiple gaps and segmentation defects

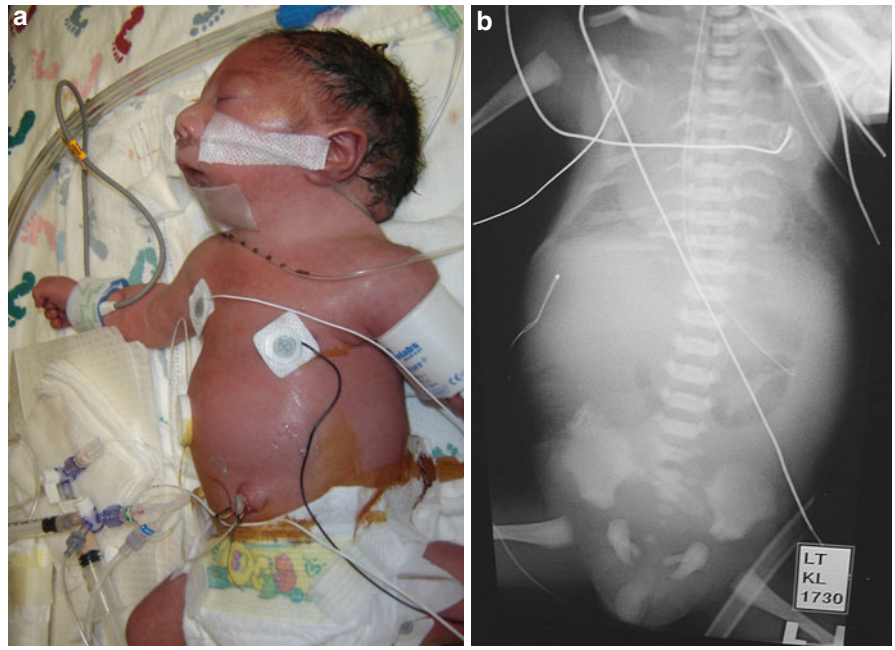

Fig. 2 (**a**, **b**) Another infant with cerebro-costo-mandibular syndrome showing severe micro/retrognathia, a narrow chest, and rib malformations with multiple gaps

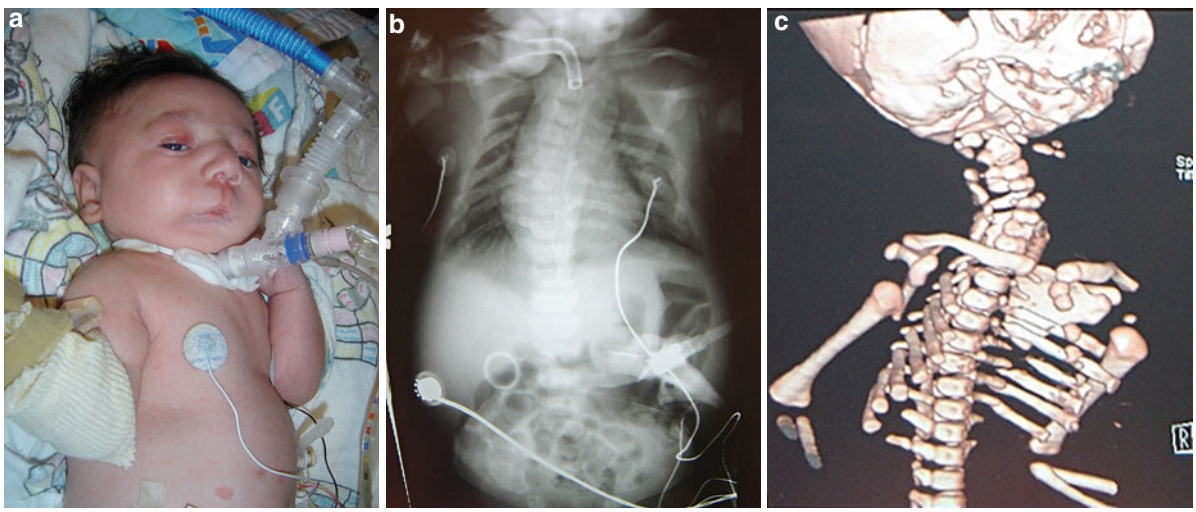

Fig. 3 (**a**–**c**) A neonate presented with severe respiratory distress, requiring tracheostomy. He has severe retromicrognathia and a small chest. Radiographs showed malformations of the ribs with multiple gaps and segmentation defects. A 3-D CT showed variable gaps in the posterior ribs and absence of several ribs

Charcot–Marie–Tooth Disease

Charcot–Marie–Tooth (CMT) disease is the most common inherited peripheral neuropathy. It is a pathologically heterogeneous group of hereditary motor and sensory neuropathies (HMSN), characterized by slowly progressive weakness and atrophy, primarily in the distal leg muscles. The incidence is estimated to be approximately 1 in 2,500.

Synonyms and Related Disorders

Hereditary motor and sensory neuropathy

Genetics/Basic Defects

1. Charcot–Marie–Tooth disease type 1 (CMT1) (Barisic et al. 2008; Bird 2009; Pareyson and Marchesi 2009; Szigeti and Lupski 2009)
   a. Also called hereditary motor and sensory neuropathy type I (HMSN I)
   b. The most common subtype (accounting for about 50% of CMT)
   c. A demyelinating neuropathy
   d. Autosomal dominant-demyelinating form
      i. CMT1A (90% of CMT1 patients): caused by *PMP22* duplication or point mutations (17p11.2–12)
      ii. CMT1B (5–10%): caused by mutations of the myelin protein zero (*MPZ*/*PO*) gene (1q22)
      iii. CMT1C: caused by mutations of *SIMPLE*/*LITAF* gene (16p13.1–p12.3)
      iv. CMT1D: caused by mutations of early growth response gene 2 (*EGR2*) gene (10q21.1–q22.1)
      v. CMT1E: *PMP22* (17p11.2)
      vi. CMT1F: *NEFL* gene (8p21)
2. Charcot–Marie–Tooth disease type 2 (CMT2)
   a. Also called hereditary motor and sensory neuropathy type II (HMSN II)
   b. An axonal neuropathy
   c. Accounting for 20–40% of CMT
   d. Autosomal dominant-axonal form: disease gene loci
      i. CMT2A1: *KIF1B* (1p36.2)
      ii. CMT2A2: *MFN2* (1p33–p36)
      iii. CMT2B: RAB7 (3q21)
      iv. CMT2C: unknown (12q23–q24)
      v. CMT2D: *GARS* (7p15)
      vi. CMT2E: *NEFL* (8p21)
      vii. CMT2F: *HSPB1* (*HSP27*) (7q11–q21)
      viii. CMT2G: unknown (12q12–q13.3)
      ix. CMT2H/K: *GDAP1* (8q13–q21.1)
      x. CMT2I/J: *MPZ* (1q22–q23)
      xi. CMT2L: *HSPB8*/*HSP22* (12q24.3)
   e. Autosomal recessive-axonal form CMT
      i. CMT2B1: *LMNA* (1q21.2)
      ii. CMT2B2: *Med25* (19q13.3)
      iii. CMT2H/2 K: *GDAP1* (8q13–q21.1)
3. Intermediate form of autosomal dominant CMT (rare)
   a. DI-CMTA: unknown (10q24.1–q25.1)
   b. DI-CMTB: *DNM2* (19p12–p13.2)
   c. DI-CMTC: *YARS* (1p34–p35)
   d. DI-CMTD: *MPZ* (1q22)

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4. Autosomal recessive-demyelinating form of CMT4
   a. CMT4A: The first locus identified: 8q13–q21.1 (corresponding gene, *GDAP1*)
   b. CMT4B1: *MTMR2* (11q22)
   c. CMT4B2: *MTMR13/SBF2* (11p15)
   d. CMT4C: *KIAA1985/SH3TC2* (5q32)
   e. CMT4D (HSMN-Lom): *NDRG1* (8q24.3)
   f. CMT4E: *EGR2* (10q21.1–q22, 17p)
   g. CMT4F: *PRX* (19q13.1–q13.2)
   h. CMT4G: unknown (10q23.2)
   i. CMT4H: *FGD4* (12p11.21–q13.11)
   j. CMT4J: *FIG4* (6q21)
5. Autosomal recessive-axonal form of CMT4
   a. CMT4C1 (AR CMT2B1): lamin A/C (1q21.2–q21.3)
   b. CMT4C2 (AR-CMT2C or AR-CMT2H): unknown (8q21.3)
   c. CMT4C3 (AR-CMT2B2): *ARC92/ACID1* (MED25) (19q13.3)
   d. CMT4C4 (AR-CMT2K): *GDAP1* (8q13–q21.1)
6. X-linked dominant form of CMT (CMT1X): accounting for 10–20% of CMT (the second most common form of inherited demyelinating neuropathy, next to CMT1A)
   a. CMTX1: caused by mutations in the gene for the gap junction protein 1 (*GJB1*) or connexin 32 (*Cx32*) on Xq13.1
   b. CMT3A(Dejerine– Sottas syndrome): PMP-32 (17p11.2–12)
      i. Also called hereditary motor and sensory neuropathy type III (HMSN III).
      ii. A severe demyelinating neuropathy.
      iii. Autosomal dominant new mutations (*PMP22* mutations).
      iv. Clinical symptoms overlapping with CMT1: These two disorders may represent a spectrum of related clinical phenotypes that can arise from allelic missense point mutations in the *PMP22* gene.
      v. Allelic mutations in the *MPZ* gene similarly identified in sporadic patients with DSS, also implying that CMT type 1 and DSS constitute a spectrum of peripheral neuropathy phenotypes with common genetic bases.
   c. CMT3B: *MPZ* (1q22–q23)
   d. CMT3C: unknown (8q23–q24)
   e. DSS-EGR: *EGR2* (10q21–q22)
   f. CMT3D or CMT4F: *periaxin* (19q13.1–q13.2)
7. X-linked recessive form of CMT
   a. CMTX2: unknown (Xp22.2)
   b. CMTX3: unknown (Xq26.3–q27.1)
   c. CMTX4 (Cowchock syndrome): unknown (Xq24–q26.1)
   d. CMTX5: unknown (Xq22.3)
8. Autosomal dominant-distal hereditary motor neuropathy (HMN) form of CMT
   a. Distal HMN I: unknown (7q34–q36)
   b. Distal HMN II: *HSP22*, *HSP27* (12q24.3, 7q11–q21)
   c. Distal HMN V (HMN 5A): *GARS* (7p15)
   d. Distal HMN V (Silver syndrome, HMN 5B): *BSCL2* (11q12–q14)
   e. Distal HMN VII A: unknown (2q14)
   f. Distal HMN VII B: *DCTN1* (2p13)
   g. Distal HMN ALS4: *SETX* (9q34)
9. Autosomal recessive-distal HMN form of CMT
   a. Distal HMN III: unknown (11q13)
   b. Distal HMN IV: unknown (11q13)
   c. Distal HMN VI : *IGHMBP2* (11q13.2–q13.4)
   d. Distal HMN-Jerash: unknown (9p21.1–p12)
10. Autosomal dominant-hereditary sensory and autonomic neuropathy (HSAN)
    a. HSAN I: *SPTLC1* (9q22.1–q22.3)
    b. HSAN 1B associated with cough and gastroesophageal reflux: unknown (3p22–p24)
11. Autosomal recessive–HSAN form
    a. HSAN II: *HSN2* (12p13.33)
    b. HSAN III (Riley–Day syndrome): *IKBKAP* (9q31)
    c. HSAN IV: *TRKA/NGF* (1q21–q22)
    d. HSAN V: *TRKA/NGF* (1q21–q22), *NGFβ* (1p13.2–p11.2)
    e. HSAN with deafness and global delay: unknown
    f. HSAN with spastic paraplegia: unknown (5q15.31–q14.1)
    g. X-linked HSAN associated with deafness: unknown (Xq23–q27.3)
12. Problems in classification of inherited neuropathies
    a. *PMP22* deletion causes HNPP.
    b. PMP22 duplication causes CMT1A.
    c. Deletion and duplication of *PMP22* causes HNPP and CMT1A, respectively, establishing a singular genetic mechanism as the cause of the two most common inherited neuropathies.

d. *PMP22* mutations cause DSS, CMT1A, and HNPP.
e. *MPZ* mutations cause DSS, CMT1B, and a CMT2-like phenotype.
f. *GJB1* mutations cause CMT1X.
g. *EGR2* mutations cause CMT1 and DSS.

Clinical Features

1. Family history (Jani-Acsadi et al. 2008)
   a. Autosomal dominant
      i. Multiple generations affected
      ii. Male-to-male transmission
      iii. Females and males affected
   b. Sporadic: only one member in the family affected
   c. Autosomal recessive
      i. Consanguinity
      ii. Multiple children affected
      iii. Parents unaffected
   d. X-linked
      i. No male-to-male transmission
      ii. Males may be more severely affected than females
2. Clinical phenotype of all forms of CMT
   a. Generally similar
   b. Clinical presentation with distal leg weakness and atrophy
   c. Followed by hand involvement
3. Presence of a wide range of variation and severity of symptoms in the affected areas and in the rate of progression of symptoms
4. CMT1A
   a. Accounting for 90% of CMT1 patients
   b. A wide range of variation in clinical presentation and severity among affected members of large families with CMT1A
   c. CMT1A *PMP22* duplication
      i. Asymptomatic patients
         a) Observed in some family members in large pedigrees
         b) No symptoms
         c) Normal neurologic examination including ability to walk on their heels and normal stretch reflexes
         d) Slow MNCV
         e) Duplication of *PMP22* confirming the diagnosis of CMT1A
      ii. Symptomatic patients
         a) Onset: first decade or early in the second decade
         b) Presenting symptoms in infants and children: walking on their toes and have severe tightness of the heel cord
         c) Occasional patients born with foot deformities including clubfeet
         d) Other symptoms: abnormal gait, foot deformities, or loss of balance
         e) Muscle weakness starting in the feet and legs
         f) Frequently trip over objects on the floor and sprain ankles as a result of weakness of the dorsiflexor muscles of the feet, innervated by the peroneal nerves
         g) Difficulty or inability to walk on heels
         h) Tight heel cords
         i) Foot drops with each step, forcing the patient to flex the hip, giving the steppage or equine gait
         j) Pes cavus deformity developing with age
         k) Atrophy of the legs, due to wasting of the peroneal muscles giving the stork legs or "inverted champagne bottle" appearance
         l) Weakness of the intrinsic hand muscles usually occurring late in the course of the disease
         m) Claw hands
         n) Mild sensory loss to pricking pain in the legs in some patients
         o) Frequently decreased vibratory sense
      iii. Associated symptoms
         a) Enlarged (auricular, ulnar, and peroneal) nerves in 20–25% of the patients, not related to the age of the patient or the severity of the disease.
         b) Tremor in 40% of the patients.
         c) Hip dysplasia with hip pain and a limp.
         d) Restrictive lung disease usually not a major problem in patients with CMT1.
         e) Other associated features: spastic paraparesis, deafness, optic atrophy, Marfan-like appearance, and absence of eyebrows.

f) Exacerbation of the weakness in 50% of the patients with early-onset disease during pregnancy and delivery.
g) Certain medication and neurotoxic substances may aggravate the neuropathy in patients with CMT.

d. CMT1A point mutations in *PMP22*
i. Show severe disease in childhood
ii. Found in patients that have been diagnosed with the Dejerine–Sottas syndrome

5. CMT1B
a. Accounting for less than 10% of CMT1 patients
b. *MPZ* mutations identified in CMT1B, DDS, or congenital hypomyelination phenotype
c. Differentiating from CMT1A
i. An earlier onset of the symptoms manifested by delayed ability to walk
ii. Proximal leg weakness without decreasing ambulation
iii. Slower motor NCVs

6. CMT2
a. Neuronal type (a progressive peripheral motor and sensory neuropathy)
b. Clinical phenotype similar to the type 1 CMT
i. Symptoms
a) Tingling
b) Numb feeling
c) Pain
d) Muscle cramp
e) Loss of muscle strength: distal weakness with feet involvement first
f) Walking instability
g) Increased loss of strength
h) Increased sensory loss
ii. Signs
a) Atrophied hands
b) Atrophied legs
c) Postural tremors
d) Fasciculations
e) Pes cavus
f) Claw toes
g) Steppage gait
h) Leg atrophy
i) Short calf muscles
j) Abnormal Romberg sign
k) Absent biceps, triceps, knee, and ankle jerks

c. Other characteristics
i. Generally a later onset of the symptoms than seen in type 1
ii. Pes cavus and short calf muscles: predominantly present in patients with early-onset disease
iii. Less involvement of the hand muscles
iv. No clinical evidence of palpable enlarged nerves
v. No sensory deterioration
vi. Normal or slightly diminished motor nerve conduction velocities

7. Autosomal recessive CMT (CMT4)
a. Progressive motor and sensory neuropathy
b. Rare heterogeneous forms with a broad spectrum of clinical severity
c. Presentation of symptoms in infancy by delay in walking
d. Early and rapidly progressive deformities of the feet and spine
e. A high incidence of associated features such as sensorineural hearing loss
f. Weakness beginning in the feet but affecting both distal and proximal muscles
g. No enlargement of superficial nerves
h. Presence of three pathologic forms

8. X-linked CMT (CMTX)
a. Inheritance
i. Dominant form in 90% of cases
ii. Recessive form in 10% of cases
b. A disease-causing mutation and a family pedigree consistent with X-linked dominant inheritance
i. Presence of a disease-causing mutation in the *GJB1* (*Cx32*) gene
ii. Lack male-to-male transmission
c. Males and females with peripheral motor and sensory neuropathy
i. Affected males
a) More severe phenotype than the affected females
b) More severe progressive peripheral motor and sensory neuropathy than that seen in CMT1A
c) Moderately slow median nerve MNCV: 34.5 +/− 6.2 m/s
d) Reduced motor and sensory nerve amplitudes (median nerve CMAP): 3.7 +/− 3.7 mV

ii. Affected females
a) Normal, or mild to moderate signs and symptoms
b) Moderately slow MNCV: 45.8 +/− 7.3 m/s
c) Reduced motor and sensory nerve amplitudes (median nerve CMAP): 7.8 +/− 3.4 mV

d. Signs and symptoms
i. Typical presenting symptom: weakness of the feet and ankles
ii. Initial physical findings: depressed or absent tendon reflexes with weakness of foot dorsiflexion at the ankle
iii. Typical adult patients
a) Bilateral foot drop
b) Symmetrical atrophy of muscles below the knee with stork leg appearance
c) Pes cavus
d) Atrophy of intrinsic hand muscles especially the thenar muscles of the thumb
e) Absent tendon reflexes in both upper and lower extremities
f) Proximal muscles usually remaining strong
g) Mild to moderate sensory loss (deficits of position, vibration, and pain/temperature) commonly occurring in the feet

e. Other characteristics
i. Symptoms typically develop between ages 5 and 25 years
ii. Onset commonly within the first decade in males
iii. Earlier onset with delayed walking in infancy as well as later onset beyond the fourth decades possible
iv. Mild symptoms may be overlooked by patient and physician.
v. Severe motor slowing in most families, consistent with a demyelinating form of the disease
vi. A predominant axonal type also been described

9. Dejerine–Sottas syndrome (DSS)
a. The syndrome still used to define the rare cases of severe hypo-demyelinating neuropathy of early onset
b. Criteria for diagnosis
i. Early onset of the disease by age 2 years with delayed motor milestones.
ii. Severe motor, sensory, and skeletal muscle deficits, frequently extending to proximal muscles. Sensory ataxia and scoliosis also present.
iii. Very low conduction velocities, usually <12 m/s.
iv. Nerve biopsy reveals severe hypomyelination and basal lamina reduplication, with multiple onion bulb formation.
v. Presence of the enlarged nerves
c. De novo point mutations in either *MPZ* or *PMP22* found in most DSS cases
d. May be a variant of CMT1A or CMT1B

10. Congenital hypomyelination (CH)
a. An ill-defined and extremely rare disease merging into Dejerine–Sottas disease.
b. A clinical syndrome characterized by infantile hypotonia due to distal muscle weakness is flexia and very slow NCVs. Severe weakness may lead to early death.
c. Severe contractures of joints or arthrogryposis multiplex congenita in severe cases.
d. Mutation analysis showing *MPZ* mutations, suggesting some of the DSS and CH are part of a spectrum of the demyelinating form of CMT1B.

11. Hereditary neuropathy with liability to pressure palsies (HNPP)
a. Also called familial recurrent polyneuropathy or tomaculous neuropathy
b. Clinical manifestations
i. Periodic/transient/recurrent episodes of numbness, muscular weakness, and atrophy
ii. Palsies after relatively minor compression or trauma of the peripheral nerves (the axillary, median, radial, ulnar, and peroneal nerves)
c. Nerve conduction abnormalities mainly localized at common entrapment sites
d. Nerve biopsy: occurrence of focal myelin thickenings (tomacula) in several fibers
e. Commonly associated with deletion of *PMP22* gene

Diagnostic Investigations

1. Two types of CMT, currently distinguishable by the value of motor nerve conduction velocity (MNCV) of median nerve on electrophysiologic examination and nerve biopsy findings
   a. Demyelinating form (CMT1)
      i. Slowing of MNCV (15–30 m/s)
      ii. Hypertrophy of peripheral nerves with onion bulb formation and segmental demyelination
   b. Axonal form (CMT2)
      i. Normal or mildly slow MNCV (>40 m/s)
      ii. Normal size nerves
      iii. No evidence of segmental demyelinations
2. Motor nerve conduction velocity of the median nerve (MNCV)
   a. Uniform conduction slowing
      i. CMT1A
      ii. CMT1B
      iii. CMT4
      iv. Dejerine–Sottas syndrome
   b. Multifocal conduction slowing
      i. CMTX
      ii. Hereditary neuropathy with liability to pressure palsies (HNPP)
   c. Incompletely characterized electrophysiology
      i. *PMP22* point mutations
      ii. *MPZ* point mutation
      iii. *EGR2* mutations
   d. Usually normal in CMT2
3. EMG testing: evidence of an axonal neuropathy in CMT2
   a. Positive waves
   b. Polyphasic potentials
   c. Fibrillations
   d. Reduced amplitudes of evoked motor and sensory responses
4. Compound motor action potentials (CMAP): greatly reduced in CMT2
5. Nerve biopsy
   a. CMT1A
      i. Regression of onion bulb
      ii. Significantly increased ratio of axon diameter/total fiber diameter, indicating arrested remyelination
   b. CMT1B
      i. Demyelinating process with onion bulb formation (sural nerve biopsy).
      ii. Ultrastructural finding of uncompacted myelin is consistent with the accepted function P_o as a homophilic adhesion molecule.
   c. CMT2
      i. No histological evidence of well-formed onion bulbs on the nerve biopsies
      ii. Loss of myelinated fibers with signs of regeneration, axonal sprouting, and atrophic axons with neurofilaments
   d. Autosomal recessive-demyelinating CMT with three pathologic forms:
      i. Classical onion bulbs
      ii. Basal laminar onion bulbs
      iii. Focally folded myelin sheaths
   e. CMTX
      i. Nerve hypertrophy or onion bulb formation: rare
      ii. A primary axonal neuropathy with axonal sprouting in most affected individuals
      iii. Prominent demyelination consistent with a CMT1 phenotype in some cases
   f. Congenital hypomyelination: hypomyelination (few thin myelin lamella) without active myelin breakdown products and early onion bulb formations
   g. Hereditary neuropathy with liability to pressure palsies (HNPP): demyelination and remyelination with tomacula or sausage-like thickening on the myelin sheath
6. Molecular genetic testing
   a. CMT1
      i. CMT1A
         a) Sequence analysis for point mutations in the *PMP22* gene
         b) Mutation scanning for point mutations in the *PMP22* gene
      ii. CMT1B
         a) Sequence analysis for point mutations in the *MPZ* gene
         b) Mutation scanning for point mutations in the *MPZ* gene
      iii. CMT1C: direct DNA/linkage analysis for point mutation in *LITAF*
      iv. CMT1D
         a) Sequence analysis for point mutations in the *EGR2* gene
         b) Mutation scanning for point mutations in the *EGR2* gene

b. CMT2E: sequence analysis for mutations in *NEFL*
c. CMT4
   i. CMT4E: molecular genetic testing for *EGR2*
   ii. CMT4F: molecular genetic testing for *PRX*
d. CMTX: sequence analysis to detect mutations in the *GJB1* coding region (accounting for about 90% of mutations in patients with CMTX)
e. Molecular genetic testing approach
   i. In cases of HNPP
      a) Test for the *PMP22* deletion (since this is by far the major cause)
      b) If negative, then sequence *PMP22*
   ii. In CMT patients with uniform slowing of motor NCVs between 10 and 35 ms
      a) Test for the *PMP22* duplication (since this is the major cause of CMT1)
      b) If negative, sequence *PMP22*, *MPZ*, *GJB1*, and *EGR2*
   iii. In DSS with appropriately slowed NCVs
      a) Test for the duplication: usually negative
      b) Sequence *PMP22*, *MPZ*, *GJB1*, *EGR2*, and *PRX* genes
   iv. In cases where CMT1X is the most likely diagnosis (based on intermediate slowing of NCVs, no male-to-male transmission)
      a) Sequence *GJB1* alone: the appropriate initial test
      b) If negative, sequence *MPZ* and *NEFL*
   v. In cases of suspected CMT2
      a) Probably premature to test for *MPZ* and *NFEL* mutations alone (the only commercially available tests)
      b) Await a comprehensive battery in the future

Genetic Counseling

1. Recurrence risk (Bird 2009)
   a. Patient's sib
      i. Autosomal dominant CMT
         a) Majority of CMT1 patients carry the *PMP22* duplication and represent de novo mutation cases: recurrence risk to sib not increased unless a parent is affected, in which case the recurrence risk is 50%
         b) Patients with de novo *MPZ* mutation: recurrence risk to sibs not increased unless a parent is affected, in which case the recurrence risk is 50%
      ii. Autosomal recessive CMT: 25%
      iii. X-linked dominant CMT (patients with Cx32 mutation)
         a) A carrier mother has a 50% risk of transmitting the disease-causing mutation with each pregnancy. Sons who inherit the mutation will be affected. Daughters who inherit the mutation will be carriers and may or may not be affected.
         b) A noncarrier mother: recurrence risk to sibs low but not zero since the risk of germ-line mosaicism in mothers is not known.
   b. Patient's offspring
      i. Autosomal dominant CMT: Patients with *PMP22* duplication, *PMP22* deletion, or *MPZ* mutation will have a 50% risk of transmitting the disease to the offspring.
      ii. Autosomal recessive CMT: not increased unless the spouse is a carrier or affected.
      iii. X-linked dominant CMT (patients with Cx32 mutation)
         a) All the daughters of an affected male inherit the mutation but may or may not have symptoms.
         b) None of his sons will be affected.
2. Prenatal diagnosis available to pregnancies at risk for CMT1A, CMT1B, CMT2E, CMT4E, CMT4F, and CMTX
   a. Identify the disease-causing allele of an affected family member before prenatal diagnosis
   b. Mutation analysis of fetal DNA obtained from amniocentesis or CVS
   c. CMT1
      i. Prenatal diagnosis of CMT1A by FISH
         a) Parental blood samples confirmed to be duplicated for *PMP22* by FISH
         b) Interphase FISH assay performed on amniotic fluid specimens and chorionic villus samples to detect a submicroscopic 17p12 duplication in the fetus with CMT1A
      ii. Preimplantation diagnosis for CMT1A: selection of healthy embryos is made based on the presence of the nonduplicated haplotype and heterozygosity of a marker

d. CMT2E: molecular genetic testing of DNA extracted from fetal cells obtained from amniocentesis or CVS for testing of *NEFL* mutation when both disease-causing alleles of an affected family member are identified
e. CMT4E and CMT4F: molecular genetic testing of DNA extracted from fetal cells obtained by amniocentesis or CVS for testing of *EGR2* and *PRX* mutations, respectively, when both disease-causing alleles of an affected family member are identified
f. CMTX
   i. Prenatal diagnosis available to pregnancies of women who are heterozygotes for a disease-causing *GJB1* mutation that has been identified in an affected family member
   ii. Amniocentesis or CVS
      a) Determination of the fetal sex
      b) DNA extracted from cells from male fetuses tested to determine if a disease-causing mutation is present

3. Management
   a. No specific treatment to reverse or slow the natural disease process
   b. Supportive care (Jani-Acsadi et al. 2008)
      i. Musculoskeletal dysfunctions: scoliosis, foot deformities, and hand atrophy
         a) Evaluation by physiatry
         b) Physical therapy
         c) Occupational therapy
         d) Orthotics and assistive devices
         e) Corrective surgery
      ii. Respiratory dysfunction
         a) Pulmonary evaluation
         b) Continuous positive airway pressure (CPAP)
         c) Bi-level positive airway pressure (BiPAP)
         d) Scoliosis correction
      iii. Sensory dysfunction
         a) Pain control
         b) Topical medications (lidocaine patch)
         c) Antidepressants: tricyclics (amitriptyline, nortriptyline, desipramine)
         d) Anticonvulsants: gabapentin, pregabalin
         e) Lamotrigine, carbamazepine
      iv. Iatrogenic neurology
         a) Avoid medications that are known to cause nerve damage: chemotherapeutic drugs (vincristine, cis-platinum, mivacurium), Taxol, cisplatin, isoniazid, and nitrofurantoin
         b) Refer to CMTA Web site regarding updated lists of medication (www.charcot-marie-tooth.org)

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Fig. 1 (**a**, **b**) Two patients with Charcot–Marie–Tooth disease showing stork-like legs and pes cavus deformities

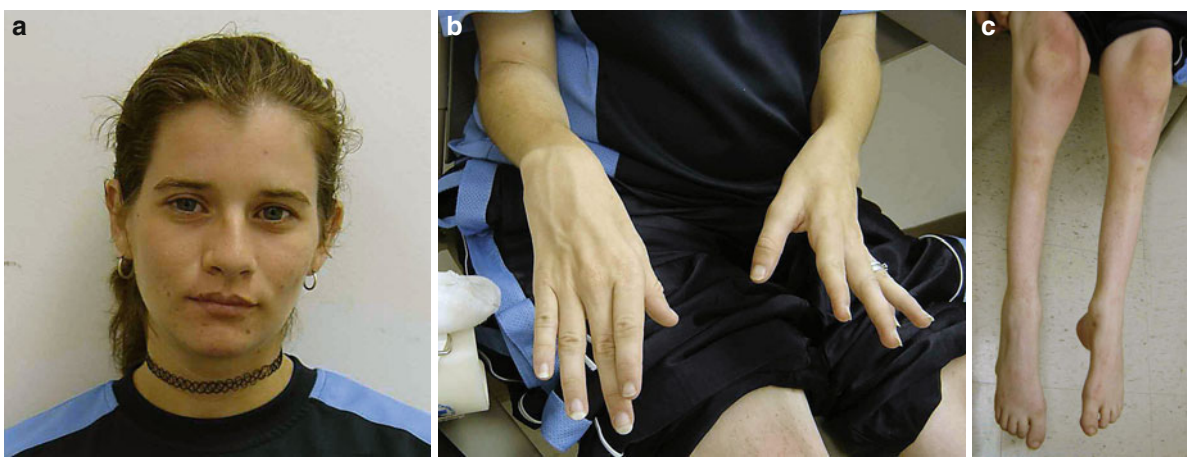

Fig. 2 (**a**–**c**) A 23-year-old female with Charcot–Marie–Tooth disease showing stork legs with muscle wasting, pes cavus deformities, and foot drop. She has absent deep tendon reflexes. Her onset of disease began in the third grade with a history of tripping, falling, and clumsiness. Family history revealed affected individuals in three generation

Fig. 3 An 11-year-old girl was evaluated for "stork-like legs." She was noted to have loss of balance, tip-toe walking, and muscle weakness, particularly in her lower extremities. On examination, she was noted to have claw hands (finger contractures at PIP), "stork-like" legs, muscle weakness in the lower extremities, tight heel cord, pes cavus, and absent deep tendon reflexes. The motor nerve and sensory nerve conduction tests showed severe prolonged latency and severe reduced amplitude. The left median, radial, tibial, and peroneal motors, median, ulnar, radial, and sural sensories were absent. The study showed electrophysiologic evidence of a severe sensorimotor polyneuropathy. A complete CMT molecular evaluation showed her to possess one known recessively inherited mutation in the *GDAP1* gene and one or more DNA variants of unknown significance

Fig. 4 A 26-year-old mother was diagnosed to have Charcot–Marie–Tooth disease type 1A at 15 years of age with complaints of weakness and pain in the arms, shoulders, hips, and neck and had a slight decrease in the pulmonary function test. Her DNA testing showed duplication of peripheral myelin protein n*PM-22*) gene, inherited from her father. The 5-month-old daughter is asymptomatic and carries no *PMP22* gene mutation

Fig. 5 A 31-year-old man with Charcot–Marie–Tooth disease type 1A, confirmed molecularly to have *PMP22* gene mutation associated with 17p12 microduplication. A son died at 3 month of age of ACTA1-related nemaline myopathy. The baby's chromosome microarray analysis showed 17p12 and 16q23.1 microduplications. Duplication of *PMP22* gene on 17p12 is associated with Charcot–Marie–Tooth disease type 1A. The clinical significance of 16q23.1 is unclear

CHARGE Syndrome

CHARGE syndrome is a genetic disorder characterized by a specific and a recognizable pattern of anomalies, namely, *C*oloboma, *H*eart defects, *A*tresia of choana, *R*etardation of growth and/or development, *G*enitourinary defects, and *E*ar anomalies and/or deafness. The pattern of anomalies associated with CHARGE syndrome was described independently by Hall and Hittner et al. in 1979. However, the acronym "CHARGE association" was coined by Pagon in 1981. At present, with its recognizable pattern and definition CHARGE is referred to as a syndrome (Pampal 2010; Zentner et al. 2010). The prevalence is estimated to be approximately 1 in 10,000 (Jongmans et al. 2006; Lalani et al. 2006).

Synonyms and Related Disorders

Coloboma, heart defects, atresia of choana, retardation of growth and/or development, genitourinary defects, and ear anomalies and/or deafness

Genetics/Basic Defects

1. Sporadic in almost all cases (Zentner et al. 2010)
2. Familial in a small number of cases with parent-to-child transmission of *CHD7* mutations (Lalani et al. 2006; Delahaye et al. 2007; Jongmans et al. 2008; Vuorela et al. 2008; Wincent et al. 2008; Pauli et al. 2009)
   a. Parents generally have a mild CHARGE phenotype or are asymptomatic
   b. Their children display more severe defects (a full spectrum of CHARGE features)
   c. Somatic mosaicism for a CHD7 mutations has been described in an asymptomatic mother of two affected siblings (Jongmans et al. 2008)
   d. Germ-cell mosaicism has also been described in an asymptomatic father of two affected children (Pauli et al. 2009)
3. Cause: De novo mutations in the gene encoding chromodomain helicase DNA binding protein 7 (*CHD7*), located on chromosome 8q12.1, are the major cause of CHARGE syndrome.
4. Individuals with *CHD7* mutations: more commonly have the following findings compared to those without the mutations:
   a. Ocular colobomas
   b. Temporal bone anomalies (semicircular canal hypoplasia/dysplasia)
   c. Facial nerve paralysis
5. Pathogenetic mechanism: Haploinsufficiency for *CHD7* is the most likely pathogenic mechanism underlying CHARGE syndrome:
   a. Nonsense or frameshift mutations: majority of *CHD7* disruptions
   b. Chromosomal abnormalities
      i. Interstitial deletion of 8q12.2-q13 (Arrington et al. 2005)
      ii. A balanced translocation disrupting 8q12 (Johnson et al. 2006)
      iii. Several chromosomal abnormalities not involving CHD7 have been reported to confer a phenotype similar to those seen in CHARGE patients (Clementi et al. 1991; North et al. 1995; Wieczorek et al. 1997; De Krijger et al. 1999; Lev et al. 2000)
   c. Recently, CHARGE patients without detectable single-base mutation were found to have

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heterozygous deletions of CHD7 (Wincent et al. 2009). In fact, CHD7 deletion was originally detected by array-CGH (Vissers et al. 2004). Alterations in copy number have been reported but represent only a small fraction of the reported disruptions of CHD7 (Bergman et al. 2008).

d. Other conditions with CHD7 mutations having significant clinical overlap with CHARGE syndrome
   i. Kallmann syndrome (Ogata et al. 2006; Kim et al. 2008; Jongmans et al. 2009)
   ii. Omen-like syndrome (Gennery et al. 2008)
   iii. 22q11.2 deletion syndrome (Sanka et al. 2007)

Clinical Features

1. Major criteria
   a. Eye anomalies
      i. *C*oloboma (80–90%) of the iris, choroid disc, and optic nerve
      ii. Microphthalmia/anophthalmia
      iii. Secondary retinal detachments and cataracts
      iv. Total or partial vision loss
      v. Superior palpebral ptosis, epicanthus, and telecanthus
   b. Choanal *A*tresia (50–60%)
   c. *E*ar anomalies/deafness (90%)
      i. External ears
         a) Asymmetry
         b) Posteriorly rotated
         c) Dystopia
         d) Prominent
         e) Increased width
         f) Decreased height
         g) Cup-shaped
         h) "Snipped-off" helical fold
         i) Prominent antihelix discontinuous with the antitragus
         j) Triangular concha
         k) Small or absent lobes
      ii. Middle ears
         a) Chronic serous otitis media approaching 100%
         b) Eustachian tube anomalies associated with choanal atresia or palatal cleft
         c) Ossicular malformations
         d) Conductive hearing loss
      iii. Inner ears
         a) Cochlear defects
         b) Sensorineural hearing loss
      iv. Temporal bone malformations
   d. Cranial nerve dysfunction (70–90%)
      i. Cranial nerve I: anosmia
      ii. Cranial nerve II: unilateral or bilateral facial palsy
      iii. Cranial nerve VIII: sensorineural deafness and vestibular problems
      iv. Cranial nerves IX and/or X: velopharyngeal incoordination and swallowing problems
2. Minor criteria
   a. *H*eart disease (cardiovascular malformations) (75–85%)
      i. Conotruncal defects (e.g., tetralogy of Fallot)
      ii. AV canal defects
      iii. Aortic arch anomalies
      iv. Others
         a) Double outlet right ventricle
         b) Hypoplastic left/right heart
   b. Growth and mental *R*etardation (70–100%)
      i. Growth deficiency
      ii. Short stature
      iii. Delayed motor milestones
      iv. Hypotonia
      v. Mental retardation
   c. *G*enital anomaly (70–80%)
      i. Hypogonadotropic hypogonadism and delayed puberty
      ii. Males: micropenis, cryptorchidism, delayed/incomplete pubertal development
      iii. Females: hypoplastic labia, delayed/incomplete pubertal development
   d. Orofacial cleft
      i. Cleft lip/palate (15–20%)
      ii. Laryngeal cleft
   e. Tracheoesophageal fistula/esophageal atresia (15–20%)
   f. Distinctive face (70–80%)
      i. Broad forehead
      ii. Square face
      iii. Facial asymmetry
      iv. Ptosis
      v. Arched eyebrows
      vi. Shallow supraorbital ridges
      vii. Iris coloboma
      viii. High nasal bridge
      ix. Full nasal tip

x. Microretrognathia
xi. Cleft lip/palate
xii. Laterally protruding ears
xiii. Prognathism, prominent mandibular mentum, and generalized facial narrowing with advancing age
xiv. Occasional broad or webbed neck with sloping shoulders

3. Occasional findings
   a. Thymic/parathyroid hypoplasia: DiGeorge sequence without chromosome 22q11 deletion (rare)
   b. Renal anomalies (15–25%)
      i. Dysgenesis
      ii. Horseshoe/ectopic kidney
      iii. Hydronephrosis
   c. Hand anomalies
      i. Polydactyly, ectrodactyly, thumb hypoplasia (rare)
      ii. Altered palmar flexion creases (50%)
   d. General appearance
      i. Webbed neck (rare)
      ii. Sloping shoulders (occasional)
      iii. Accessory or hypoplastic nipples (rare)
   e. Abdominal defects
      i. Omphalocele (rare)
      ii. Umbilical hernia (15%)
   f. Spine anomalies (rare)
      i. Scoliosis
      ii. Hemivertebrae
   g. CNS malformations
      i. Midline defects (corpus callosum agenesis, arhinencephaly, septal agenesis, meningoencephalocele, partial vermis agenesis) (22%)
      ii. Asymmetry (cerebral, ventricular, cerebellar) (18%)
      iii. Hindbrain anomalies (brain stem hypotrophy demonstrated by CT scan or MRI, vermian agenesis) (14%)
4. Different diagnostic criteria for CHARGE syndrome (Sanlaville and Verloes 2007; Pampal 2010)
   a. Clinical criteria (Pagon et al. 1981): presence of four criteria out of six, and at least one major
      i. Major criteria
         a) Choanal atresia
         b) Ocular coloboma
      ii. Minor criteria
         a) Heart defects of any type
         b) Retardation (of growth and/or of development)
         c) Genital anomalies
         d) Ear anomalies (abnormal pinnae or hearing loss)
   b. Diagnosis criteria of CHARGE (Verloes 2005): typical CHARGE (presence of either all three major signs or two major signs with two minor signs); partial CHARGE (two majors plus one minor); and atypical CHARGE (two majors but no minors or one major plus two minors)
      i. Major signs
         a) Ocular coloboma
         b) Choanal atresia
         c) Hypoplastic semicircular canals
      ii. Minor signs
         a) Rhomboencephalic dysfunction (brain stem and cranial nerve III–XII anomalies, including sensorineural deafness)
         b) Hypothalamo-hypophyseal dysfunction (including growth hormone and gonadotrophin defects)
         c) Mental retardation
         d) Malformation of mediastinal organs (heart, esophagus)
         e) External or middle ear malformations
   c. Diagnostic criteria of CHARGE (Blake and Prasad 2006): presence of either all four major signs or three major signs plus three minor signs
      i. Major signs (classical four Cs)
         a) Coloboma (of iris, retina, choroid, disc; microphthalmia)
         b) Choanal atresia/stenosis (unilateral or bilateral, membranous or bony)
         c) Cranial nerve dysfunction: facial palsy (unilateral or bilateral), sensorineural deafness and/or swallowing problems
         d) Characteristic ear anomalies: external ear (lop or cup-shaped); middle ear (ossicular malformations, chronic serous otitis), mixed deafness, cochlear defects
      ii. Minor signs
         a) Characteristic CHARGE facies (sloping forehead, flattened nasal tip)
         b) Orofacial cleft (cleft lip and/or palate)
         c) Cardiovascular malformations: all types, especially conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch
         d) Tracheoesophageal fistula: all types

e) Genital hypoplasia: males (micropenis, cryptorchidism); females (hypoplastic labia); both males and females (delayed, incomplete pubertal development)
f) Developmental delay: delayed motor milestones, language delay, mental retardation
g) Growth deficiency: short stature, growth hormone deficiency

iii. Occasional signs
a) Renal anomalies: duplex system, vesicoureteric reflux
b) Spinal anomalies: scoliosis, osteoporosis
c) Neck/shoulder anomalies: sloping, Sprengel deformity, kyphosis
d) Hand anomalies: fifth finger clinodactyly, camptodactyly, cutaneous syndactyly

d. Another major diagnostic criteria by Amiel et al. (2001): emphasized the importance of temporal bone imaging in the diagnosis of the disease along with characteristic clinical findings

Diagnostic Investigations

1. Audiology, tympanometry, BAER, and CT of temporal bones for evaluation of hearing loss (Blake and Prasad 2006)
2. Visual analysis and electroretinogram and functional vision testing: to identify and document severity of visual loss
3. Dilated fundoscopic exam for colobomas
4. Nasal pharyngeal feeding tube passage and CT scan of upper airway for evaluation of choanal atresia
5. Blood urea nitrogen, creatinine, electrolytes, and calcium: to evaluate renal function and exclude hypocalcemia (if present, evaluate T-cells for signs of DiGeorge sequence)
6. Hormonal studies
   a. Luteinizing hormone releasing hormone and human chorionic gonadotropin tests in cases of hypogenitalism
   b. Growth hormone (GH) stimulation levels to exclude GH deficiency as a cause of growth retardation
   c. Prepubertal bone age X-ray, followed by screening for hypogonadotrophic hypogonadism in early puberty for growth
7. Echocardiography for cardiovascular malformations
8. Holter monitoring: to detect cardiac rhythm abnormalities
9. Abdominal ultrasound and voiding cystourethrogram: to exclude renal anomalies
10. Skeletal survey: to exclude skeletal anomalies, especially cervical spine anomalies and scoliosis
11. Head CT scan and/or MRI for brain malformations and defective formation of the ossicles of the middle ear, cochlear, and semicircular canals. Olfactory bulbs and tracts imaging may be pathognomonic for CHARGE syndrome (Chalouhi et al. 2005).
12. Chromosome analysis for associated chromosomal anomalies
13. FISH to exclude 22q11 deletion
14. *CHD7* gene mutation testing available clinically
15. Comparative genomic hybridization for patients with CHARGE syndrome but with normal *CHD7* mutation analysis results

Genetic Counseling

1. Recurrence risk (Lalani et al. 2009)
   a. Patient's sib
      i. A parent affected or with a CHD7 mutation: a 50% risk
      ii. Neither parent affected: the empiric risk is approximately 1–2% due to germ-line mosaicism. Typically, CHARGE syndrome is caused by a *CHD7* de novo mutation, the risk to the sibs is small. However, several sib pairs born to unaffected parents have been reported (Jongmans et al. 2006; Lalani et al. 2006), likely due to germ-line mosaicism confirmed in a report (Pauli et al. 2009).
   b. Patient's offspring
      i. Severely affected individuals do not reproduce
      ii. Each child of a mildly affected individual: a 50% risk of inheriting the mutations
2. Prenatal diagnosis
   a. Ultrasonography: difficult unless in the pregnancy at risk
   b. Molecular genetic testing: possible for pregnancies at increased risk by analysis of DNA extracted from fetal cells obtained by amniocentesis or CVS, provided the disease-causing allele

of an affected family member has been identified prior to prenatal diagnosis
   c. Preimplantation genetic diagnosis: possible for families in which the disease-causing mutation has been identified
3. Management
   a. Feeding problems/failure to thrive
      i. Use of antispasmodics
      ii. Nissen fundoplication
      iii. Gastrostomy tube for feeding
   b. Developmental delay/mental retardation
      i. Early infant intervention
      ii. Special education
   c. Respiratory problems: may require tracheostomy for aspiration of secretions
   d. Choanal stenosis/atresia
      i. Airway stabilization and circulatory support
      ii. Requires surgical opening for the posterior choanae by placing stents to keep the nasal passages open if there is obstructed breathing
      iii. Choanoplasty
   e. Congenital heart defects: corrective surgery when indicated
   f. Colobomas: requires ophthalmologic care
   g. External ear anomalies/hearing loss
      i. Hearing aids for deafness
      ii. Surgery for ear canal and temporal bone abnormalities
   h. Management of other associated anomalies

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Fig. 1 (**a**, **b**) A boy with typical CHARGE association at ages 11 (*front view*) and 15 (*lateral view*). The patient had bilateral colobomas, choanal atresias, growth and mental retardation, hypogonadism, and ear anomalies with hearing loss

Cherubism

In 1933, Jones first described familial occurrence of painless enlargement of the jaws in three siblings. Later in 1938, Jones reported observations on the same family under the title "familial multilocular cystic disease of the jaws" and coined the term "cherubism" after the cherubs of Renaissance art for the full round cheeks and the upward cast of the eyes giving the children a peculiarly grotesque, cherubic appearance.

Cherubism is a benign maxillary bone dysplasia of childhood, usually showing an autosomal dominant inheritance with variable penetrance and spontaneously resolving after puberty. The prevalence of cherubism is 1 or less in 10,000.

Genetics/Basic Defects

1. Inheritance (Faircloth et al. 1991)
   a. Autosomal dominant with variable penetrance
   b. Familial in 80% of cases
   c. Males affected twice as often as females
   d. 80% overall penetrance
      i. 100% in males
      ii. 50–70% in females
   e. Variable expressivity
2. Cause
   a. Gene responsible for cherubism: mapped to chromosome region 4p16.3 (Mangion et al. 1999)
   b. Caused by mutations in the gene encoding SH3-binding protein *SH3BP2*
      i. Familial cherubism: all mutations are present in exon nine and affect three amino acids within a conserved six amino acid sequence (Hatani and Sada 2008)
      ii. Sporadic cherubism: description of a *SH3BP2* mutation in a case of nonfamilial case (Imai et al. 2003) and in an aggressive case of sporadic cherubism (Carvalho et al. 2008)
      iii. Novel mutations in the *SH3BP2* gene have been described in sporadic central giant cell lesion (which is indistinguishable histologically from cherubism), suggesting that both conditions share the same genetic alteration (Carvalho et al. 2009)

Clinical Features

1. Variable size of the jaw lesions in cherubism
   a. Minor lesions of both jaws
   b. Massive involvement of both jaws
2. Natural history:
   a. Classically normal at birth.
   b. Onset usually between 14 months and 5 years. However, the severe cases are evident at birth.
   c. Progresses until puberty.
   d. Usually progression stops after puberty.
   e. Regression of the bone lesions (involution of the disease) without treatment in some cases.
   f. Rapidly growing and extensively deforming lesions of the maxilla and the mandible including the coronoids and condyles in severely affected individuals.
3. Characteristic "eyes raised to heaven" cherubic appearance: an appearance of the cherubs portrayed in Renaissance art
   a. Fullness of the lower half of the face (cheeks and jaw)

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   b. Retraction of the lower lids by the stretched skin over the cheeks pulling down the lower eyelids. Consequently, a thin line of sclera is exposed beneath the iris and the eyes appear to be raised heavenward in a manner reminiscent of a "the cherubs in Renaissance paintings"
4. Painless hard enlargement of the jaws
5. Exclusively affecting maxilla and mandible
   a. Mandible usually involved
   b. Involvement of the maxilla in 60% of cases
   c. Painless lesions
   d. Bilateral enlargement with loss of bone in the jaws and its replacement with large amount of fibrous tissue
   e. Dental effect by bone lesion
      i. Premature loss of deciduous teeth
      ii. Displacement of permanent dentition
   f. Swelling usually abates by the third decade, whereas radiographic changes commonly persist into the fourth decade
6. Submandibular lymph node enlargement in 45% of cases
7. Ocular manifestations (Carroll and Sullivan 2001)
   a. Lower lid retraction
   b. Proptosis
   c. Diplopia
   d. Globe displacement
   e. Visual loss due to optic nerve atrophy
   f. Rare extension of lesion into the orbits
8. Rare upper airway involvement
   a. Displaced tongue affecting speech, mastication, swallowing, and respiration
   b. Obstructive apnea
9. Extremely rare extrafacial skeletal involvement
   a. Upper humerus
   b. Bilateral triquetral bones
   c. Anterior ribs
   d. Upper femoral necks
10. Rare associated syndromes
   a. Noonan syndrome
   b. Ramon syndrome
      i. Cherubism
      ii. Short stature
      iii. Mental retardation
      iv. Gingival fibromatosis
      v. Epilepsy
   c. Fragile X syndrome
   d. Craniosynostosis
11. Functional impairment (Tiziani et al. 1999)
   a. Mastication problems
   b. Speech difficulty
   c. Tooth alteration
   d. Loss of normal vision
12. Psychological consequences
13. Differential diagnosis
   a. Four main types of fibrous dysplasia
      i. Monostotic fibrous dysplasia: Only one bone is affected.
      ii. Polyostotic: Multiple bones are affected.
      iii. McCune-Albright syndrome:
         a) Polyostotic form
         b) Accompanied by pigmentary lesions
         c) Endocrine dysfunction presenting as precocious puberty in females
      iv. Craniofacial form of fibrous dysplasia:
         a) Only bones of the craniofacial complex are affected.
         b) Onset in the second decade in majority of patients.
         c) Generally unilateral lesions, tend to become static once skeletal maturity is reached.
         d) Clinically difficult to differentiate from cherubism if the skeletal abnormalities are localized to the jaws.
         e) Molecularly different from cherubism.
   b. Infantile cortical hyperostosis
      i. Diagnosed in the first 6 months of life
      ii. Radiographically does not produce cystic areas
      iii. Characterized by thickening of the mandibular lower border
      iv. Does not have bilateral expression
   c. Osteitis fibrosa cystica secondary to hyperparathyroidism
      i. Increased serum alkaline phosphatase
      ii. Increased serum calcium
      iii. Decreased serum phosphorus
      iv. Increased urinary phosphorus
   d. Various tumors of the jaws

Diagnostic Investigations

1. Orthodontic assessment: commonly required as the jaw distortion leads to permanent dental abnormalities

   a. Malocclusive bite
   b. Premature loss of deciduous teeth
   c. Wide-spaced, misplaced, unerupted, or absent permanent teeth
2. Ophthalmologic examination: for rare individuals who may have
   a. Lower lid retraction
   b. Proptosis
   c. Diplopia
   d. Globe displacement
   e. Visual loss caused by optic atrophy
3. Serum alkaline phosphatase levels may be elevated (Kozakiewicz et al. 2001)
4. Radiography (Tiziani et al. 1999)
   a. Extensive involvement of the mandible and the maxilla
   b. Multilocular radiolucent areas in the mandible and maxilla with expansion of the bony cortex
      i. Often very extensive
      ii. With a few irregular bony septa
      iii. Multilocular rarefactions replaced by sclerosis with progressive calcification in the adult
   c. Absent and displaced teeth in the involved areas
5. CT scan
   a. Superior in making the diagnosis
   b. Determining the degree of severity
6. Histological changes in cherubism
   a. Replacement of the normal bony architecture with proliferating fibrous tissue containing numerous giant cells (Ayoub and El-Mofty 1993)
   b. Mononuclear fibroblastic stroma
      i. Nonneoplastic fibrous lesions rich in multinucleated giant cells identified as osteoclasts
      ii. Irregular bone formation
   c. A peculiar perivascular cuffing of collagen: considered by some to be pathognomonic for the condition (Adante and Breen 1996)
   d. Histological resemblance to the following disorders (Mangion et al. 1999):
      i. Giant cell tumor
      ii. Giant cell granulomas
      iii. Ossifying fibroma
      iv. Fibrous dysplasia of the jaw
      v. Paget disease of bone
7. Molecular genetic testing (Baskin et al. 2011)
   a. To confirm the diagnosis in a proband with the suggestive clinical findings and typical radiologic and/or histologic manifestations.
   b. Sequence analysis: *SH3BP2* sequence variants in exon 9 detects an estimated 80% of mutations.

Genetic Counseling

1. Recurrence risk (Baskin et al. 2011)
   a. Patient's sib: The risk depends on the genetic status of the parents
      i. An affected parent: a 50% risk
      ii. Clinically unaffected parents and/or the parents not detected to have a disease-causing mutation: a low recurrence risk but greater than that of the general population because of the possibility of germ-line mosaicism
   b. Patient's offspring: a 50% risk of inheriting the mutation
2. Prenatal diagnosis
   a. Ultrasonography: not possible since the lesion is postnatal in nature
   b. Molecular analysis possible on fetal DNA obtained by amniocentesis or CVS if the disease-causing mutation (*SH3BP2*) has been identified in an affected family member
   c. Preimplantation genetic diagnosis: possible for families at risk in which the disease-causing mutation has been identified
3. Management
   a. Although cherubism represents a benign and localized maxillary dysplasia, it requires prompt surgical but conservative treatment and careful follow-up to avoid permanent lesions (malocclusion and/or edentulism) (Mortellaro et al. 2009)
   b. Observation
      i. Generally self-limiting lesions and subside with age
      ii. Surgical intervention required only in cases with esthetic or functional problems
   c. Tracheostomy to secure the airway for upper airway obstruction
   d. Teeth extraction from the sites of fibrous changes
   e. Curettage alone or in combination with surgical contouring: considered the treatment of choice
   f. Resection of the orbital lesions may be required to improve visual impairment
   g. Prompt recurrence likely if surgery is performed at an early age

h. Radiation therapy ineffective and contraindicated in view of the following risks:
   i. Osteoradionecrosis
   ii. Interference with dentofacial growth and development
   iii. Affect on future surgical procedures
i. Experimental use of calcitonin to treat cherubism described recently

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Fig. 1 (**a**, **b**) A boy with cherubism showing full cheeks and jaw and the retraction of the lower eyelids with symmetrical augmentation on both mandibular angles

Chiari Malformation

In 1891, Chiari first described a dysplasia of the nervous system consisting of herniation of the cerebellar tonsils into foramen magnum. There are three types of Chiari malformations. The commonest ones are type I and type II, and the latter has been named the Arnold–Chiari malformation. (De Reuck and Theinpont 1976)

Synonyms and Related Disorders

Chiari malformation type I with syringomyelia; Chiaari malformation type II (Arnold-Chiari malformation)

Genetics/Basic Defects

1. Classification of Chiari malformations according to the severity
   a. Type I (CMI) (the milder malformation)
      i. Ectopia of the cerebellar tonsils (caudal herniation of the cerebellar tonsils and inferior cerebellum through the foramen magnum)
      ii. Usually an isolated feature encountered in adults
   b. Type II (CMII) (the more severe malformation)
      i. Downward displacement of the cerebellar medulla and fourth ventricle into the spinal canal
      ii. Almost always associated with meningomyelocele
      iii. May be associated with polygyria, cortical heterotopia, and dysgenesis of the corpus callosum
   c. Type III (CMIII) (the most severe malformation) (Caldarelli et al. 2002)
      i. Downward displacement of most of the cerebellum into a high cervical/low occipital encephalocele
      ii. Malformation consisting of anatomical anomalies typical of Chiari type II malformation with those of a high cervical/occipital encephalocele
2. Acquired Chiari I malformation caused by conditions leading to increased intracranial pressure
   a. Head injury
   b. Hydrocephalus
   c. Craniosynostosis
3. Brainstem dysfunction, sensory disturbance, and motor loss caused by impaction of the tonsils against the cervicomedullary structures

Clinical Features

1. Patients with Chiari I malformation
   a. Asymptomatic in majority of patients
   b. General symptoms
      i. Headache
      ii. Fatigue
      iii. Memory loss
      iv. Pressure on the neck
      v. Back pain
      vi. Insomnia
      vii. Poor circulation
      viii. Nausea
      ix. Menstrual problems
      x. Sexual alterations

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xi. Hypothermia
xii. Bronchial aspirations
xiii. Respiratory alterations
xiv. Drop attacks
xv. Rare reports of sudden death

c. Ocular symptoms
i. Loss of vision
ii. Intolerance of bright light
iii. Diplopia

d. Otolaryngologic symptoms
i. Vestibular manifestations
a) Imbalance
b) Swaying
c) Dizziness
d) Positional vertigo
e) Spontaneous vertigo
f) Nystagmus
g) Hearing loss
h) Tinnitus
ii. Alterations of cranial pairs
a) Dysphagia
b) Dysphonia
c) Alterations in tongue mobility
d) Loss of smell
e) Facial hyposthesia
iii. Sleep apnea

e. Cerebellum compression symptoms
i. Ataxia
ii. Nystagmus
iii. Gait difficulties
iv. Opisthotonos
v. Horner's syndrome
vi. Paralysis of the last cranial nerves
vii. Hypotonia
viii. Trembling
ix. Dysarthria
x. Dysmetria

f. Associated CNS anomalies
i. Stenosis of the aqueduct of Silvia
ii. Meningomyelocele
iii. Syringomyelia (cystic dilation of the spinal cord)

g. Symptoms associated with syringomyelia
i. Known to accompany 50–70% of patients with Chiari I malformations
ii. Obstructed cerebrospinal fluid at the site of cerebellar tonsillar herniation shows perivascular movement of CSF from the spinal subarachnoid space into the spinal cord with each Valsalva maneuver and causes syringomyelia
iii. Tingling, hyposthesia, and burning sensation in the extremities
iv. Thermalgesic anesthesia
v. Alteration in muscular reflexes
vi. Areflexia
vii. Alteration of kinesthesia
viii. Motor skill dysfunction
ix. Headache or nonradicular pain in the shoulder, back, and limbs
x. Headache usually suboccipital and upper cervical in location and is exacerbated by Valsalva maneuvers
xi. Associated with the development of a painful, rapidly progressive, or left-curving scoliosis
xii. Recent reports of spontaneous radiographic improvement of childhood Chiari malformations and syringomyelia

h. Chiari I malformation in children and adolescents (Genitori et al. 2000)
i. Natural history of an asymptomatic Chiari I malformation in children
a) Not well understood
b) Rarely reported to resolve spontaneously
c) Asymptomatic at the time of diagnosis in many children
d) Degree of tonsillar ectopia correlating well with the presence of neurologic signs and symptoms
e) Rare reports of sudden death
ii. Group I (asymptomatic)
a) Age at diagnosis: 3 months to 17 years
b) Associated conditions: hydrocephalus, craniofacial syndromes, epilepsy, occult spinal dysraphism
iii. Group II (brain stem compression)
a) Age at diagnosis: 7 months to 26 years
b) Associated conditions: craniofacial syndromes, hydrocephalus, precocious puberty
c) Symptoms: neck pain, vertigo, headache, numbness, swallowing difficulties, apnea, opisthotonos, brachialgia, hyposthenia, spasticity, and hemifacial pain
iv. Group III (presence of syringomyelia). Symptoms are:
a) Numbness
b) Sensory loss

c) Neck pain
d) Vertigo
e) Scoliosis
f) Hyposthenia
g) Headache
h) Muscle hypotrophy
i) Swallowing difficulties
j) Limb pain

2. Patients with Chiari II malformation
   a. Almost invariably associated with myelomeningocele (90%)
   b. Brain stem signs in 20% of patients with Chiari II malformation in children and adolescence
      i. Vertigo
      ii. Bioccipital headache
      iii. Cerebellar dysfunction
      iv. Progressive paresis of the arms
3. Patients with Chiari III malformation (Caldarelli et al. 2002)
   a. Rarest of the Chiari malformations
   b. Associated with a high cervical or occipital encephalocele
   c. Prognosis for nearly all reported patients
      i. Various degree of developmental delay
      ii. Epilepsy
      iii. Hypotonia
      iv. Spasticity
      v. Upper and/or lower motor neuron deficits
      vi. Lower cranial nerve dysfunction
   d. CNS anomalies usually observed in an occipital encephalocele
      i. A small cranial fossa
      ii. Caudal displacement of cerebellar tonsils and vermis
      iii. Medullary kinking
      iv. Tectal beaking
      v. Obvious hydrocephalus

Diagnostic Investigations

1. CT or MRI
   a. Chiari I malformation
      i. Incidental detection in asymptomatic individuals
      ii. Herniation of the tonsils >5 mm below the foramen magnum on MRI considered diagnostic
   b. Chiari II malformation (Gammal 1988)
      i. Caudal cerebellum (100%)
      ii. Kinking of medulla on spinal cord (79%)
      iii. Elongation of brainstem and low medulla, stretched aqueduct, and fourth ventricle (75%)
      iv. Beaking of quadrigeminal plate (60%)
      v. Large massa intermedia (55%)
      vi. Large fourth ventricle (25%)
      vii. Hydromyelia (15%)
   c. Chiari III malformation (Caldarelli et al. 2002)
      i. An occipitocervical meningoencephalo-cele protruding through a bony defect involving the lower occipital squama and/or the posterior arch of the first cervical vertebrae
      ii. A small posterior cranial fossa with low tentorial attachment
      iii. Scalloping of the clivus
      iv. Massive herniation of the hypoplastic cerebellar structures into the malformation
      v. Beaking of the tectal plate
      vi. Dysgenesis of the corpus callosum
      vii. Severe ventricular dilatation (hydrocephalus)
2. Brainstem auditory evoked potentials (BAEP) (Koehler et al. 2001)
   a. Consistently abnormal in symptomatic Chiari II malformation
   b. Showing a positive predictive value of 88% in predicting central neurologic sequelae in newborns and infants

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: not increased
2. Prenatal diagnosis
   a. Prenatal ultrasound diagnosis of Chiari I malformation (Iruretagoyena et al. 2010)
      i. A lip of cerebellum is downwardly displaced with the tonsils, but the fourth ventricle remains in the posterior fossa
      ii. Enlarged third ventricle
      iii. Cerebellar hypoplasia with marked cystic enlargement of the fourth ventricle
      iv. This condition may coexist with syringomyelia, which is a cyst formation on the cervical portion of the spinal cord

b. Prenatal ultrasound diagnosis of Chiari II malformation
   i. Classic "lemon and banana" signs, the gold standard in the early screening of Chiari II malformation
   ii. Clivus-supraocciput angle below fifth centile of nomogram in cases of Chiari II malformation
c. Strategy for fetal sonographic and MRI diagnosis of CMII when ultrasound study shows ventriculomegaly/hydrocephalus
   i. Presence of myelomeningocele by ultrasound: suspect CMII
   ii. Absence of myelomeningocele by ultrasound: proceed to MRI
   iii. Presence of tight posterior fossa by MRI
      a) Presence of myelomeningocele: suspect CMII
      b) Absence of myelomeningocele: suspect CMII (with open defect) or conditions other than CMII, such as craniosynostosis, swollen hindbrain, and tumor
   iv. Absence of tight posterior fossa by MRI: CMII not likely
d. Prenatal ultrasound and MRI diagnosis of Chiari III malformation (Smith et al. 2007)
   i. Repeat US at 19 weeks demonstrated neural tissue in the cyst, consistent with an encephalocele.
   ii. MR imaging at 23 weeks confirmed the presence of an occipital encephalocele, demonstrated additional bony defect in the upper cervical spine, and identified abnormal morphology and position of the brainstem consistent with the diagnosis of Chiari III.
   iii. Postnatal MRI and CT confirmed the fetal MRI findings and demonstrated the utility of fetal MRI in the early evaluation of sonographically detected posterior fossa abnormalities.

3. Management
   a. Chiari I malformation
      i. Conservative treatment for asymptomatic patients
      ii. Main treatment consisting of decompressing the structures trapped in the foramen magnum
         a) Suboccipital craniectomy with or without dural patch grafting and cervical laminectomies: the most often used procedure
         b) Syringosubarachnoid shunt when indicated
      iii. Shunting of hydrocephalus
      iv. Major preexisting sensory or motor deficits: poor prognosticators for functional recovery
   b. Chiari II (Arnold–Chiari) malformation
      i. Seen most often in children with myelomeningocele
      ii. Shunting of hydrocephalus often resolves brainstem symptoms and surgical decompression may not be necessary.
      iii. Surgical decompression of posterior fossa and upper cervical spine may be required if brainstem compression symptoms remain after shunting.
      iv. Surgical intervention indicated to prevent further deterioration of the motor function and to diminish the progress of spasticity and scoliosis from tethered cord syndrome
   c. Chiari III malformation (Caldarelli et al. 2002)
      i. Primary closure of the malformation: usually the treatment of choice
      ii. CSF shunting of the associated hydrocephalus postponed to a later phase
      iii. Neonates often require intensive care treatment for the associated severe respiratory distress

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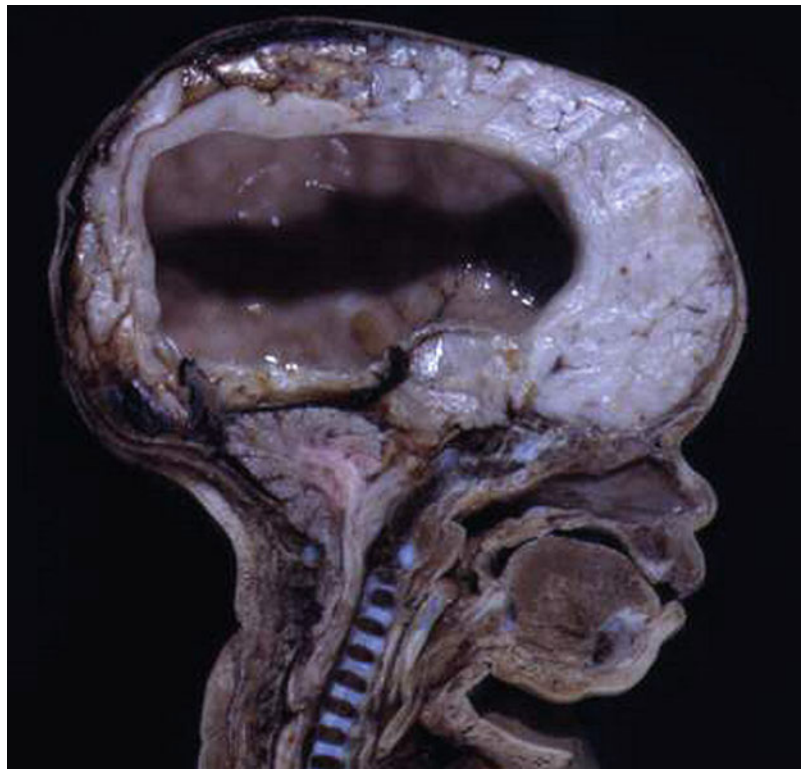

Fig. 1 Sagittal section of a neonate with a large ruptured lumbar meningomyelocele. Arnold–Chiari malformation is evident: The brain stem and lower portion of cerebellum herniate through the foramen magnum and overlap the cervical cord which is severely flattened. The brain shows hydrocephalus

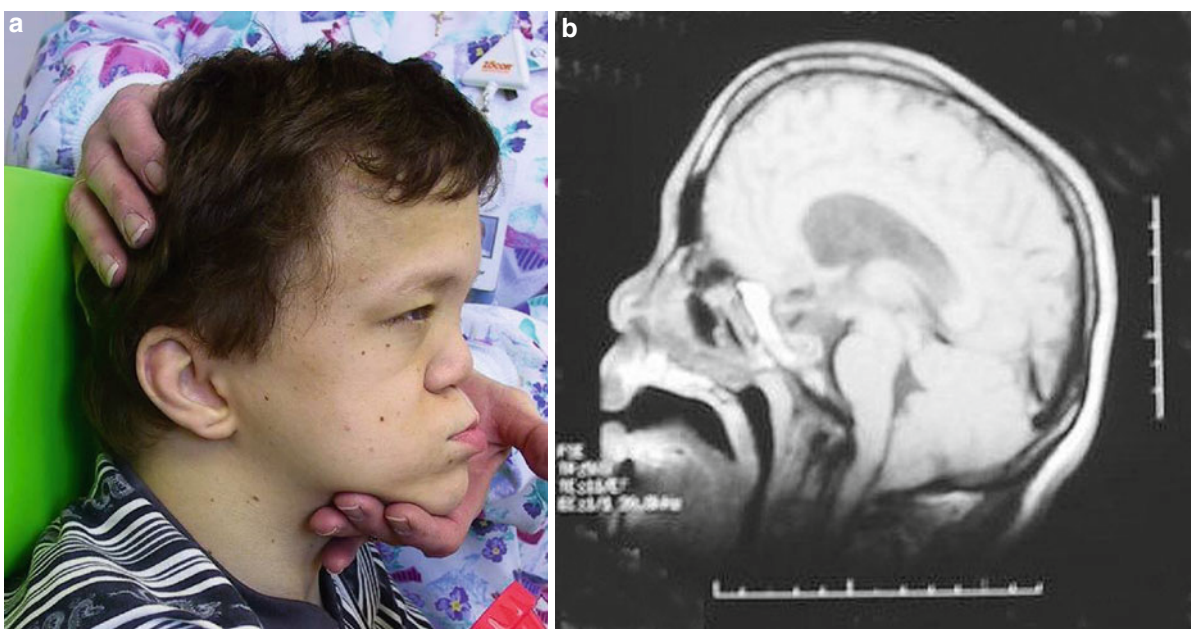

Fig. 2 (**a**, **b**) A patient with multiple congenital anomalies (mental retardation, flat facial plane, epicanthus inversus, blepharophimosis, cataracts, nystagmus, elbow flexion contractures, and vertical talus) with Chiari I malformation (MRI of the brain)

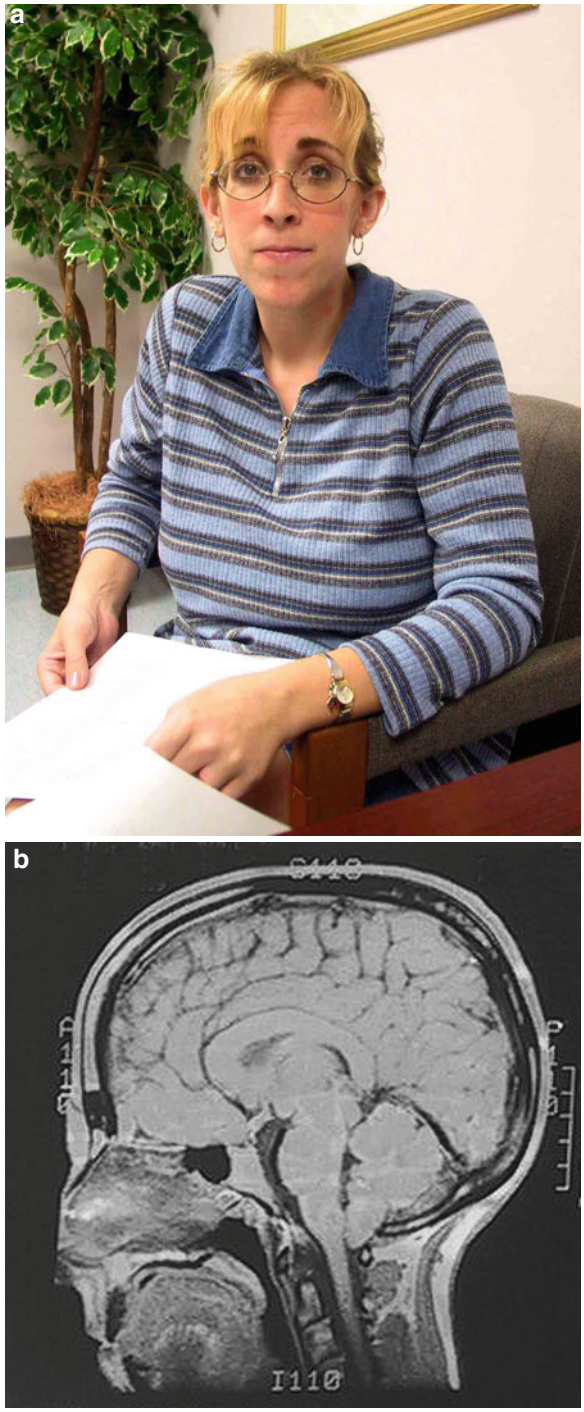

Fig. 3 (**a**, **b**) A 28-year-old female with Chiari I malformation with normal phenotype but complaining headache, dizziness, and neck pain worsened by pregnancy

Chondrodysplasia Punctata

Chondrodysplasia punctata (CDP) refers to the radiographic appearance of punctate calcifications, due to abnormal cartilaginous stippling, the result of calcium deposition in the areas of enchondral bone formation, described in a variety of chondrodysplasias.

Synonyms and Related Disorders

Chondrodystrophia calcificans punctata; Conradi-Hunermann syndrome; Conradi-Hunermann-Happle syndrome; Happle syndrome; Rhizomelic form of Chondrodysplasia punctata

Genetics/Basic Defects

1. Genetic heterogeneity of chondrodysplasia punctata
   a. Rhizomelic chondrodysplasia punctata type I (RCDP1)
      i. Autosomal recessive disorder
      ii. Caused by mutations in *PEX7*, mapped at 6q22–q24, which encodes the cytosolic peroxisomal targeting signal type 2 (PTS2)-receptor protein peroxin 7
      iii. Genotype–phenotype correlations
         a) Classic RCDP1: all patients homozygous for the L292X mutation
         b) Phenotype determined by the other allele if the patients are compound heterozygotes for L292X and another mutation
         c) A milder phenotype associated with several *PEX7* alleles
   b. Rhizomelic chondrodysplasia punctata type 2 (RCDP2)
      i. Autosomal recessive disorder
      ii. Caused by mutations in the gene that encodes peroxisomal dihydroxyacetone phosphate acyltransferase (DHAPAT)
   c. Rhizomelic chondrodysplasia punctata type 3 (RCDP3)
      i. Autosomal recessive disorder
      ii. Caused by mutations in the gene (mapped at 2q31) that encodes peroxisomal alkyl-dihydroxyacetone phosphate synthase (ADHAPS)
   d. Relatively mild autosomal dominant Conradi–Hünermann syndrome
      i. Chondrodysplasia punctata, tibia-metacarpal type
      ii. Chondrodysplasia punctata, humero-metacarpal type
   e. X-linked dominant type only in females (Conradi–Hünermann–Happle syndrome) (CDPX2) (Becker et al. 2001)
      i. Lethal in males
      ii. Caused by mutations of the 3β-hydroxysteroid-Δ^8-Δ^7-isomerase (also called emopamil-binding protein, EBP)
      iii. The gene encoding EBP mapped to Xp11.22–p11.23
      iv. EBP: catalyzes an intermediate step in the conversion of lanosterol to cholesterol
      v. Presence of gonadal and somatic mosaicism in CDPX2

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f. X-linked recessive type with a deletion of the short arm of the X chromosome (CDPX1)
   i. Caused by defects in arysulfatase E, a vitamin K-dependent enzyme
   ii. The locus of the disease identified through the characterization of patients with chromosomal abnormalities involving the Xp22.3 region
   iii. The gene of CDPX1, named *ARSE*, encoding a new sulfatase (arylsulfatase E), showing a high sequence homology to steroid sulfatase
   iv. Point mutations of the *ARSE* gene detected in the DNA of karyotypically normal patients with chondrodysplasia punctata

2. Causes of stippled cartilaginous calcifications (Borochowitz 1991)
   a. Peroxisomal disorders
      i. Zellweger syndrome
         a) A peroxisomal disorder
         b) An autosomal recessive inheritance
         c) Associated stippled calcifications of the epiphyses, particularly common in the patella
         d) Severe hypotonia
         e) Characteristic facies with a high forehead, hypertelorism, epicanthal folds, Brushfield spots, and shallow supraorbital ridges
         f) Club foot deformity
         g) The affected infants usually die early in infancy.
         h) Involvement of other organ systems, especially the brain (migrational disorders) and kidneys (cortical cystic disease of the kidneys)
      ii. Rhizomelic chondrodysplasia punctata
   b. Genetic disorders
      i. Conradi–Hunermann chondrodysplasia punctata
      ii. X-linked dominant chondrodysplasia punctata
      iii. Smith-Lemli-Opitz syndrome
      iv. Greenberg dysplasia (cholesterol biosynthesis disorder)
         a) An autosomal recessive disorder
         b) Appears to be caused by an error of sterol metabolism at the level of 3β-hydroxysteroid-Δ14 reductase
         c) Non-immune hydrops fetalis
         d) Mid-face hypoplasia
         e) Micrognathia
         f) Rhizo-mesomelic dwarfism with relatively long and broad hands and feet
         g) Narrow thorax
         h) Protuberant abdomen
         i) Radiographic findings of grossly irregular and deficient ossification of the short tubular bones, fragmented ossification at the ends of the long tubular bones, small pelvic bones with irregular "moth-eaten" contours, platyspondyly with multiple ossification centers of the vertebral bodies, and deficient ossification of the calvaria
      v. CHILD syndrome
         a) Congenital hemidysplasia
         b) Ichthyosiform erythroderma
         c) Limb defects (unilateral hypomelia with ipsilateral epiphyseal stippling)
      vi. Dappled diaphyseal dysplasia (lethal short-limbed dysplasia, type Carty)
         a) An autosomal recessive disorder
         b) All cases were stillborn or died in utero
         c) Fetal hydrops
         d) Polyhydramnios
         e) Short limbs with relatively long hands and feet
         f) Small thorax
         g) Protuberant abdomen
         h) Radiographic findings of fragmented appearance of the ribs, small islands of ossification from disruption of the facial bones, axial and appendicular skeleton, and absent ossification of the calvaria
      vii. Acrodysostosis
      viii. Binder syndrome
      ix. De Barsy syndrome
         a) Cutis laxa
         b) Corneal clouding
         c) Mental retardation
         d) Stippled epiphysis
      x. GM1 gangliosidosis
      xi. Galactosialidosis
      xii. Fibrochondrogenesis
      xiii. Mucolipidosis II

xiv. De Lange syndrome
xv. X-linked ichthyosis
xvi. Keutel syndrome
  a) Stippled epiphysis (knees, elbows)
  b) Brachytelephalangism
  c) Pulmonary stenosis
xvii. Osebold-Remondini syndrome
xviii. Hypothyroidism
xix. Chromosome translocation
xx. Trisomy 21 and 18
xxi. Turner syndrome
xxii. Brachytelephalangic chondrodysplasia punctata
  a) An X-linked recessive disorder
  b) Male infants affected with a very small nose, anteverted and grooved nares
  c) Benign type of chondrodysplasia punctata
  d) Also observed in a patient with Xp terminal deletion with ichthyosis and mental retardation
  e) Distal phalangeal hypoplasia: the most characteristic radiological sign of this form
xxiii. Chondrodysplasia punctata, metacarpal type
  a) Including tibial-metacarpal type and humeral-metacarpal type
  b) An autosomal dominant disorder
  c) Named for a specific long bone but with overlap in the long bone involved
  d) All have short metacarpals
  e) Affected children with a hypoplastic midface, a depressed nasal bridge, small mouth, micrognathia, short neck, and short limbs
  f) Radiographically, with short metacarpals associated with short tibias in the tibia-metacarpal type and short humeri in humero-metacarpal type
xxiv. Sheffield-type chondrodysplasia punctata
  a) Heterogeneous group of patients with punctate epiphyses, particularly in the calcaneus and spine
  b) A benign course
  c) Distal phalangeal hypoplasia
  d) Probably not a specific entity but rather a heterogeneous group of disorders that can be included in other entities
xxv. Pacman dysplasia
  a) A single case report with peculiar bone dysplasia, stippling in many areas, short bowed bones, and periosteal cloaking
  b) Osteoclasts with an unusual appearance reminiscent of the Pacman figures in computer games on bone histology
  c) The entire coccygeal and sacral regions replaced by stippling
  d) Dense stippling also observed in the thoracic region
  e) Considerable stippling also observed in the epiphyses of the proximal femur, talus, calcaneus, cuboid, and the bones of the hand
  f) Wide periosteal cloaking of many bones and poor ossification
  g) Bowed femora
  h) Superior inferior sagittal clefting in the AP views in the upper spine

c. Vitamin K disorders
  i. Warfarin embryopathy
    a) Associated with maternal use of warfarin sodium
    b) Consistent features: saddle nose deformity, hypertelorism, frontal bossing, high-arched palate, short neck, and short stature
    c) Other features: rhizomelia, micromelia, flexion contractures, optic atrophy, psychomotor retardation, cataracts, congenital heart disease, and renal anomalies
  ii. Vitamin K epoxide reductase deficiency
d. Acquired in utero
  i. Fetal alcohol syndrome
  ii. Phenacetin intoxication
  iii. Fetal hydantoin syndrome
  iv. Femoral hypoplasia unusual facies syndrome
  v. Maternal diabetes
  vi. Maternal systemic lupus erythematosis
  vii. Febrile illness
e. Other conditions involving unusual calcification that may be confused with puncta
  i. Amelia and other absence deficiency
  ii. Cerebrocostomandibular syndrome
  iii. Dysplasia epiphysealis hemimelica

iv. Calcifying arthritis
v. Metachondromatosis

3. Etiological classification of chondrodysplasia punctata to aid clinician to reach an accurate diagnosis when CDP is detected (Irving et al. 2008)
   a. Group 1 (Inborn errors of metabolism)
      i. Group 1a (Abnormalities of peroxisomal function)
         a) Rhizomelic CDP1 (*PEX7*, 6q22-q24)
         b) Rhizomelic CDP2 (*DHAPAT*, 1q42)
         c) Rhizomelic CDP3 (*AGPS*, 2q31)
         d) Zellweger syndrome (*PEX1*, *PEX2*, *PEX3*, *PEX5*, *PEX6*, *PEX10*, *PEX12*, *PEX13*; 7q21, 8q, 6q, 12p13.3, 6p21.1, 1p36, 17q11.2, 2p15 respectively)
      ii. Group 1b (Abnormalities of cholesterol synthesis)
         a) Greenberg dysplasia/HEM (*LBR*, 1q42.1)
         b) CDP Conradi-Hunermann (CDPX2) (*EBP*, Xp11.23–p11.22)
         c) CHILD syndrome (*NSDHL*, *EBP*; Xq28, Xp11.23–p11.22 respectively)
      iii. Group 1C (Other metabolic disorders)
         a) Mucolipidosis type II
         b) Mucopolysacharidosis type III
         c) GM1 gangliosidosis
   b. Group 2 (Disruption of vitamin K metabolism)
      i. Warfarin embryopathy
      ii. Familial multiple coagulation factor deficiency (*VKORC1*, *GGCX*; 16p11.2, 2p12 respectively)
      iii. Maternal vitamin K deficiency
      iv. Fetal phenytoin exposure
      v. Keutel syndrome (Keutel et al. 1972; Monroe et al. 1999) (*MGP*, 12p13.1–p12.3)
         a) Abnormal calcification with cartilaginous calcification of the ears, nose, trachea, bronchi and ribs
         b) Peripheral pulmonary stenosis
         c) Sensorineural hearing loss
         d) Short-terminal phalanges
         e) Developmental delay and seizures, secondary to intracerebral calcification
      vi. CDP X-linked recessive/brachytelephalangic (CDPX1) (*ARSE*, Xp22.3)
   c. Group 3 (Chromosomal abnormalities)
      i. Trisomy 21
      ii. Trisomy 18
      iii. Other chromosomal aberrations
   d. Unknown etiology
      i. Maternal systemic lupus erythematosus
      ii. Fetal alcohol syndrome
      iii. CDP-TM (tibial-metacarpal type) (Rittler et al. 1990)
      iv. Dappled diaphyseal dysplasia
      v. Astley-Kendall dysplasia (Astley and Kendall 1980)
      vi. Pacman dysplasia (Miller et al. 2003)

Clinical Features

1. Recessive rhizomelic form
   a. Classic RCDP1
      i. Skeletal abnormalities
         a) Severe symmetric shortening of the proximal limb segments (more severe in humeri than femora)
         b) Stippled (punctate) epiphyses involving knees, hips, elbows, shoulders, hyoid bone, larynx, sternum, and ribs
      ii. Peripheral calcifications
      iii. Facial dysmorphism
         a) Frontal bossing
         b) A short, saddle nose
      iv. Ocular features
         a) Cataracts: the most common ocular defect developing in virtually all patients: usually present at birth or appear in the first few months of life and are progressive
         b) Optic atrophy
         c) Posterior embryotoxon
         d) Strabismus
         e) Adhesions between iris and cornea in the ring of Schwabe
      v. Severe failure to thrive with profound postnatal growth deficiency
      vi. Gross developmental retardation
      vii. Contractures and stiff, painful joints, causing irritability in infancy
      viii. Other complications
         a) Seizures
         b) Recurrent respiratory tract infections caused by neurological compromise, aspiration, immobility, and a small chest with restricted expansion
         c) Spastic quadriplegia

d) Ichthyotic skin changes
e) Cleft soft palate
f) Cervical spine stenosis
g) Congenital heart disease
h) Ureteropelvic junction obstruction

ix. A high mortality
a) About 60% survive the first year.
b) About 39% survive the second year.
c) Only a few survive beyond age 10.

b. Mild RCDP1
i. Only a few patients reported
ii. Consistent features
a) Chondrodysplasia
b) Cataracts
iii. Variable expression
a) Punctate calcifications
b) Rhizomelia
c) Mental and growth deficiency

2. X-linked dominant form (CDPX2)
a. Phenotype
i. Usually a mild form of the disease identified in adult females
ii. May be a stillborn
iii. Occurring almost only in females
iv. Presumably lethal in males, although a few affected males have been reported
b. Lyonization (skewed X-chromosome inactivation) in females resulting in phenotypic variability and asymmetric findings
c. Showing increased disease expression in successive generations (anticipation): another striking clinical feature of CDPX2 that may be associated with skewed methylation
d. Skin lesions
i. The hallmark of the X-linked dominant form
ii. Congenital ichthyosiform erythroderma, distributed in a linear or blotchy pattern
iii. Systematized atrophoderma mainly involving the fair follicles
iv. Circumscribed alopecia
v. Sparse eyebrows and lashes
vi. Nails: flattened and split into layers
e. Epiphyseal calcification in the first year of life
f. Limb shortening
i. Rhizomesomelic
ii. Usually asymmetric
iii. Severely affected infants with bilateral findings resembling those of RDCP1
g. Other later signs
i. Palmoplantar keratosis
ii. Follicular atrophoderma
iii. Segmental cataracts
iv. Tooth and bone abnormalities

3. X-linked recessive chondrodysplasia punctata, brachytelephalangic type (CDPX1)
a. Clinical reports available so far are mainly those of patients who are nullisomic for Xp22.3 in which chondrodysplasia punctata is part of a complex phenotype due to a "contiguous gene syndrome"
b. Wide spectrum of manifestations, ranging from aborted fetus, neonatal death, midfacial hypoplasia, and brachytelephalangy
c. Facial anomalies with severe nasal hypoplasia
d. Short stature
e. Cardinal manifestations
i. Epiphyseal stippling
ii. Hypoplasia of the distal phalanges
f. Abnormalities of proximal and middle phalanges after healing of the punctate calcifications: typical diagnostic signs
g. Without limb shortening or cataracts
h. Presence of ichthyosis attributed to the involvement o of the STS gene in the patients with Xp deletion
i. Mild ichthyosis that improves with age: may be part of the CDPX phenotype

4. Chondrodysplasia punctata, tibia-metacarpal type
a. Symmetrical rhizomelic shortness of the upper limbs
b. Punctate epiphyseal calcifications noted at birth
c. Abnormal face (flattened mid-face and nose)
d. Short hands
e. Normal height
f. Normal mentation

Diagnostic Investigations

1. Radiography
a. Classic RCDP1
i. Bilateral shortening of the humerus and to a lesser degree the femur
ii. Punctate calcifications in the epiphyseal cartilage at the knee, hip, elbow, shoulder, hyoid bone, larynx, sternum, and ribs
iii. Radiolucent coronal clefts of the vertebral bodies that represent unossified cartilage

iv. Abnormal epiphyses and flared and irregular metaphyses secondary to resolved punctate calcification after age 1–3 years

b. Tibia-metacarpal type
   i. Shortened and bowed tibia and radii
   ii. Overgrowth of the fibulae
   iii. Ulnar hypoplasia
   iv. Calcific stippling of the proximal bones
   v. Punctate calcifications of the trachea, thyroid cartilage, entire spine, and sacrum
   vi. Clefting (coronal and/or sagittal) of the vertebral bodies
   vii. Symmetrical brachymetacarpy: shortened 2nd, 3rd, and 4th metacarpals
   viii. Shortened radial head
   ix. Patella dislocation

2. Biochemical/molecular studies
   a. RCDP1 (Braverman et al. 2010)
      i. Deficiency of red blood cell plasmalogens
      ii. Increased plasma concentration of phytanic acid
      iii. Deficiencies in plasmalogen biosynthesis and phytanic acid hydroxylation in cultured skin fibroblasts
      iv. PEX7 receptor defect in RCDP1 predicted by the following:
         a) Deficiency of plasmalogens in red blood cells
         b) Increased plasma concentration of phytanic acid
         c) Normal plasma concentration of very long chain fatty acids
      v. Molecular genetic analysis: *PEX7* gene mutation analysis and sequencing
   b. RCDP2
      i. Deficiency of the peroxisomal enzyme dihydroxyacetone phosphate acyltransferase (DHAPRT) in cultured skin fibroblasts
      ii. *DHAPRT* gene mutation analysis by sequencing of coding regions
   c. RCDP3: deficiency of the peroxisomal enzyme, akkyl-dihydroxyacetone phosphate synthase (ADAPS) in cultured skin fibroblasts
      i. Deficiency of the peroxisomal enzyme, akkyl-dihydroxyacetone phosphate synthase (ADAPS) in cultured skin fibroblasts
      ii. *ADHAPS* gene mutation analysis
   d. X-linked dominant form (CDPX2)
      i. Diagnosis confirmed by measuring the plasma concentration of sterols which show accumulation of precursors, 8(9)-cholesterol and 8-dehydrocholesterol
      ii. Identify molecular defect in human *EBP* in CDPX2 patients
   e. X-linked recessive form (CDPX1): ARSE gene mutation analysis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal recessive RCDP1: 25%
      ii. Autosomal dominant form: not increased unless one of the parents is affected
      iii. X-linked recessive form: 50% of brothers affected when the mother is a carrier
      iv. X-linked dominant form
         a) 50% of sisters and brothers (lethal) affected when the mother is a carrier
         b) Possibility of an apparently normal mother being a carrier to be considered when examining seemingly sporadic cases
   b. Patient's offspring
      i. Autosomal recessive RCDP1: do not reproduce
      ii. Autosomal dominant form: 50%
      iii. X-linked recessive form: 50% risk of daughters to be carriers; none of sons will be affected
      iv. X-linked dominant form: affected mother: 50% of sons affected (lethal in male); 50% of daughters affected
2. Prenatal diagnosis
   a. Radiography
      i. Stippling of the bones of the extremities and pelvis
      ii. Abnormalities of the vertebral bodies
   b. Ultrasonography
      i. Rhizomelic form
         a) Severe rhizomelic limb shortening
         b) Punctuate epiphyseal calcifications
         c) Associated sonographic findings: profound hypoplasia of the humeri,

metaphyseal flaring, a flattened midface, joint contracture, clubfoot deformity, and hydramnios

ii. Nonrhizomelic form
   a) Asymmetric, variable limb shortening without a clear pattern of rhizomelia or mesomelia
   b) Calcifications in the long bone epiphyses, which may be recognizable in the second trimester or may not be recognizable even in the third trimester
   c) Other sonographic findings: spinal deformities, frontal bossing, a depressed nasal bridge, ascites, and polyhydramnios

iii. X-linked dominant form
   a) Growth retardation
   b) Skeletal asymmetry
   c) Polyhydramnios

c. Assays of plasmalogen biosynthesis in cultured chorionic villi or amniocytes for pregnancies at 25% risk for RCDP1
d. Enzyme activity of alkyl-dihydroxyacetone phosphate synthase (ADHAPS) and subcellular localization of peroxisomal thiolase performed on uncultured chorionic villi
e. Molecular prenatal diagnosis in X-linked dominant chondrodysplasia punctata to identify disease-causing *EBP* mutation in the fetus

3. Management
   a. Mainly supportive
   b. G-tube placement for poor feeding and recurrent aspiration
   c. Cataract extraction to preserve vision
   d. Orthopedic procedures to correct contractures to improve function
   e. X-linked dominant form
      i. Emollients for ichthyosis
      ii. Splinting for clubbed feet
      iii. Surgery for polydactyly
      iv. Ophthalmological care for cataracts

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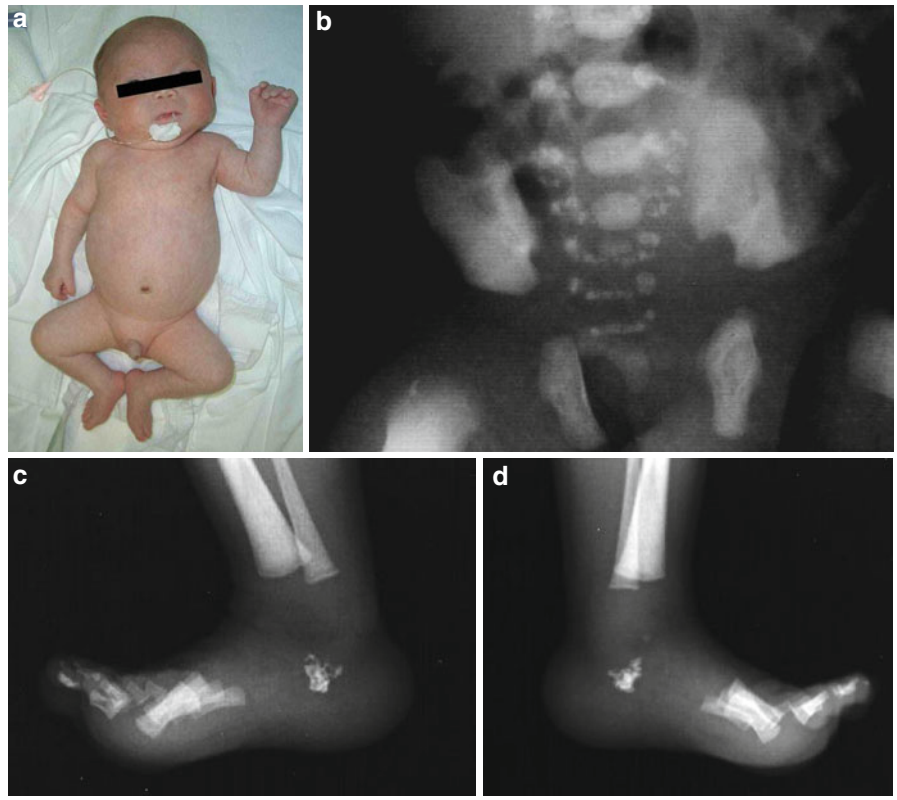


Fig. 1 (**a**–**d**) Patient 1 (a Japanese newborn boy) with X-linked recessive form of chondrodysplasia punctata. Radiographs show paravertebral and calcaneus punctate calcification

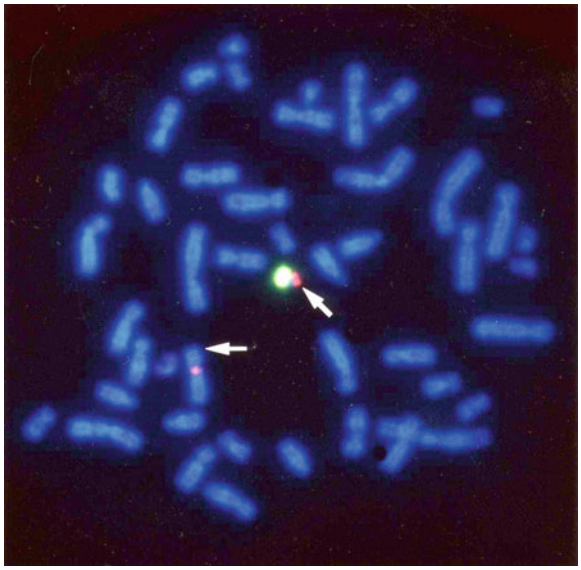


Fig. 2 FISH (patient 1) with a SHOX (short stature homeobox containing gene) probe for Xp22.3 (a pink signal) and Yp11.3 (a pink signal) showing a deleted pink Xp22.3 signal. The pink signal in the X chromosome is an X peri-centromere probe (SXZ1) and the green signal is a Yq12 probe (DXZ1)

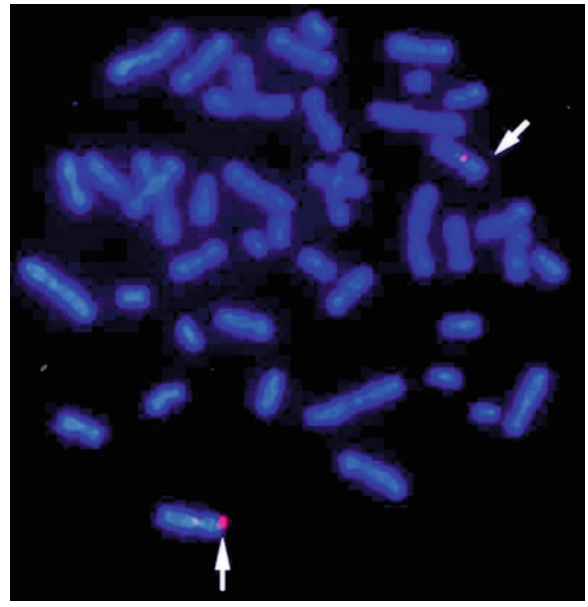


Fig 3 The mother of patient 1 is a carrier of del(X)(p22.3p22.3) (SHOX-). Her FISH showed that a red signal (a probe for Xp22.3; SHOX gene) is deleted in one of her X chromosomes

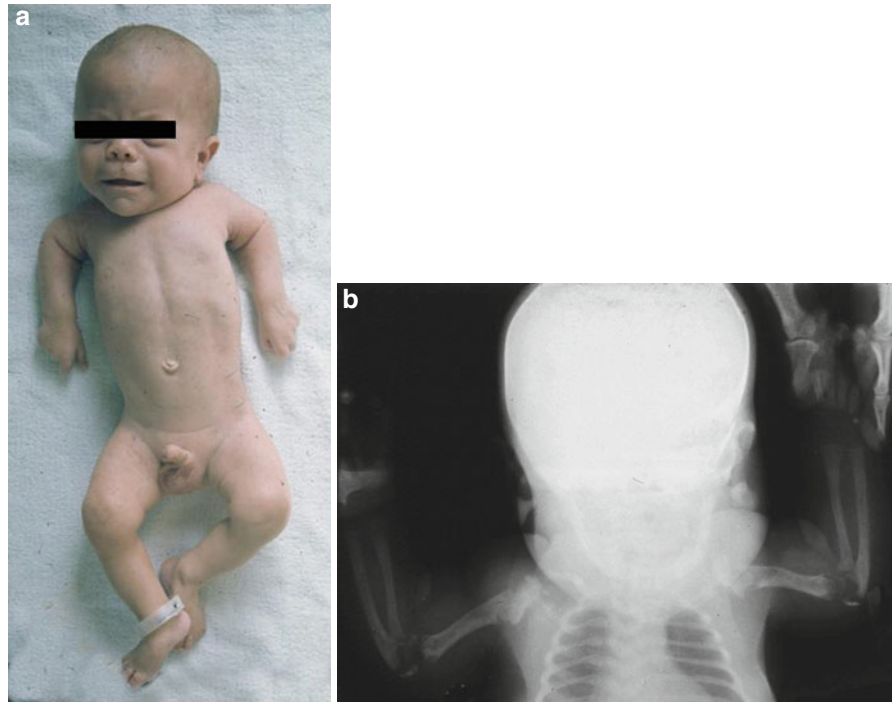


Fig. 4 (**a**, **b**) A neonate with rhizomelic form of chondrodysplasia punctata, showing short humeri and punctate calcifications in the shoulder and/or elbow joints illustrated by radiograph

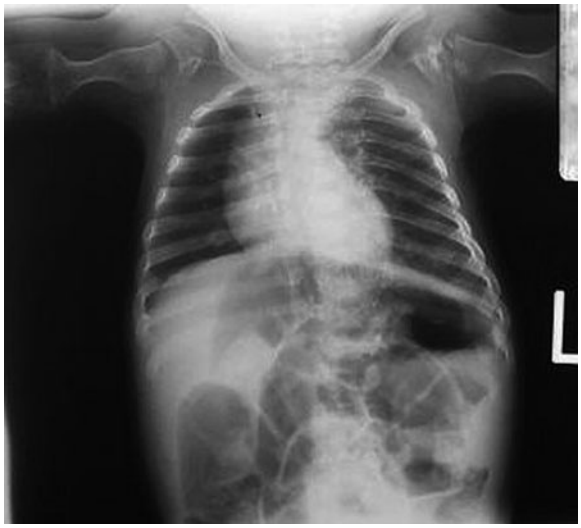
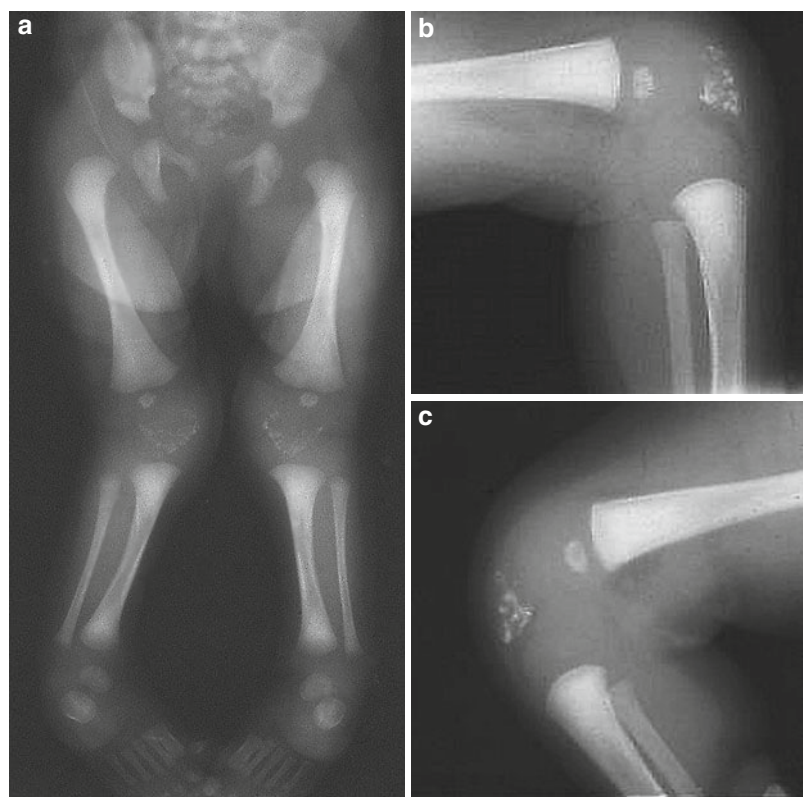


Fig. 5 Radiograph of another neonate with rhizomelic form of chondrodysplasia punctata, showing similar radiographic features

Fig. 6 (**a**, **b**) Another neonate with chondrodysplasia punctata showing depressed nasal bridge and underdeveloped nasal cartilage. The infant has punctate calcifications in the proximal femoral heads



Figs. 7 (**a**–**c**) Radiographs of a child with an autosomal dominant chondrodysplasia punctata showing punctate calcifications in the knees

Chromosome Abnormalities in Pediatric Solid Tumors

Consistent chromosome abnormalities have been described in many pediatric solid tumors. These findings led to direct molecular investigation and a better understanding of tumor pathogenesis. Clinical correlation often produced useful prognostic information (Karnes et al. 1992).

Synonyms and Related Disorders

CNS primary tumor; Neuroblastoma; Other pediatric solid tumors; Retinoblastoma; Wilms tumor

Genetics/Basic Defects

1. Somatic mutation theory of cancer (Mertens et al. 1994)
   a. Resulting from the accumulation of specific genetic changes
   b. Several lines of evidence
      i. Monoclonal origin of most tumors, suggesting that they derive from a single progenitor cell
      ii. Several tumors occurring not only sporadically but also as familial hereditary traits
      iii. Mutagenic nature of most carcinogenic agents, at least in experimental systems
      iv. Acquired genetic changes in the tumor cells, many of which are detectable at the chromosome level and several of these mutations have been shown to be tumorigenic in experimental animals
2. Chromosome abnormalities in neoplastic cells
   a. Technical improvement in basic cytogenetic techniques
      i. Use of colchicine to arrest dividing cells in metaphase and hypotonic solutions to improve spreading of the chromosomes
         a) Description of the correct chromosome number in humans
         b) The first specifically neoplasia-associated chromosome aberration, the Ph1 chromosome in chronic myeloid leukemia
      ii. Introduction of chromosome banding techniques
         a) Possible to identify individual chromosome pairs
         b) To detect and characterize even subtle rearrangements.
   b. Clonal chromosome aberrations in neoplasms
      i. Primary aberrations
         a) Nonrandomly associated with particular tumor types
         b) Sometimes observed as the sole karyotypic deviation
         c) Thought to constitute early and essential events in carcinogenesis
         d) Increased genomic instability thought to be one of the consequences of the acquisition of a primary cancer chromosome rearrangement
         e) Many primary aberrations affect cellular oncogenes, often fusing them with other genes to encode hybrid proteins or

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disrupting the normal control sequences of the oncogene, causing its inappropriate expression
ii. Secondary aberrations
a) Occurrence of new abnormalities facilitated by primary aberrations
b) Nonrandom
c) Distribution of the secondary aberrations dependent on both the primary abnormality and the tumor type in which they occur
iii. Cytogenetic noise
a) Resulting from acquired instability
b) Random changes with little or no selective value

3. Mechanisms by which chromosomal aberrations arise (Albertson et al. 2003)
a. Aberrations that lead to aneuploidy
i. Polyploidy
ii. Aneuploidy
iii. Reciprocal translocation
iv. Nonreciprocal translocation
v. Amplification (double minutes)
vi. Amplification (HSR)
vii. Amplification (distributed insertions)
b. Aberrations that leave the chromosome apparently intact
i. Loss of heterozygosity (LOH) (somatic recombination)
ii. Loss of heterozygosity (duplication/loss)
4. Identification of specific chromosome rearrangements in neoplasms
a. Leukemia and lymphoma
i. Crucial for more detailed studies utilizing molecular genetic techniques
ii. Possible to compare cytogenetic findings with morphologic, immunologic, and clinical parameters such as the response to therapy and survival
iii. Diagnostic and prognostic implications of karyotyping
b. Solid tumors
i. In general, more complex karyotypes observed in solid tumors
ii. Have distinct patterns of primary and secondary aberrations closely associated with histopathologic entities
iii. Identification of only a few genes as a consequence of recurrent structural rearrangements
iv. Fusion of transcription factor gene with other loci, a common feature
v. Tumor suppressor genes
a) Important in solid tumors
b) Thought to encode inhibitors of unrestrained growth
c) Behave in a recessive manner at the cellular level (i.e., loss or structural disruption of both wild-type alleles is required to unleash a neoplastic phenotype)
5. Retinoblastoma (RB) (Mertens et al. 1994)
a. A prototype tumor for understanding basic concepts in cancer genetics
b. Genetics of retinoblastoma
i. Thought to be a single gene disorder caused by mutation of the *RB1* gene
ii. Sporadic, nonhereditary form in most cases
a) Unilateral or unifocal retinoblastoma
b) A mutation in the RB1 locus occurred later in embryogenesis
iii. Hereditary form (one third of tumors)
a) Bilateral or multifocal retinoblastoma
b) Predisposition inherited as an autosomal dominant trait
c) Mutations inherited from a carrier parent in 25% of the cases
d) A new mutation occurring very early in embryogenesis in 75% of cases
e) Overall estimates of the penetrance of the trait: 85–95%
c. Retinoblastoma gene, *RB1*
i. The first cancer-predisposition gene to be cloned
ii. Chromosome map: 13q14
iii. More than 100 different mutations reported to date
a) Missense mutations
b) Nonsense mutations
c) Splice-site mutations
d) Small and large deletions
d. Knudson's "two-hit hypothesis" of tumorigenesis
i. In the unaffected individual, both RB1 genes are intact and serve as guardians of the retina.
ii. Retinoblastoma develops as a result of two separate mutations.
iii. Sporadic tumors: two separate mutations occurring somatically in the same retinal cell
iv. Heritable retinoblastoma: The first mutation is germinal and the second somatic.

e. Inherited form of retinoblastoma
   i. Critical gene for retinoblastoma located in band 13q14, suggested by cytogenetic analyses of tumor cells and lymphocytes
   ii. Homozygous loss of DNA markers from 13q14 in tumor cells from individuals with familial retinoblastoma vs. heterozygous loss of these DNA markers in normal cells, suggested by molecular genetic investigations

6. Neuroblastoma (NB)
   a. A malignant tumor derived from undifferentiated neural crest cells that are committed to differentiate into the sympathetic nervous system
   b. Inheritance
      i. Sporadic in most cases
      ii. A few clustered familial cases reported indicating an autosomal dominant inheritance with incomplete penetrance
   c. Molecular biology (Lee et al. 2003)
      i. The amplification (i.e., increased number of DNA copies) of the oncogene MYCN (N-myc), located on chromosome 2p24, and changes in the normal diploid chromosomal content
         a) Both are correlated with disease prognosis and disease recurrence
         b) The amplification can be in the form of the double minute chromosomes, which are extragenomic segments of DNA, or in homogeneously staining chromosomal regions
      ii. Variable DNA content of neuroblastoma
         a) Near-triploid DNA index regardless of any clinical or biologic features predicts a smaller risk of progression to higher-stage diseases
         b) Diploid/tetraploid index tends to predict higher risk of progression or multiple relapses
      iii. Other molecular markers (receptors for nerve growth factors) associated with neuroblastoma
         a) Trk A: associated with favorable neuroblastomas
         b) Trk B: expressed in unfavorable neuroblastomas

7. Wilms' tumor (WT)
   a. Biological pathways leading to the development of Wilms' tumor
      i. Complex
      ii. Involvement of several genetic loci
         a) Two genes on chromosome 11p; one on chromosome 11p13 (the Wilms' tumor suppressor gene, *WT1*) and the other on chromosome 11p15 (the putative Wilms' tumor suppressor gene, *WT2*)
         b) Loci at 1p, 7p, 16q, 17p (the *p53* tumor suppressor gene), and 19q (the putative familial Wilms' tumor gene, *FWT2*)
   b. Inheritance
      i. Sporadic in majority of cases (>95%)
      ii. Familial predisposition to Wilms' tumor is rare, affecting only1.5% of patients with Wilms' tumor
   c. Association with specific genetic disorders or recognizable syndromes
      i. WAGR syndrome
         a) Large constitutional deletions of chromosome 11p13
         b) Tumor suppressor gene: *WT1*
         c) Mechanism of gene inactivation: hemizygous deletion
         d) Wilms' tumor incidence: >30%
         e) Associated features: aniridia, genitourinary abnormalities
         f) Mental retardation
         g) Associated aniridia: caused by deletion of the *PAX6* gene in the 11p13 region in close proximity to *WT1* gene
      ii. Denys–Drash syndrome
         a) Chromosomal loss: 11p13
         b) Tumor suppressor gene: *WT1*
         c) Mechanism of gene inactivation: mutation (DNA binding domain)
         d) Wilms' tumor incidence: >90%
         e) Associated features: pseudohermaphroditism, mesangial sclerosis, renal failure
      iii. Beckwith–Wiedemann syndrome
         a) Chromosomal loss: 11p15
         b) Tumor suppressor gene: (*WT2*/*BWS*)
         c) Mechanism of gene inactivation: unknown
         d) Wilms' tumor incidence: 5%
         e) Associated features: organomegaly, hemihypertrophy, umbilical hernia,

neonatal hypoglycemia, other tumors such as hepatoblastoma
iv. Perlman syndrome
a) Renal dysplasia
b) Multiple congenital anomalies
c) Gigantism
d) Wilms' tumor
v. X-linked Simpson–Golabi–Behmel syndrome
a) Overgrowth disorder
b) Caused by mutations in the *GPC3* gene located on Xq26
c) Overlapping physical features with Beckwith–Wiedemann syndrome
d) Wilms' tumor and other embryonal tumors

8. Primary tumors of the central nervous system (Martens 1994)
a. Primitive neuroectodermal tumors (PNETs)
i. Homozygous inactivation of the *TP53* gene, a tumor-suppressor gene located in 17p, secondary to i(17p): implicated in the development of several tumor types
ii. Molecular analyses indicating the existence of a second tumor-suppressor gene, distinct from and distal to the *TP53* locus, that might be pathogenetically involved in a subset of primitive neuroectodermal tumors
b. Gliomas
i. A tumor suppressor gene in 22q implicated as an essential event in the genesis of a number of neurogenic neoplasms
ii. A candidate for such a role is *NF2*, thought to be mutated in neurofibromatosis type 2, a dominantly inherited disorder predisposing for gliomas, neurinomas, and meningiomas

Clinical Features

1. Only retinoblastoma, neuroblastoma, and Wilms' tumor will be discussed here.
2. Retinoblastoma (Martens 1994)
a. The most common malignant ocular tumor in childhood and affects approximately 1 in 18,000 children under 5 years of age in the USA (Devesa 1975)
b. A rare malignant tumor arising from cells of the embryonal neural retina
c. Develops only in infants and young children
d. Unifocal retinoblastoma: presence of a single retinoblastoma
e. Multifocal retinoblastoma: presence of more than one tumor
i. Unilateral: occurrence of multiple RB tumors in one eye
ii. Bilateral: occurrence of RB tumors in both eyes
iii. "Trilateral"retinoblastoma: occurrence of bilateral retinoblastoma plus a pinealoma
f. Presenting signs
i. White papillary reflex (leukocoria): the most common presenting sign
ii. Strabismus: the second most common presenting sign
iii. Less common signs
a) Poor vision
b) Orbital swelling
c) Unilateral mydriasis
d) Heterochromia iridis
e) Glaucoma
f) Orbital cellulitis
g) Uveitis
h) Hyphema or vitreous hemorrhage
i) Nystagmus
g. Retinoma-associated eye lesions ranging from retinal scars to calcified phthisical eyes resulting from spontaneous regression of retinoblastoma (include benign retinal tumors called retinocytoma or retinoma)
h. Patients with germline RB1 mutations: at an increased risk of developing tumors outside the eye
i. Pinealomas
ii. Osteosarcomas
iii. Soft tissue sarcomas
iv. Melanomas
3. Neuroblastoma (Davidoff and Hill 2001; Lee et al. 2003)
a. The most frequently occurring solid tumor in children
b. Responsible for 8–10% of all cancers in children and approximately 15% of all pediatric cancer deaths
c. 40% of cases diagnosed in children under 1 year of age who have a very good prognosis
d. 60% in older children and young adult who have a poor prognosis despite advanced medical and surgical management

e. Amplification of *MYCN* gene found in neuroblastomas:
   i. A powerful prognostic indicator
   ii. Associated with:
      a) Advanced stages of disease
      b) Rapid tumor progression
      c) Poor outcome
f. Clinical presentation
   i. Variable presentation
      a) Localized disease (one third to one fourth of cases)
      b) Metastatic disease (two third to three fourth of cases)
      c) Asymptomatic in small number of patients
   ii. Retroperitoneal and abdominal tumors (62–65%)
      a) A palpable mass
      b) Abdominal pain (34%)
      c) Weight loss (21%)
      d) Anorexia
      e) Vomiting
      f) Symptoms related to mass effect
   iii. Thoracic tumors (14%)
      a) Dysphagia
      b) Cough
      c) Respiratory distress
   iv. Pelvis (5%) and paraspinal tumors that compress the spinal cord
      a) Urinary dysfunction
      b) Constipation
      c) Fetal incontinence
      d) Lower extremity weakness
   v. Neck tumors
      a) Horner syndrome: present in patients with lesions in the cervical or upper thoracic sympathetic ganglia (1.7%)
      b) Airway distress
   vi. Liver metastasis
      a) Hepatomegaly
      b) Jaundice
      c) Abnormal liver function tests
      d) Abdominal pain
   vii. Bone metastases and bone marrow involvement
      a) Bone pain
      b) Palpable bony nodules
      c) Anemia
      d) Purpura
   viii. Fever (28%)
   ix. Lymph node metastases: palpable lymphadenopathy
   x. Retrobulbar and orbital metastases: periorbital ecchymoses
   xi. Severe diarrhea refractory to standard treatment due to production of vasoactive intestinal peptide by tumor cells (4%)
   xii. Acute cerebellar encephalopathy (2%)
      a) Cerebellar ataxia
      b) "Dancing eyes and dancing feet syndrome" (involuntary eye fluttering and muscle jerking)
      c) Myoclonic jerks
   xiii. Symptoms related to high catecholamine levels (0.2%)
      a) Hypertension
      b) Palpitations
      c) Flushing
      d) Sweating
      e) Malaise
      f) Headache

4. Wilms' tumor (Martens 1994)
   a. The most common kidney cancer in childhood
   b. Represents about 6% of all childhood cancers in the USA
   c. Clinical presentation
      i. Presence of an asymptomatic abdominal mass: the most common presentation
         a) Usually affects one kidney with multiple tumor foci in 8% of cases
         b) Bilateral in 6% of cases
      ii. Hypertension, gross hematuria, and fever observed in 5–30% of patients
      iii. Hypotension, anemia, and fever in a small number of patients who have hemorrhaged into their tumor
      iv. Rare respiratory symptoms related to the presence of lung metastases in patients with advanced-stage disease
   d. Association with congenital malformations
      i. Found in 60% of the bilateral cases and 4% of the unilateral cases
      ii. WAGR
      iii. Denys–Drash syndrome
      iv. Beckwith–Wiedemann syndrome
      v. Perlman syndrome
      vi. Beckwith–Wiedemann syndrome

vii. X-linked Simpson–Golabi–Behmel syndrome
e. Likelihood of developing Wilms' tumor in aniridia patients
i. Aniridia patients without other anomalies: 1–2%
ii. Aniridia patients with WAGR syndrome: 25–40%

Diagnostic Investigations

1. Cytogenetic and molecular genetic techniques used in analyzing tumor materials from patients (Cooley et al. 2009)
a. Conventional and molecular cytogenetic techniques most commonly used (Varella-Garcia 2003)
i. Metaphase cytogenetics or karyotyping (G-, Q-, and R-bandings):
a) Protein digestion and/or special dye generating banding pattern specific for each chromosome
b) Identification of numerical and structural chromosomal anomalies
ii. Fluorescence in situ hybridization (FISH)
a) A small, labeled DNA fragment used as a probe to search for homologous target sequences in chromosome or chromatin DNA
b) Identification of the presence, number of copies per cell, and localization of probe DNA
c) Applicable to interphase cells
iii. Comparative genomic hybridization (CGH)
a) Comparative hybridization of differentially labeled total genomic tumor DNA and normal reference DNA to normal human metaphases used as templates
b) Detection of variant DNA copy numbers at the chromosome level
c) Applicable to fresh or preserved specimens
iv. Multicolor karyotyping (M-FISH, SKY)
a) Hybridization with 24 differentially labeled, chromosome-specific probes allowing the painting of every human chromosome in a distinct color
b) Detection of rearrangements involving one or more chromosomes within individual metaphase spreads
c) Accurate origin identification of all segments in complex rearrangements
d) Clarification of marker chromosomes
b. Other techniques
i. Flow cytometry
ii. Reverse transcriptase-polymerase chain reaction (RT-PCR)
iii. Quantitative PCR
iv. Southern blot analysis of gene rearrangements
v. Loss of heterozygosity analysis (LOH)
vi. Restriction landmark genome scanning
vii. Representational difference analysis
viii. cDNA gene expression microarrays
ix. Proteomic methods
a) Matrix assisted laser desorption ionization-time of flight (MALDI-TOF)
b) Surface enhanced laser desorption ionization-time of flight (SELDI-TOF)
2. Cytogenetic studies in retinoblastoma
a. Cytogenetically visible changes of 13q14: infrequent in retinoblastoma
b. Deletions or unbalanced translocations leading to loss of 13q14 band (10%)
c. Monosomy 13 (10%)
d. i(6p), mostly detected as a supernumerary isochromosome (one third of cases)
e. Gain of 1q material (one third of cases)
f. Cytogenetic aberrations in retinoblastoma
i. Secondary to *RB1* mutations
ii. More related to tumor progression than to tumor establishment
3. Other studies for retinoblastoma
a. Indirect ophthalmoscopy to examine the fundus of the eye to detect retinomas, preferably by a retinal specialist
b. Imaging studies (CT, MRI, ultrasonography) to support the diagnosis and stage the tumor
c. Histopathological examination to confirm the diagnosis
d. Direct DNA testing of the RB1 gene in WBC DNA
i. Identify a germline mutation in about 80% of individuals with a hereditary predisposition to retinoblastoma

ii. Probability of detection of the RB1 gene mutation in an index case dependent on the following:
a) Whether the tumor is unifocal or multifocal
b) Whether the family history is positive or negative
c) The sensitivity of the testing methodology

4. Cytogenetic studies in neuroblastoma (Davidoff and Hill 2001; Lee et al. 2003)
a. Identification of multiple cytogenetic abnormalities in neuroblastoma
i. Allelic losses on chromosomes 1p (particularly 1p36), 11q, 14q, 7q, 2q, 3p, and 19q
ii. Allelic gains on chromosomes 17q, 18q, 1q, 7q, and 5q
b. Hyodiploid, triploid, or "near triploid", or "near-tetraploid" in modal chromosome number
i. Majority (55%) with triploid or "near-triploid" (a chromosome number between 58 and 80)
ii. Remainder with "near-diploid" (35–57 chromosomes) or "near-tetraploid" (81–103 chromosomes)
c. Frequent partial 1p monosomy (70–80% of cases) with most commonly deleted region being between 1p32 and 1p36
d. Gain on the long arm of chromosome 17 (17q)
i. Probably the most common genetic abnormality in neuroblastomas
ii. Occurring in approximately 75% of primary tumors
iii. Most often resulting from an unbalanced translocation of this region to other chromosomal sites, most frequently 1p or 11q
iv. A powerful independent finding of adverse outcome
e. Deletions of the long arms of chromosomes 11 (11q) and 14 (14q)
i. Appears to be common in neuroblastomas
ii. Both inversely related to *MYCN* amplification
f. Frequent presence of extrachromosomal double minute chromatin bodies (DMs) or homogeneously staining regions (HSRs)
i. Cytogenetic evidence of gene amplification
ii. Amplified region derived from the distal short arm of chromosome 2 (2p24) that contains the *MYCN* proto-oncogene

5. Other studies for neuroblastoma
a. Imaging studies
i. Chest radiography
ii. Ultrasound
iii. CT
iv. MRI
v. Radionucleotide bone scan
b. Blood tests
i. Elevated urinary and serum catecholamine metabolites
a) Homovanillic acid (HVA)
b) Vanillylmandelic acid (VMA)
ii. Abnormal liver function tests
c. Molecular genetic testing (Castel et al. 2007)
i. Array CGH analysis: a pangenomic technique allowing insights into gains and losses with high resolution
ii. Multiplex ligation-dependent probe amplification (MILPA)

6. Cytogenetic studies in Wilms' tumor
a. A near-diploid chromosome count
b. Triploid-tetraploid karyotypes in a few cases with tendency to have an anaplastic morphology
c. Numerical aberrations
i. Mainly involving gains of chromosomes
a) Trisomy 12: particularly frequent
b) Followed by trisomies 8, 6, 7, 13, 20, and 17
d. Structural rearrangements
i. Involve all chromosomes except the Y chromosome
ii. Recombinations of 11p (>20%)
a) Vast majority of the breakpoints assigned to 11p13 and 11p15, indicating these loci are important in sporadic Wilms' tumor
b) Loss of heterozygosity studies indicating that alleles from 11p13 and 11p15 are often lost in Wilms' tumor
iii. Loss of the long arm of chromosome 16 occurring in about 20% of Wilms' tumors: associated with poor prognosis independent of stage or tumor histology

7. Other studies in Wilms' tumor
   a. Renal ultrasound to monitor Wilms' tumor
   b. Abdominal CT scanning to determine the tumor's origin, lymph node involvement, bilateral kidney involvement, and invasion into major vessels (e.g., inferior vena cava or liver metastases)
   c. Chest radiography to detect lung metastases
   d. Histopathological examination to confirm the diagnosis
   e. Further studies of certain patients with either Wilms' tumor or associated anomalies (Coppes and Egeler 1999)
      i. Hemihypertrophy/Beckwith–Wiedemann syndrome: uniparental disomy studies to evaluate constitutional or somatic alterations of 11p15
      ii. WAGR syndrome: molecular evaluation of the 11p13 region if chromosomal studies do not reveal a deletion
         a) Fluorescence in situ hybridization (FISH)
         b) Pulsed-field electrophoresis
      iii. Denys–Drash syndrome: molecular evaluation of *WT1* to determine whether the patient indeed carries a constitutional mutation. If the mutation is present, family members need to be screened.
      iv. Aniridia
         a) Cytogenetic analysis and molecular evaluation of the WAGR region by FISH or pulsed field to rule out contiguous deletion of *Pax6* and *WT1*
         b) No further screening for Wilms' tumor if *Pax6* mutation is identified in isolated cases of aniridia
8. Cytogenetic studies of primary tumors of the central nervous system (Martens 1994)
   a. Primitive neuroectodermal tumors
      i. Near-diploid in most tumors
      ii. I(17q): the most consistent rearrangement
   b. Gliomas
      i. Mostly astrocytomas and ependymomas
      ii. No specific structural rearrangement found
      iii. Loss of 1p and gain of 1q found in a subset of tumors
      iv. Loss of chromosome 22 common in childhood gliomas
      v. Loss of material from chromosome 22, either numeric or structural aberrations, found recurrently in rhabdoid tumors, meningiomas, and neurinomas
9. Cytogenetic studies in hepatoblastoma (Mertens et al. 1994)
   a. Trisomy 2 or duplications of part of 2q: detected in half of the cases
   b. Trisomy 20
   c. Duplication of 8q through either i(8q) formation or trisomy 8
10. Cytogenetic studies in sarcomas
   a. Ewing sarcoma/primitive neuroectodermal tumor (Davidoff and Hill 2001)
      i. Reciprocal translocation t(11;22)(q24;q12)
         a) Characteristic primary rearrangement
         b) Found in nearly 90% of the tumors
         c) Causing a fusion of the transcription factor gene *FLI1* on chromosome 11 with *EWS* on chromosome 22 (*FLI1-EWS*, a fusion transcript). Only the chimeric gene expresses on the derivative chromosome 22 which contains a sequence encoding a DNA-binding domain from *FLI1*
      ii. t(21;22)(q22;q12), *ERG-EWS*
      iii. t(7;22)(p22;q12), *ETV1-EWS*
      iv. t(17;22)(q12;q12), *E1AF-EWS*
      v. t(2;22)(q33;q12), *FEV-EWS*
   b. Additional chromosome changes
      i. Trisomy 8
      ii. Der(16)t(1;16)(a10-q21;q10-13), leading to gain of 1q and loss of 16q
   c. Congenital or infantile fibrosarcoma (Mertens et al.1994)
      i. t(12;15)(p13;q25), *ETV6-NTRK3*
      ii. Hyperdiploid with few or no structural rearrangements
      iii. Nonrandom numerical changes
         a) Trisomies 11 and 20, the most frequent changes, followed by:
         b) Trisomies 17 and 8
   d. Osteosarcoma (Mertens et al. 1994)
      i. Highly complex karyotypes in the majority of cases
      ii. Chromosome number in the triploid-tetraploid range
      iii. Most common numeric aberrations involving −3, −10, −13, and −15

iv. Structural rearrangements involving chromosome arms 1p, 1q, 3p, 3q, 7q, 11p, 17p, and 22q
v. Presence of many undefined chromosome markers

e. Rhabdomyosarcoma (Mertens et al. 1994)
i. The most common soft tissue sarcoma in childhood
ii. Alveolar subtype
a) Most contain 1 or 2 recurring translocations, namely, t(2;13)(q35-37;q14) or the rare t(1;13)(p36;q14), shown to juxtapose the *PAX3* gene on chromosome 2 with the *FKHR* gene on chromosome 13, leading to the formation of a hybrid transcription factor (*PAX3-FKHR*)
b) Found in about 70% of the alveolar tumors
c) Only occasionally described in other subtypes
iii. Embryonal subtype: numerical changes with +2, +8, +11, and +20, found in 35–50% of cases

11. Other common, recurrent translocation in solid and soft tissue tumors of childhood (Davidoff and Hill 2001)
a. Alveolar soft part sarcoma: t(X;17)(p11;q25), *ASPL-TFE3*
b. Inflammatory myofibroblastic tumor: 2p23 translocations, *ALK-TPM3*
c. Desmoplastic small round cell tumor
i. t(11;22)(p13;q12), *WT1-EWS*
ii. t(11;22)(q24;q12), *FLI1-EWS*, *ERG-EWS*
d. Synovial sarcoma
i. t(X;18)(p11.23;q11.2), *SSX1-SSXT*
ii. t(X;18)(p11.21;q11), *SSX2-SSXT*
e. Malignant melanoma of soft part (clear cell sarcoma): t(12;22)(q13;q12), *ATF1-EWS*
f. Myxoid liposarcoma
i. t(12;16)(q13;p11), *CHOP-TLS*(*FUS*)
ii. t(12;22)(q13;q12), *CHOP-EWS*
g. Extraskeletal myxoid chondrosarcoma: t(9;22)(q22;q12), *CSMF-EWS*
h. Dermatofibrosarcoma protuberans and giant cell fibroblastoma: t(17;22)(q22;q13), *COLIAI-PDGFB*
i. Lipomas: t(var;12)(var;q13-15), var, *HMGI-C* (Cooper 1996)
j. Leiomyomas: t(12;14)(q13;15), *HMGI-C*, (Cooper 1996)

12. Other primary chromosome changes in solid tumors (Sandberg 1988)
a. Benign tumors
i. Meningioma and acoustic neuroma
a) −22
b) 22q−
ii. Mixed tumors of salivary glands
a) t(3;8)(p21;q12)
b) t(9;12)(p13-22;q13-15)
iii. Colonic adenomas
a) 12q− and/or +7
b) 12q− and/or +8
iv. Cortical adenoma of the kidney
a) +7
b) +17
c) −Y
b. Adenocarcinomas
i. Bladder
a) i(5p)
b) +7
c) −9/9q−
d) 11p−
ii. Prostate: del(10)(q24)
iii. Lungs (small cell carcinoma): del(3)(p14p23)
iv. Colon
a) 12q−
b) +7
c) +8
d) +12
e) 17(q11)
f) 17p–
v. Kidney: del(3)(p11p21)
vi. Uterus: 1q−
vii. Ovary
a) 6q−
b) t(6;14)(q21;q24)
viii. Endometrium
a) Trisomy 1q
b) +10
c. Embryonal and other tumors
i. Testicular (germ cell tumors): i(12p)
ii. Malignant melanoma
a) Del(6)(q11q27)
b) i(6p)
c) Del(1)(p11p22)
d) t(1;19)(q12;q13)

iii. Mesothelioma: del(3)(p13p23)
iv. Glioma: −22

13. Potential prognostic markers of neoplastic disease (Barcus et al. 2000)
    a. Breast cancer: allelic loss at 1p22-p31 (lymph node metastasis and tumor size >2 cm)
    b. Bladder cancer
        i. LOH RB (high grade/muscle invasion)
        ii. Genomic alterations (2q−, 5p+, 5q−, 6q−, 8p−, 10q−, 18q−, 20q+) (higher grade)
    c. Cervical carcinoma: LOH on chromosome (advanced stage)
    d. Colorectal cancer
        i. LOH at 18q21 or p53 expression (recurrence/poor survival)
        ii. *MSI* (microsatellite instability)and *K-ras* mutations in normal appearing colonic mucosa (predictive of colorectal cancer)
        iii. P16-hypermethylation (shorter survival in Stage T3N0M0 tumors)
    e. Gastric cancer
        i. LOH p53 (invasive disease)
        ii. LOH of 7q (D7S95) (poor prognosis (in Stage III/IV))
    f. Glioma: chromosome 22q loss (astrocytomas progression)
    g. Head and neck squamous cell carcinoma
        i. LOH of 14q (poor outcome)
        ii. LOH on 2q (poor prognosis)
        iii. LOH on 17p (chemoresistance)
    h. Melanoma: LOH in plasma (advanced stage/tumor progression)
    i. Neuroblastoma
        i. N-myc amplification (poor prognosis)
        ii. TrkA expression (good prognosis)
        iii. High telomerase expression (aggressive behavior)
    j. Neuroblastomas, 4s-: N-myc amplification, 1p deletion, 17q gains, elevated telomerase activity (poor prognosis)
    k. Non-small cell lung cancer
        i. Allelic imbalances on 9p (poor prognosis)
        ii. LOH 11p (poor prognosis)
    l. Primitive neuroectodermal tumor
        i. LOH of 17p (metastatic disease)
        ii. C-myc amplification (poor prognosis)
    m. Prostate cancer: LOH on 13q (advanced stage)
    n. Retinoblastoma: LOH at RB1 locus (tumoral differentiation, absence of choroidal invasion)

14. Chromosome abnormalities observed in some solid tumors (Cooley et al. 2009)
    a. Genitourinary
        i. Renal
            a) Clear cell round cell carcinoma (RCC): −3 or del(3p), del(3p) with gain 5q, del(3p) with loss 5q, −14/del (14q)
            b) Papillary RCC: +7, +17, −Y, 9p−
            c) t(Xp11.2) RCC: (X;17)(p11.2;q25), t (X;17) (p11.2;q23), t(X;1)(p11.2;p34)
            d) t(6;11) RCC: t(6;11)(p21;q12)
            e) Chromophobe RCC: loss 1, 2, 6, 10, 13, 17, 21
            f) Oncocytoma: 1p−, t(11q13)
            g) Rabdoid: −22/22q−
            h) Congenital mesoblastic nephroma: t (12;15)(p12;q25), +11, +17, +20
        ii. Bladder, papillary: del(9)(p21), 8p−, +7, +17
        iii. Wilms' tumor: 16q−, +1q, 1p−, −22, 17p−
        iv. Prostate: +17q31, 8p22−, +8q24, 10q−, 17p13−
    b. Gastrointestinal
        i. Liver
            a) Hepatoblastoma: +20, +2, +8, t (1q12q21)
            b) Hepatic mesenchymal hamartoma: t(11;19)(q13;q13.4), t(19q13.4)
        ii. Salivary gland
            a) Pleomorphic adenoma: t(3;8)(p21;q12)
            b) Mucoepidermoid cancer: t(11;19) (q21;p13)
            c) Warthin tumor: t(11;19)(q21;p13)
    c. Breast
        i. Invasive intraductal: dmin (double minute), hsr (homogeneously staining region)
        ii. Secretory breast: t(12;15)(p13;q25)
    d. CNS
        i. Astrocytic tumors: +7, −10/10q−, 9p21−, 19q−
        ii. Glioblastoma: +7, 10q−, 9p−
        iii. Anaplastic: 1p−, 19q−, der(1;19)(q10;p10)
        iv. Mixed oligoastocytoma: +7, −10/10q−, 15q−
        v. Oligoastrocytoma: 19q−, 1p−

e. Ependymoma
   i. Spinal: +7, −22q, 14q−
   ii. Intracranial: +1q, 6q−, +7, 9p−
f. Mudulloblastoma: i(17q), 17p−, −10/10q−, +7
g. Supratentorial primitive neuroectodermal tumor +1q, 16q−, 19p−
h. Atypical teratoid/rhabdoid tumor: −22 or del (22q11.23)
i. Meningioma: −22 or del(22q11.2), 1p−,−14/14q−
j. Choroid plexus tumors
   i. Carcinoma: loss 2, 3, 4, 5, 6, 8, 10, 11, 13, 14, 15, 16, 17, 18, 19, 22
   ii. Papilloma: gain 7, 8, 9, 12, 14, 15, 17, 18, 19, 20
k. Small round cell tumors
   i. Alveolar RMS: t(2;13)(q37;q14), t(1;13)(p36;q14), t(X;2)(q13lq35); t(2;2)(q35;p23)
   ii. Embryomal rhabdomyosarcoma: gain 2, 7, 8, 11, 12, 13, 20; loss 1p, 3p, 9q, 10q, 16q, 17p, 22
   iii. Neuroblastoma: del(1p), del(11q) w/o *MYCN* amp, del(1p), +17q, *MYCN* amp, triploidy w/o above abnormalities
   iv. Ewing sarcoma/peripheral neuroectodermal tumor: t(11;22)(q24;q12) & variants, t(21;22)(q22;q12), del(9p), 17p−, der(1;16)(q10;p10)
   v. Desmoplastic small round cell tumor: t(11;22)(p13;q12)
   vi. Clear cell sarcoma: t(12;22)(q13;q12)
   vii. Retinoblastoma: del(13q14), gain 1q, 6p
   viii. Lymphomas: Specific translocations
l. Bone, soft tissue
   i. Congenital fibrosarcoma/congenital mesoblastic nephroma: t(12;15)(p12;q25), +11, +17, +20
   ii. Synovial sarcoma: t(X;18)(p11.2;q11.2)
   iii. Lipoma: t(3;12)(q27–28;q14–15), variants
   iv. Liposarcoma
      a) Myxoid, round cell: t(12;16)(q13;p11)
      b) Myxoid: t(12;22)(q13;q12), variant
      c) Well differentiated: rings, markers, dmin
m. Leiomyoma: t(12;14)(q15;q24)
   i. Alveolar soft part sarcoma: der(17)t(X;17)(p11.2;q25)
   ii. Extraskeletal myxoid chondrosarcoma: t(9;22)(q22;q12), t(9;17)(q22;q11.2), t(9;15)(q22;q21), t(3;9)(p11;q22)
n. Dermal tumors
   i. Dermatofibrosarcoma protuberans: der(22)t(17;22)(q22;q13.1) or r(22)t(17;22)
   ii. Giant cell fibroblastoma: t(17;22)(q22;q13.1)
   iii. Bednar tumor: der (22)t(17;22) (q22;q13.1) or r(22)t(17;22)
   iv. Hidradenoma: t(11;19)(q21;p13)
o. Non-small cell lung cancer: 3p−, +7, *EGFR* high copy number or amplification
p. Dysgerminoma, ovary: i(12p), 12p overrepresentation
q. Testicular germ cell tumors, seminoma, nonseminoma: i(12p), 12p amplification

Genetic Counseling

1. Recurrence risk
   a. Retinoblastoma
      i. Predisposition to retinoblastoma which is caused by germline mutations in the *RB1* gene: transmitted in an autosomal dominant fashion
      ii. Use *RB1* mutation analysis to clarify the genetic status of at-risk sibs and offspring when a previously characterized germline cancer-predisposing mutation is available
      iii. Use indirect testing using polymorphic loci linked to the *RB1* gene in some families to clarify genetic status of at-risk family members if *RB1* direct DNA testing is not available or is uninformative
      iv. Use empiric recurrence risk estimates in all families in which direct DNA testing of *RB1* and linkage analysis are unavailable or uninformative
      v. Risk to patient's siblings
         a) When there is an existing family history: a 45% chance for siblings of bilaterally affected cases and a 30% chance for siblings of unilaterally cases to develop disease
         b) When there is absence of any family history: 2% risk for siblings of bilaterally

affected cases and 1% for siblings of unilaterally affected cases to develop disease
c) There is an additional risk to siblings in the absence of any family history or documented mutation in parental leukocyte DNA because of germline mosaicism. If neither parent has the cancer-predisposing *RB1* germline mutation that was identified in the index case, germline mosaicism in one parent is possible and the risk to each sib of having retinoblastoma is 3–5%.
d) If the index case has mosaicism for an *RB1* cancer-predisposing mutation (the mutation arose as a post-zygotic event) and that neither parent has an *RB1* germline mutation, the risk to the sibs is not increased and thus it is not warranted to test the sibs for the *RB1* mutation identified in the index case.

vi. Risk for patient's offspring
a) About 45% by the age 6 years (consistent with an autosomal dominant inheritance with 90% penetrance) for the offspring of survivors of hereditary (multifocal, bilateral) retinoblastoma
b) About 2.5% for the offspring of survivors of unilateral retinoblastoma
c) The low (∼1%), but not negligible, risk to the offspring of index cases with unifocal disease and a negative family history reflects the possibility of a germline *RB1* mutation with low penetrance or mutational mosaicism.

b. Genetic counseling for retinoblastoma in the presence of positive family history (Vogel 1979; Isidro et al. 2011)
i. Multiplex disease (>2 affected members): The index patient had retinoblastoma and one or more close relatives are also affected
a) Affected individuals definitely carry a germline mutation
b) A 50% chance exists that a known carrier will pass the mutant copy of the retinoblastoma gene to each child and there is 50% penetrance, there is a 50% × 90% = 45% chance that each child will develop retinoblastoma

ii. Multiplex disease (>2 affected members): The index patient did not develop retinoblastoma as a child but a parent is known to be a carrier
a) Approximately 10% risk that an asymptomatic son or daughter of a known carrier is also a carrier
b) The risk that his or her offspring will inherit a mutation is about 5% and the risk of the disease is 90% × 5% = 4.5%

iii. Simplex disease (only one family member affected): The index patient had multifocal retinoblastoma
a) The patient very likely has a germline mutation
b) The risk to each offspring is 50% for being a carrier and 45% for developing the disease

iv. Simplex disease (only one family member affected): The index patient had unifocal retinoblastoma (one tumor in one eye only)
a) A 12% risk exists that the patient carries a germline mutation (i.e., has hereditary retinoblastoma) and an 88% risk that he or she does not (nonhereditary retinoblastoma)
b) The risk for the first child of the index patient is 6% for being a carrier and 5.4% for developing the disease
c) If the first child does not develop retinoblastoma, the risk for the next child is less
d) If at least one child develops retinoblastoma, the index patient definitely has the hereditary type of the disease and risk for family members are as described for mutiplex families

v. Simplex disease (only one family member affected): Two unaffected parents have one child with retinoblastoma
a) The risk of the parents' second child's developing retinoblastoma is about 1% if the first child had unifocal disease and about 6% if the first child had multifocal disease
b) These risks decrease with every unaffected child that passes the years of highest risk (year 0–5) without developing the disease

vi. Simplex disease (only one family member affected): The index patient is an adult of childbearing age who did not develop retinoblastoma but a sibling had retinoblastoma
  a) A small risk exists that one of the parents is an asymptomatic carrier and the index patient is also an asymptomatic carrier
  b) The carrier risk for the index patient is 0.1% if the affected sibling had unilateral retinoblastoma and 0.6% if the affected sibling had bilateral retinoblastoma
  c) The risk that the first child of the index patient will develop retinoblastoma is approximately half of these numbers, i.e., 0.05% or 0.3%, respectively

c. Neuroblastoma
  i. Risk for patient's sibling: low unless a parent has hereditary form of neuroblastoma
  ii. Risk for patient's offspring: 50%

d. Wilms' tumor
  i. Risk for patient's sibling: low unless a parent has hereditary form of Wilms' tumor
  ii. Risk for patient's offspring: 50%

2. Prenatal diagnosis
  a. Retinoblastoma
    i. Prenatal testing possible if the germline *RB1* mutation in the parent is known or if *RB1* linkage analysis is informative in the family
    ii. Mutation analysis on fetal DNA obtained from amniocentesis or CVS
    iii. Use prenatal ultrasonography to detect intraocular tumors if the disease-causing RB1 mutation is identified in the fetus
  b. Adrenal neuroblastoma (Kesrouani et al. 1999)
    i. Prenatal diagnosis adrenal neuroblastoma by ultrasonography usually made in the 3rd trimester
    ii. Sonographic appearance of the adrenal neuroblastoma varies
      a) Solid
      b) Purely cystic (50%)
      c) Mixed echo pattern (related to necrosis, hemorrhage, or spontaneous tumoral involution)
      d) Fetal hydrops
      e) Hydropic placenta with metastases in the placenta
    iii. Needle biopsy for selection of the group with favorable biological parameters (N-myc, DNA index)
    iv. Frequently producing catecholamines and hence maternal symptoms could aid the diagnosis
    v. Elevated catecholamines in the amniotic fluid
  c. Wilms' tumor by prenatal ultrasonography
    i. A solid echogenic mass with a clearly defined capsule
    ii. Areas of hemorrhage and necrosis may be seen within the mass.

3. Management
  a. Surgeries for most solid tumors
  b. Determining the genetic changes present in the tumor of an individual patient: becoming increasingly important for managing the oncology patient
  c. Retinoblastoma (Chintagumpala et al. 2007)
    i. Goals of treatment: preservation of sight and life
    ii. Management of intraocular disease
      a) Enucleation
      b) External beam radiation (EBR) therapy
      c) Brachytherapy: involves the placement of a radioactive implant
      d) Thermotherapy
      e) Chemothermotherapy
      f) Laser photocoagulation
      g) Cryotherapy
      h) Chemotherapy
    iii. Management of extraocular disease: Patients with extraocular disease, having a very poor prognosis with respect to survival, may benefit from a combination of conventional chemotherapy and EBR and those with distant metastatic disease may benefit from high-dose chemotherapy and EBR in conjunction with bone marrow stem cell transplantation
  d. Neuroblastoma (Lee et al. 2003)
    i. Localized, low-risk disease:
      a) Primary curative surgery
      b) Minimal therapy: low-dose radiation or chemotherapy
      c) Supportive care with surveillance

ii. Intermediate-risk patients: combination therapy with radiation, chemotherapy, and surgery
iii. High-risk patients
   a) Combination of radiation, myeloablative chemotherapy, and surgery (delayed)
   b) Autologous bone marrow transplant
   c) Research protocols

e. Wilms' tumor: The usual approach in most patients is nephrectomy followed by chemotherapy with or without postoperative radiotherapy.

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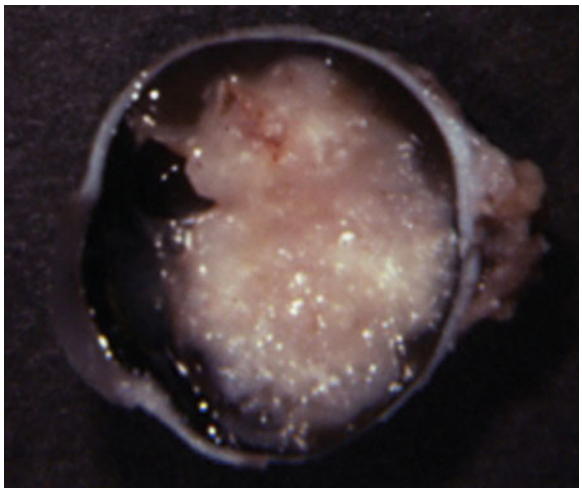

Fig. 1 Notice the *white* firm neoplasm (retinoblastoma) filling the vitreous space of the eye

Fig. 2 Large, well-circumscribed ovoid Wilms tumor in the upper pole of the kidney. Barely identifiable small areas of hemorrhage and necrosis are present

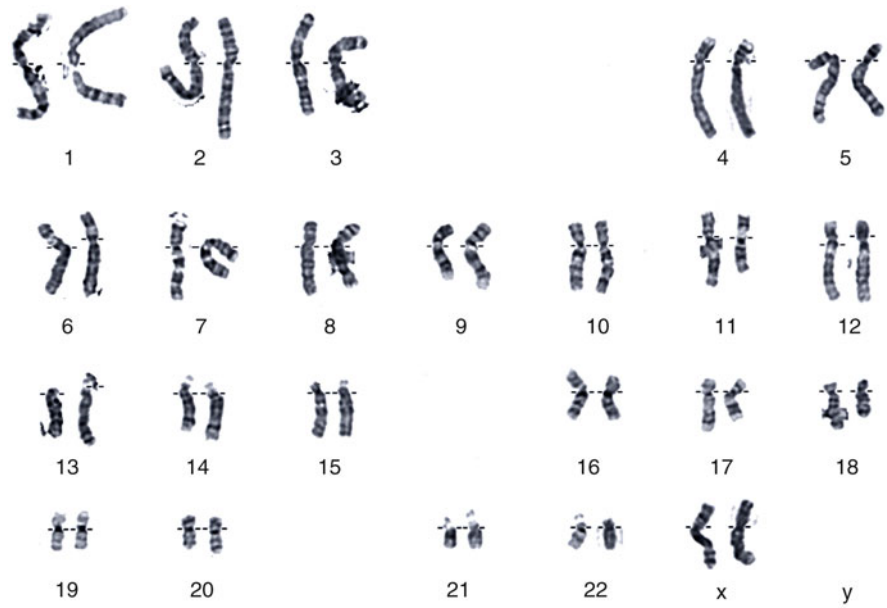

Fig. 3 Karyotype of a patient with Wilms tumor showing 46, XY,der(11)(p11.2q13.5)del (11)(p13p15.1)

Fig. 4 Note a lobulated meningioma encroaching the brain at the inferior surface of left frontal lobe

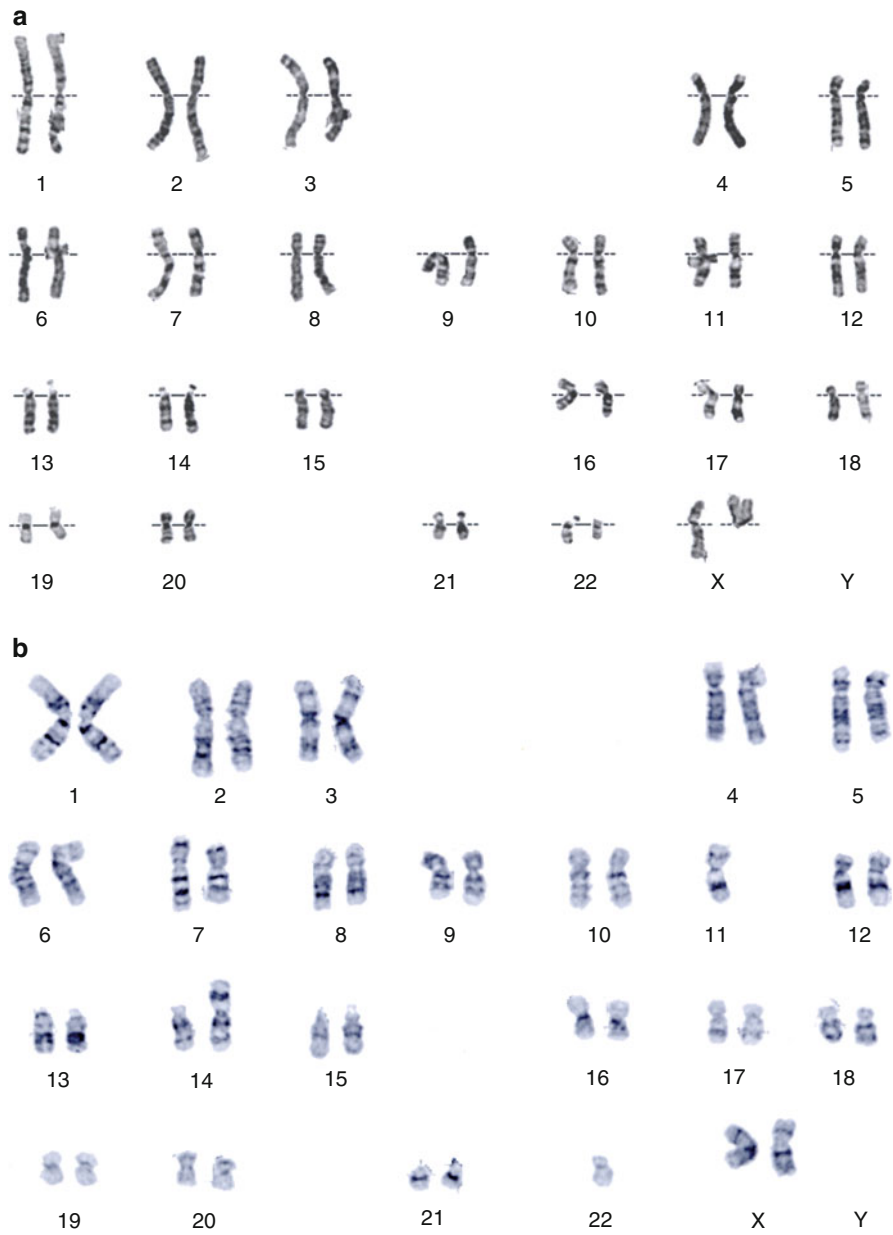

Fig. 5 (**a, b**) Karyotypes of two patients with meningioma showing 46,XX,del(22)(q12) (the first picture) and 44,XX, del(7)(q32q36),-11,der(14)t (11;14)(q12;p11),-22 (the second picture), respectively

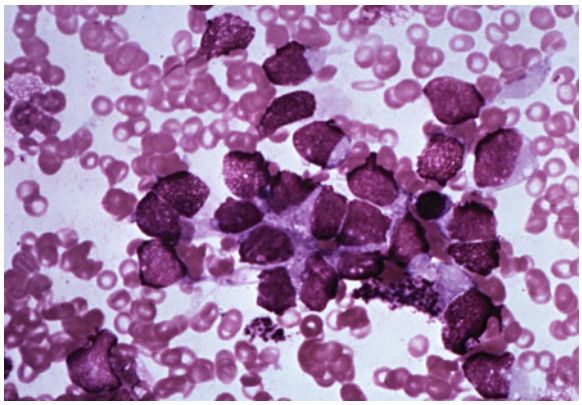

Fig. 6 Neuroblastoma smear. Note the anaplastic neuroblastic cells mixed with blood

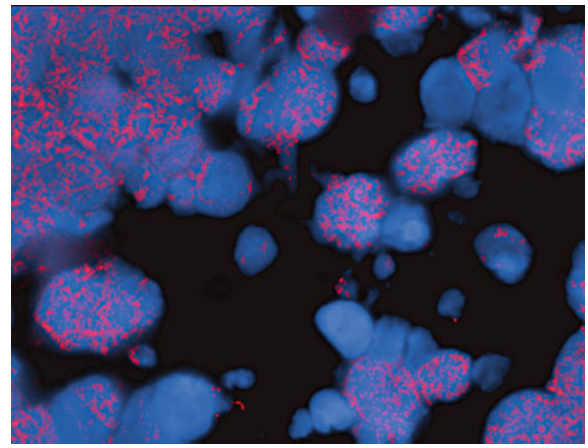

Fig. 7 N-MYC amplification in a patient with neuroblastoma. Gross copy number of the orange signal is noted (LSI® N-MYC (2p24.1) SpectrumOrange TM probe)

Cleft Lip and/or Cleft Palate

Cleft lip and/or palate (CL/CP) is the most common craniofacial malformation with an estimated incidence of approximately 1 in 700 to 1 in 1,000 live births among Caucasians. (Carinci et al. 2000). CL/CP may occur as an isolated finding or may be found in association with other congenital malformations.

Genetics/Basic Defects

1. Environmental agents (De La Pedraja et al. 2000)
   a. Cleft lip and cleft palate
      i. Alcohol
      ii. Anticonvulsants (phenytoin, sodium valproate)
      iii. Isotretinoin
      iv. Steroids
      v. Methotrexate
      vi. Maternal infections in the first trimester
         a) Rubella
         b) Toxoplasmosis
      vii. Maternal smoking
   b. Isolated clefts
      i. Little evidence linking to any single teratogenic agent, except anticonvulsant phenytoin
      ii. Use of phenytoin during pregnancy is associated with a tenfold increase in the incidence of cleft lip
   c. Cleft lip: Incidence of cleft lip in infants in mothers who smoke during pregnancy is twice that of those born to nonsmoking mothers
2. Genetic factors
   a. Syndromic clefts associated with malformations involving other developmental regions
      i. About 25% of neonates with CL/CP show associated malformations, syndromes or aneuploidy (Berge et al. 2001)
      ii. Van der Woude syndrome: the most commonly recognized syndrome associated with CL/CP, an autosomal dominant disorder characterized by CL/CP and blind sinuses or pits of the lower lip
      iii. Microdeletion of chromosome 22q11.2 (velocardiofacial syndrome, DiGeorge syndrome, and conotruncal anomaly face syndrome): currently the most common syndromic diagnoses among patients with clefts of the secondary palate alone
      iv. Other syndromes associated with clefts of the secondary palate alone:
         a) Stickler syndrome
         b) Ectrodactyly–ectodermal clefting (EEC) syndrome
         c) Popliteal pterygium syndrome
   b. Nonsyndromic cleft of the lip and/or palate (Carinci et al. 2000)
      i. An embryopathy derived from failure in fusion of the nasal process and/or palatal shelves
      ii. Genetic factors play an important role in the etiology of cleft lip and/or palate since one in five patients in different populations has a positive family history of CL/CP
      iii. Isolated CL/CP is considered multifactorial in origin and demonstrates strong familial aggregation with a significant genetic component
      iv. No evidence of classic Mendelian inheritance attributable to any single gene,

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although a number of genes or loci have been implicated, including transforming growth factor-alpha, retinoic acid receptor alpha, *BCL3*, *MSX-1* and several regions on chromosome 6p23-24 (OFC1), 2q13 (OFC2), 19q13.2 (OFC3), and other loci such as 4q25–4q31.3 and 17q21

c. Molecular signaling events in embryonic palatal development (Yu et al. 2009)
   i. Failure of palatal shelf formation
      a) Recent studies have identified several molecular networks operating between the palatal shelf epithelium and mesenchyme during different steps of palatogenesis
      b) These networks include signaling molecules and growth factors such as sonic hedgehog (Shh), members of the transforming growth factor β (TGfβ) super family, including bone morphogenetic proteins (Bmps) and Tgfβs, fibroblast growth factors (Fgfs) and their receptors (FgfR), effectors and targets
   ii. Fusion of the palatal shelf with the tongue or mandible
      a) Severe reduction of the expression of *Jagged 2* (*Jag2*), thereby encoding a ligand for the Notch family receptors and ectopic Tgfβ3 production in the nasal epithelia of mice
      b) Mutations in TBX22 have been reported in families with X-linked cleft palate and ankyloglossia
   iii. Failure of palatal elevation
      a) Mutations of *Pax9, Pitx1*, or *Osr2* can lead to failed palatal shelf elevation and cleft palate defect
      b) The implication of GABA in palate development was demonstrated by genetic studies of mice lacking the β3 subunit of the GABA receptor that developed CP without other craniofacial malformations
   iv. Failure of palatal shelves to meet after elevation: Mutations in *Msx1* and *Lhx8* and conditional inactivation of *Tgfbr2* in CNC cells or *Shh* in the epithelium all result in retarded palatal shelf development
   v. Persistence of middle edge epithelium: Mutations of *CDH1*/E cadherin, which deletes the extracellular cadherin repeat domains required for cell-cell adhesion, have recently been associated with CL/CP in families with hereditary diffuse cancer

Clinical Features

1. Classification of different types of orofacial clefting
   a. Cleft lip with or without cleft palate (CL/CP)
      i. Unilateral cleft lip
      ii. Unilateral cleft lip and cleft palate
      iii. Bilateral cleft lip
      iv. Bilateral cleft lip and cleft palate
   b. Cleft palate only
      i. Cleft palate
      ii. Submucous cleft palate
      iii. Velopharyngeal insufficiency
      iv. Robin sequence and robin complexes
   c. Median clefts
      i. Median cleft lip
      ii. Persistent infranasal furrow
      iii. Median frenular cleft
      iv. Median mandibular cleft
   d. Alveolar clefts (oral-facial-digital syndromes)
   e. Tessier type clefts including lateral and oblique facial clefts
2. Racial difference in CL/CP (De La Pedraja et al. 2000)
   a. Whites: approximately 1 in 1,000 births
   b. African Americans: 0.41 per 1,000 births
   c. Asians: approximately twice of whites
3. Sex difference in CL/CP and isolated clefts of the secondary palate (De La Pedraja et al. 2000)
   a. Children born with CL/CP: 60–80% are males
   b. Isolated clefts of the secondary palate: more frequently in females
4. Sites of clefts
   a. Isolated cleft lip: 21%
   b. CL/CP: 46%
   c. Clefts of the secondary palate alone: 33%
   d. Unilateral clefts
      i. More common in the left than the right (2:1)
      ii. Much more common than bilateral (9:1)
      iii. Associated with palatal clefts in 68% of cases
   e. Bilateral clefts of the lip: associated with palatal clefts in 86% of cases

5. Types of cleft lip
   a. Microform
      i. Presence of a vertical groove and vermilion notching
      ii. Associated with varying degrees of lip shortening
   b. Unilateral incomplete cleft lip
      i. Present with varying degrees of lip disruption
      ii. Associated with an intact nasal sill or Simonart band (a band of fibrous tissue from the edge of the red lip to the nostril floor)
   c. Complete cleft lip: characterized by disruption of the lip, alveolus, and nasal sill
6. Incidence of cleft lip +/− palate (CL/CP) and cleft palate alone (CPA) (Robin et al. 2006)
   a. Overall incidence of CL/CP and CPA: 1–2/1,000 children
   b. CPA: about 1/1,500
      i. More common if submucous CP/CA is included
      ii. Bifid uvula occurs in 1 of 80 patients and often occurs in isolation, with no clefting of the palatal muscles
   c. Incidence of CL/CP: varies by race
      i. Highest among American Indians, at 3.6 cases per 1,000 live births
      ii. Lowest among African Americans, with 0.3 cases per 1,000 live births
      iii. The incidence of CPA does not vary by race
   d. Of all CL/CP and CPA
      i. 20% of all clefts are isolated cleft lip (18% unilateral, 2% bilateral)
      ii. 50% are CL/CP (38% unilateral, 12% bilateral)
      iii. 30% are CPA
   e. CL/CP is twice as common in males; CPA is twice as common in females
7. Secondary medical problems with the presence of cleft plate
   a. Difficulty in sucking
   b. Inadequate intake of formula
   c. Aspiration
   d. Deviated nasal septum (airway obstruction)
   e. Hearing impairment
   f. Recurrent ear infections
   g. Malocclusion
   h. Abnormal craniofacial growth
   i. Inability to generate a pressure gradient between the oral and nasal chambers (hinders sucking in most infants)
   j. Speech dysfunction
      i. The most serious untoward consequence associated with cleft palate
      ii. Hypernasality or escape of sound into the nasal cavity associated with the production of many consonant phonemes and vowels in the English language except m, n, and ng
   k. Cosmetic disfigurement associated with orofacial clefting

Diagnostic Investigations

1. Speech and hearing evaluation
2. Echocardiography for associated cardiac anomalies
3. Karyotyping if indicated, especially to detect del (22)(q11.2)
4. Molecular genetic analysis for a known mutation in a syndromic CL/CP

Genetic Counseling

1. Recurrence risk (Chen 1988; Tolarova 1972)
   a. Recurrence risk for nonsyndromic CL +/− CP
      i. Unaffected parent
         a) No previously affected child: about 0.1% (general population risk) (Bonaiti-Pellie and Smith 1974; Kirschner and LaRossa 2000)
         b) With one previously affected child: about 4%
         c) With two previously affected children: about 14%
      ii. One affected parent
         a) No previously affected child: about 4%
         b) With one previously affected child: about 12%
         c) With two previously affected children: about 25%
      iii. Two affected parents
         a) No previously affected child: about 35%
         b) With one previously affected child: about 45%
         c) With two previously affected children: about 50%
   b. Recurrence risk for nonsyndromic CP
      i. Unaffected parent

a) No previously affected child: about 0.04% (general population risk) (Kirschner and LaRossa 2000)
b) With one previously affected child: about 3.5%
c) With two previously affected children: about 13%

ii. One affected parent
a) No previously affected child: about 3.5%
b) With one previously affected child: about 10%
c) With two previously affected children: about 24%

iii. Two affected parents
a) No previously affected child: about 2.5%
b) With one previously affected child: about 40%
c) With two previously affected children: about 45%

c. Presence of a microform such as a forme fruste cleft lip, submucous cleft palate, or bifid uvula suggest genetic factors within the family, which would alter the inheritance risks (e.g., striking association with lower-lip pits in the van der Woude syndrome).

d. Recurrence risk for CL/CP with associated anomalies
i. Mendelian diseases and syndromes
a) Autosomal dominant inheritance (e.g., Apert syndrome)
b) Autosomal recessive inheritance (e.g., Smith-Lemli-Opitz syndrome)
c) X-linked inheritance (e.g., oto-palato-digital syndrome)

ii. Chromosome disorders (e.g., trisomy 13)

2. Prenatal diagnosis
a. Prenatal ultrasonography
i. CL/CP not reliably diagnosed until the soft tissues of the fetal face become distinct by 13–14 weeks by transabdominal (TA) sonography and by transvaginal (TV) sonography slightly earlier
ii. Fetal palate best seen in the axial plane
iii. Fetal lips optimally visualized in the coronal view
iv. To demonstrate isolated CL/CP
v. To demonstrate associated anomalies (limb and spine anomalies, most common with 33%; cardiovascular anomalies, 24%)

b. Fetal echocardiography in case of fetal cardiac anomalies
c. Fetal karyotyping in case of associated fetal anomalies

3. Management
a. Medical
i. A highly specialized multidisciplinary approach from birth to adulthood
ii. Airway management
iii. Establishment of feeding
iv. Speech, hearing, and language therapies

b. Surgical
i. Primary surgery on the lip: usually carried out around the age of 3 months followed by palatal repair at around 6 months
ii. Preventative and restorative dental care
iii. Orthodontics
iv. Secondary surgery in the form of alveolar bone grafting
v. Pharyngeal flap or sphincter pharyngoplasty for velopharyngeal incompetence

c. Psychological issues (Endrica and Kapp-Simon 1999)
i. Parental stress
ii. Parent-child relationship
iii. Behavioral and emotional adjustment
iv. Self-concept and personality
v. Cosmetic disfigurement
vi. Social functioning
vii. Congnitive development and adjustment
viii. Cleft Lip and Palate Association (CLAPA), a helpful source of support and information for both families and professionals

d. Recent observation suggests beneficial effects of folic acid supplementation during pregnancy in the prevention of facial clefting

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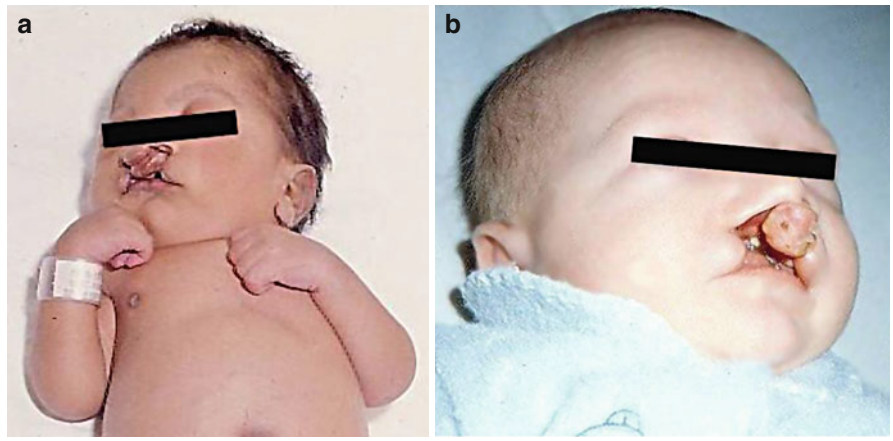

Fig. 1 (**a, b**) Two infants with bilateral cleft lips and cleft palate

Fig. 2 An infant with unilateral cleft lip and cleft palate

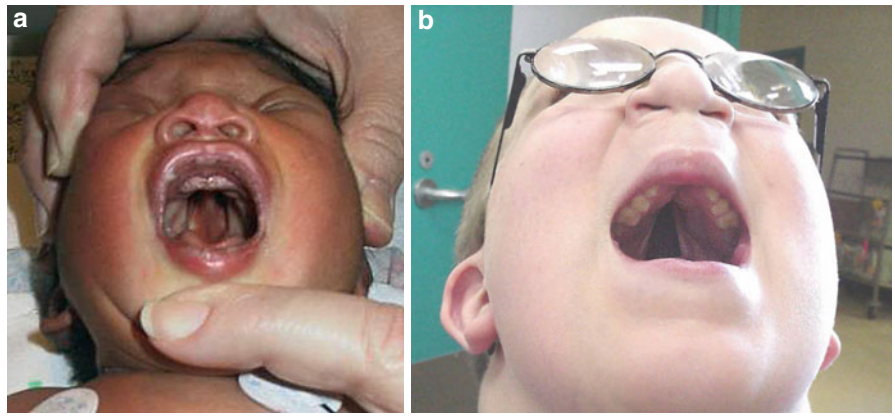

Fig. 3 (**a, b**) An infant and a boy with cleft palate

Fig. 4 A boy with high-arched palate

Fig. 5 An infant with bilateral CL/CP associated with trisomy 13

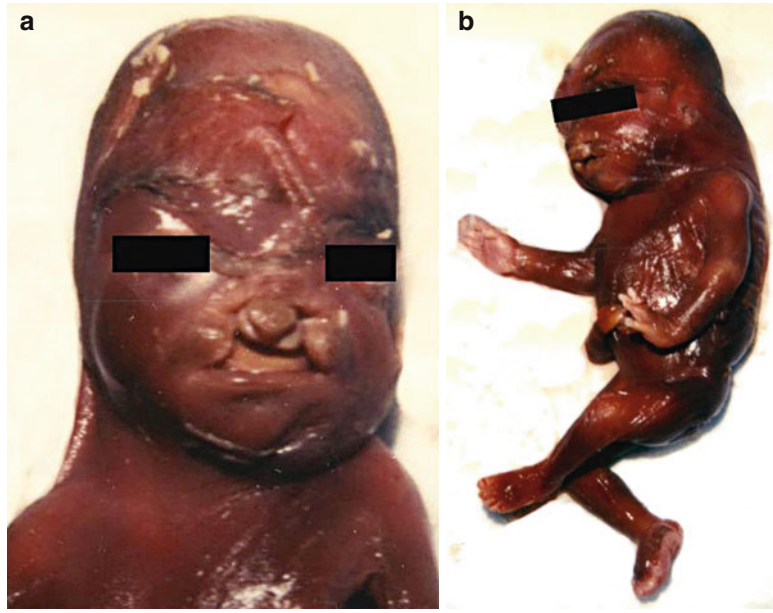

Fig. 6 A stillborn with CL/CP and other multiple congenital anomalies including massive cystic hygroma

Cleidocranial Dysplasia

Cleidocranial dysplasia is a generalized skeletal dysplasia affecting not only the clavicles but almost the entire skeletal system. It is characterized by aplasia or hypoplasia of the clavicles, enlarged calvaria with frontal bossing, multiple Wormian bones, delayed tooth eruption, supernumerary unerupted teeth, distal phalanges with abnormally pointed tufts, hypoplasia of the pelvis, and numerous other abnormalities (Jensen 1990)

Synonyms and Related Disorders

Cleidocranial dysostosis

Genetics/Birth Defects

1. Inheritance: autosomal dominant
2. About 20–40% of cases represent new mutations (Martinez-Frias et al. 1988)
3. Cause
   a. Caused by mutations in *CBFA1* (*RUNX2*) gene resulting in haploinsufficiency. Types of mutations identified are:
      i. Deletion
      ii. Insertion
      iii. Missense
      iv. Nonsense
   b. The gene for cleidocranial dysplasia called core-binding factor A1 (*CBFA1*) (a member of the runt family of transcription factors), mapped to 6p21. The alternative gene name is called *RUNX2*
   c. *CBFA1* encodes a transcription factor that activates osteoblast differentiation and plays a role in differentiation of chondrocytes
4. Germline line mosaicism has been reported (Pai et al. 2007)
5. No significant genotype/phenotype correlations observed

Clinical Features

1. Significant intra- and interfamilial variability of phenotypic expression (Mundlos 1999)
2. Abnormal craniofacial growth
   a. Head
      i. Abnormally large, wide-open fontanels at birth
      ii. A large brachycephalic head
      iii. A broad forehead with frontal bossing
      iv. Delayed closure of the fontanels and sutures
      v. Poorly developed midfrontal area showing a frontal groove owing to incomplete ossification of the metopic suture
      vi. Soft skull in infancy
   b. Face
      i. Frontal and parietal bossings, separated by a metopic groove
      ii. A depressed nasal bridge
      iii. Hypertelorism with possible exophthalmos
      iv. A small, flattened facial appearance (midface hypoplasia) with mandibular prognathism
      v. An anatomic pattern of dentofacial deformity consistent with the diagnosis of vertical maxillary deficiency (short face syndrome, type 2)

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   c. Oral/dental
      i. High arched palate
      ii. Clefts involving soft and hard palates
      iii. Persistence of the deciduous dentition with delayed eruption of the permanent teeth: a relatively constant finding
      iv. Impaction of supernumerary permanent teeth
      v. Crowding/malocclusion
      vi. Dentigerous cysts
3. Otolaryngologic manifestations (Segal and Puterman 2007)
   a. Hypoplasia of the maxilla and zygoma resulting in small face and sometimes asymmetric
   b. Small or absent mastoid air cells
   c. A high rate of Eustachian tube dysfunction
   d. A higher prevalence of submucosal cleft palate
   e. Narrow external auditory canals
   f. Increase rates of recurrent childhood ear infections and various degrees of hearing loss
   g. Clumping of the ossicles, stapes fixation, and sclerosis of the footplate have been described (Hawkins et al. 1975)
4. Shoulders and thorax
   a. Ability to bring shoulders together
   b. Dimplings in the skin secondary to mild hypoplasia of the clavicles
   c. Sloping, almost absent shoulders secondary to severe hypoplasia or absence of the clavicles
   d. Narrow thorax: may lead to respiratory distress during early infancy
5. Mildly disproportionate short stature with short limbs comparing to the trunk and more apparent in the upper limbs than the lower
6. Spine
   a. Scoliosis
   b. Kyphosis
7. Hands
   a. Brachydactyly
   b. Short distal phalanges
   c. Tapering fingers
   d. Nail dysplasia/hypoplasia
   e. Short, broad thumbs
   f. Clinodactyly of the fifth fingers
8. Other abnormalities
   a. Hearing loss
   b. Abnormal gait
   c. Joint hypermobility
   d. Muscular hypotonia
9. Intelligence: normal
10. Cesarean section often required in the pregnant female due to dysplastic pelvis

Diagnostic Investigations

1. Radiographic findings: generalized failure of midline ossification
   a. Skull
      i. Delayed closure of the anterior fontanel (open fontanel) and sagittal and metopic sutures, often open for life
      ii. Unossified areas of the skull becoming smaller with increasing age
      iii. Multiple Wormian bones formation, particularly around the lambdoid suture
      iv. Small or absent nasal bones
      v. Segmental calvarial thickening
      vi. Underdeveloped maxilla
      vii. Delayed union of the mandibular symphysis
      viii. Platybasia
      ix. Small cranial base
      x. A large foramen magnum
      xi. Hypoplastic sinuses (paranasal, frontal, mastoid)
   b. Clavicles
      i. Absent clavicles: rare
      ii. Pseudarthrosis of one or both clavicles
      iii. Hypoplasia of the acromial end: common
      iv. Two separate fragments
      v. Absent sternal end with presence of the acromial end
      vi. Bilaterality is the rule but not always the case
   c. Chest
      i. Small bell-shaped thoracic cage
      ii. Short, oblique ribs
      iii. Presence of cervical ribs
      iv. Scapula often hypoplastic with deficient supraspinatus fossae and acromial facets
      v. Associated deficiency in musculature
   d. Pelvis
      i. Widened pubis symphysis resulting from delay in ossification during adulthood
      ii. Hypoplasia and anterior rotation of the iliac wings
      iii. Wide sacroiliac joints
      iv. Delayed ossification of the pubic bone
      v. Large femoral epiphyses

vi. Unusual shape of femoral head reminiscent of a "chef's hat"
vii. Broad femoral necks
viii. Frequent coxa vara

e. Spine
i. Hemivertebrae
ii. Posterior wedging
iii. Spondylolysis and spondylolisthesis
iv. Syringomyelia
v. Spina bifida occulta of the cervical, thoracic, or lumbar region

f. Tubular bones
i. Presence of both proximal and distal epiphyses in the second metacarpals and metatarsals leading to excessive growth and length
ii. Frequent cone-shaped epiphyses and premature closure of epiphyseal growth plates leading to shortening of bones
iii. Wide epiphyses
iv. Unusually short distal phalanges and the middle phalanges of the second and fifth fingers
v. Poorly developed terminal phalanges giving a tapered appearance to the digit
vi. Occasional hypoplasia, dysplasia, and aplasia of nails

g. Dentition: impacted, supernumerary teeth

2. Cytogenetic study: visible complex chromosome rearrangements occasionally seen (Purandare et al. 2008)
3. Molecular genetic studies of mutations involving *RUNX2* (Mendoza-Londono and Lee 2009)
a. Sequence analysis
b. Deletion/duplication analysis

Genetic Counseling

1. Recurrence risk
a. Patient's sib: not increased unless a parent is affected with the disorder or has germ line mosaicism
b. Patient's offspring: 50%
2. Prenatal diagnosis
a. Ultrasonography (Stewart et al. 2000; Hermann et al. 2009)
i. Hypoplastic clavicles
ii. Less calcified cranium than expected for gestational age
iii. Other craniofacial and skeletal anomalies
b. Prenatal diagnosis and preimplantation genetic diagnosis: Direct DNA testing possible for those families with a known mutation in the *RUNX2*
3. Management (Cooper et al. 2001)
a. Hearing evaluation
b. Evaluate the presence of submucous cleft palate
c. Evaluation of obstructive sleep apnea
d. Medical and surgical therapy for upper airway obstruction, recurrent and chronic sinusitis and otitis
e. Monitor skeletal and orthopedic complications
f. Early surgical and orthodontic intervention of unerupted permanent teeth to induce eruption
g. Orthognathic surgery to correct midface hypoplasia to reduce or correct significant upper respiratory complications and malocclusions
h. Surgical and orthodontic management of vertical maxillary deficiency (Dann et al. 1980)
i. Women with cleidocranial dysplasia at risk for a Cesarean section delivery

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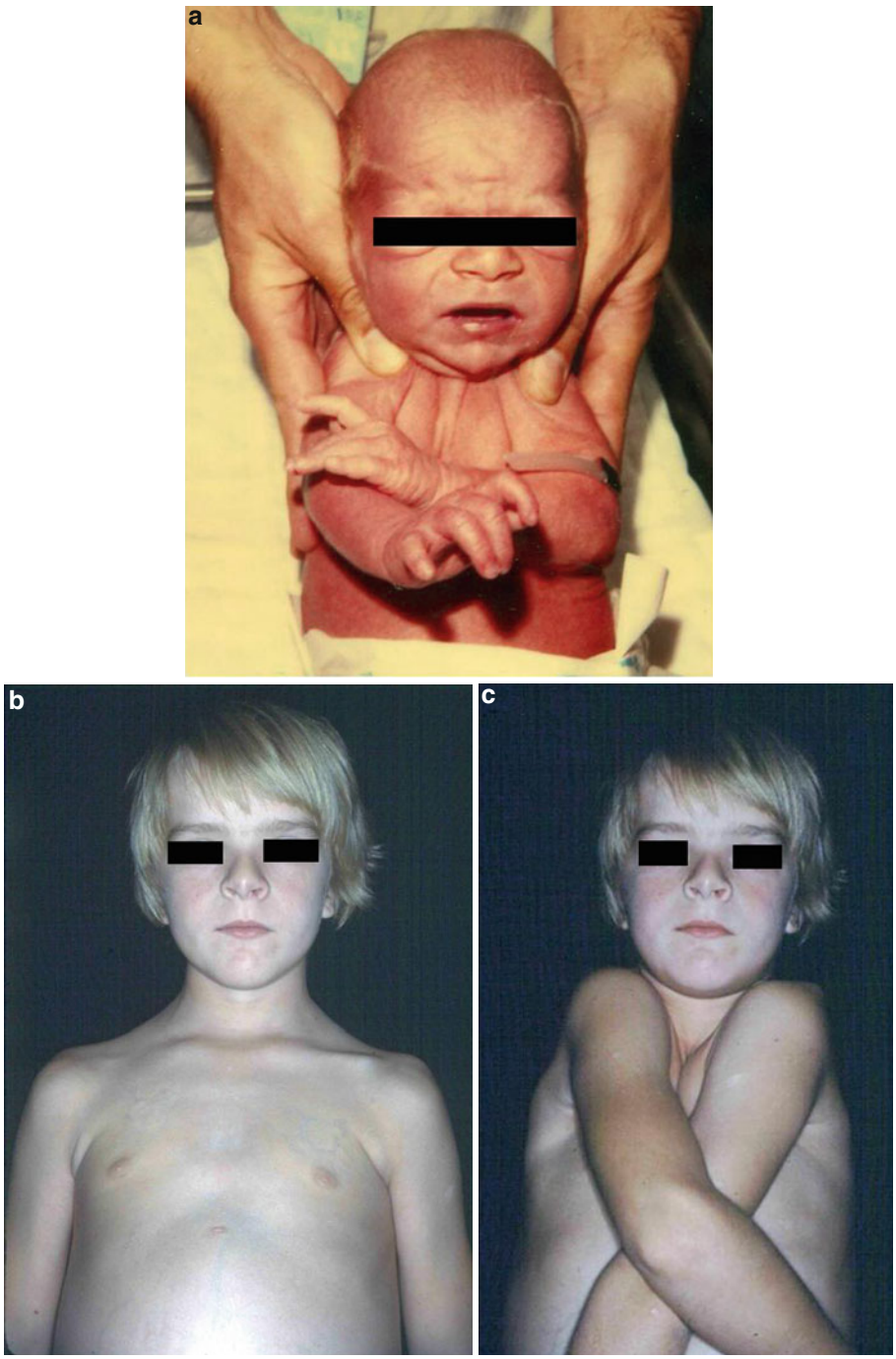

Fig. 1 (**a**–**c**) An infant and a child with cleidocranial dysplasia showing a large brachycephalic skull, frontal bossing, a large anterior fontanel, widely spaced eyes, flat nasal bridge, and easily proximated shoulders

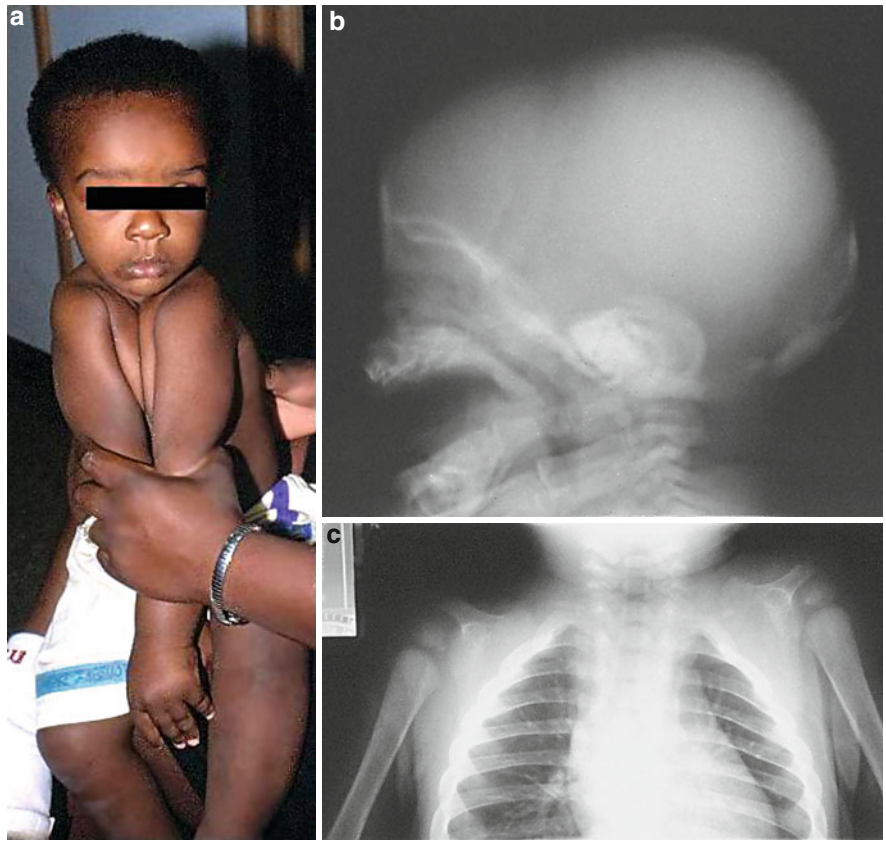

Fig. 2 (**a**–**c**) A child with cleidocranial dysplasia showing prominent forehead, wide anterior fontanel and cranial sutures, wide eyes, depressed nasal bridge, and easily proximated shoulders. Radiographs show poorly ossified skull, wide fontanels, cone-shaped thorax, and absence of clavicles

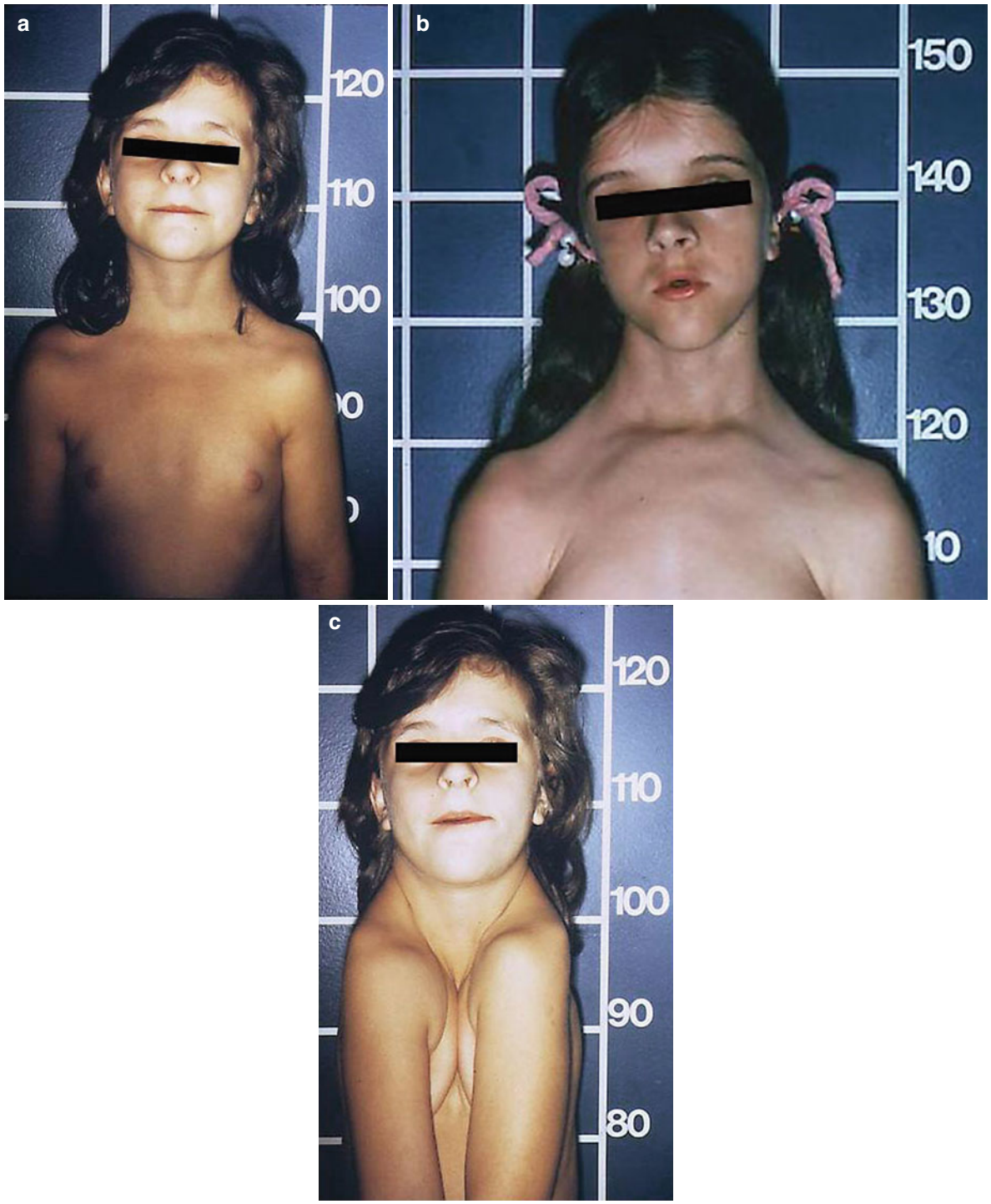

Fig. 3 (**a**–**c**) A girl with cleidocranial dysplasia at different ages showing short stature, frontal bossing, wide cranial sutures, wide set eyes, depressed nasal bridge, and sloping and easily proximated shoulders

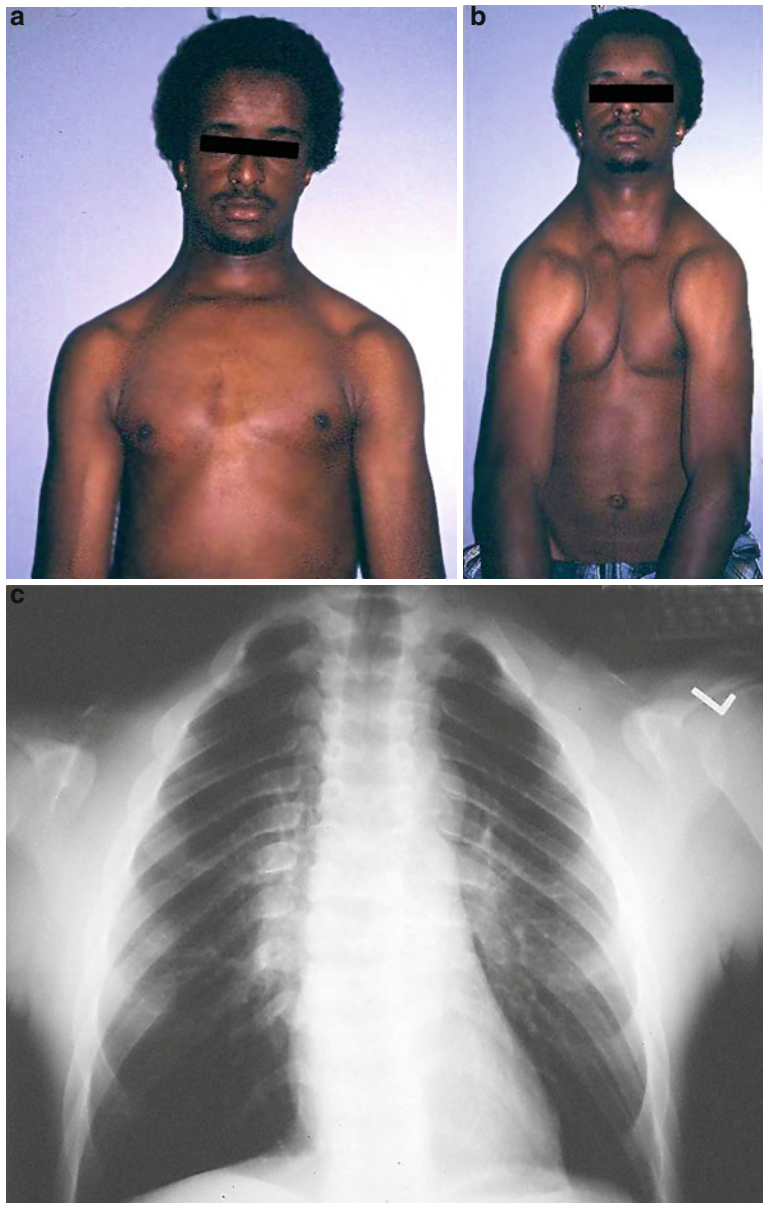

Fig. 4 (**a**–**c**) An adult with cleidocranial dysplasia showing widened cranial sutures, a characteristic face, and sloping and easily proximated shoulders. Radiograph showed a cone-shaped thorax with absent clavicles

Fig. 5 (**a**–**e**) A father and a son with cleidocranial dysplasia showing characteristic clinical findings and a dysplastic left clavicle presenting as two separate fragments, illustrated by radiograph

Fig. 6 (**a**–**d**) Another adult patient with cleidocranial dysplasia, showing typical clinical and dental features (radiograph)

Cloacal Exstrophy

Cloacal exstrophy is a rare congenital malformation resulting in exstrophy of the urinary, intestinal, and genital systems and is associated with anomalies of other organ systems. The term OEIS complex (omphalocele, exstrophy of the bladder, imperforate anus, and spinal defects) are used to describe the spectrum of malformations in cloacal exstrophy (Kaya et al. 2000). The incidence of cloacal exstrophy is estimated to be 1/200,000–1/400,000 live births (Dick et al. 2001), although the true incidence may be as high as 1 in 10,000–50,000, taking into account lack of diagnosis in stillborn infants (Keppler-Noreuil 2001).

Synonyms and Related Disorders

OEIS complex (omphalocele-exstrophy of the bladder-imperforate anus-spinal defects)

Genetics/Basic Defects

1. Genetics
   a. Recurrence of OEIS complex in siblings can be explained by the following mechanisms:
      i. Autosomal recessive inheritance
      ii. Multifactorial determination
      iii. Gonadal mosaicism for a dominant mutation
      iv. Environmental factors
      v. Subclinical maternal disorder
      vi. An unbalanced translocation between 9q and Y chromosome resulting in a 9q34.1-qter deletion, as a potential cause (Thauvin-Robinet et al. 2004)
      vii. Mutations in a group of homeobox genes such as HLXB9 and HOX family which are involved in the development of embryonic mesoderm (Manner and Kluth 2005)
   b. Higher incidence of OEIS complex in monozygotic twins than in dizygotic twins suggests a possible genetic contribution to the occurrence of these defects.
2. Basic defects of OEIS complex (Lee et al. 1999)
   a. Resulting from a single localized defect in the early caudal mesoderm at approximately 29 days of development
   b. Resulting in the following sequence of events:
      i. Failure of cloacal septation leading to a persistence of the cloaca with a rudimentary mid-gut and imperforate anus
      ii. Failure of breakdown of the cloacal membrane leading to exstrophy of the cloaca, omphalocele, and lack of fusion of the pubic rami
      iii. The lumbosacral somites giving rise to abnormal vertebrae in which there is protrusion of the dilated spinal cord (hydromyelia) and a cystic, skin-covered mass in the lumbosacral region
3. Cloaca and cloacal exstrophy
   a. Cloaca
      i. A transient embryological structures
      ii. The term “cloaca” literally means “sewer” in Latin
      iii. The term used to represent the emptying of the gastrointestinal and urogenital tracts into a common sinus

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iv. Defined as a common chamber (orifice) in the perineum into which the urinary, genital and intestinal tract drain
b. Cloacal exstrophy: The common orifice empties onto the anterior abdominal wall

Clinical Features

1. Classic exstrophy of the cloaca (Lee et al. 1999)
   a. Lower abdominal defect
   b. Exposure of intestinal and bladder mucosa
   c. Accompanied by the following anomalies
      i. Omphalocele
      ii. Imperforate anus
      iii. Urogenital anomalies
2. Gastrointestinal malformations
   a. Omphalocele
   b. Imperforate anus
   c. Rectovestibular/rectovesical fistula
   d. Small bowel anomalies
      i. Foreshortened small bowel
      ii. Rotational anomalies
   e. Meckel diverticulum
   f. Inguinal hernias
3. CNS malformations
   a. Spina bifida: the most common CNS malformation
      i. Leptomeningocele
      ii. Myelomeningocele
      iii. Meningocele
      iv. Spina bifida occulta
      v. Cord tethering
   b. Craniosynostosis
4. Skeletal malformations
   a. Vertebral anomalies
      i. Presence of extra vertebrae
      ii. Hemivertebrae and associated scoliosis
      iii. Absent vertebrae
   b. Pubic diastasis
   c. Lower extremity anomalies
      i. Clubfoot deformities
      ii. Limb deficiencies
5. Genitourinary malformations
   a. Bladder anomaly
      i. Open
      ii. Separated into two halves
      iii. Flanking the exposed interior of the cecum
      iv. Openings to the remainder of the hindgut
      v. Prolapse of the terminal ileum as a "trunk" of bowel onto the cecal plate
   b. Renal anomalies
      i. A single kidney
      ii. Rudimentary kidney
      iii. Pelvic ectopic kidney
      iv. Ureteropelvic junction obstruction
      v. Malrotation
      vi. Crossed renal ectopia
   c. Ureteral anomalies
      i. Duplication
      ii. Ectopic insertion
      iii. Distal stricture and megaureter
   d. Male genitalia anomalies
      i. Small and bifid penis
      ii. Hemiglans located caudal to each hemibladder
   e. Female genitalia anomalies
      i. Bifid clitoris
      ii. Uterine duplication
      iii. Vaginal duplication
      iv. Vaginal agenesis
6. Prognosis
   a. Used to be uniformly fatal malformation in its worst form
   b. Currently with an 80–100% survival rate due to early surgical repair but accompanied by lifelong severe morbidity

Diagnostic Investigations

1. Evaluation of associated malformations
2. Karyotyping for genetic sex
3. Renal ultrasonography for renal and upper urinary tract anomalies
4. Voiding cystourethrography to assess bladder capacity in early childhood in preparation for continence reconstruction
5. Radiographic studies to demonstrate spinal dysraphism (Dick et al. 2001)
   a. Plain spinal radiographs
   b. Myelography
   c. CT
   d. CT myelography
   e. Spinal MRI to identify occult abnormalities that predispose to symptomatic spinal cord tethering

Genetic Counseling

1. Recurrence risk (Mathews et al. 1998)
   a. Patient's sib: recurrence in subsequent pregnancies noted in one report
   b. Patient's offspring: Lack of offspring from patients with cloacal exstrophy making the determination of inheritance difficult
2. Prenatal diagnosis by ultrasonography
   a. Elevated maternal serum α-fetoprotein (AFP) in OEIS complex. The open ventral wall defect likely results in AFP leakage.
   b. Ultrasonography (Austin et al. 1998)
      i. Major ultrasound criteria
         a) Non-visualization of the bladder (91%)
         b) A large midline infraumbilical anterior wall defect or cystic anterior wall structure (persistent cloacal membrane) (82%)
         c) Omphalocele (77%)
         d) Lumbosacral myelomeningocele (68%)
      ii. Minor (less frequent) ultrasound criteria
         a) Lower limb defects (23%)
         b) Renal anomalies (23%)
         c) Ascites (14%)
         d) Widened pubic arches (18%)
         e) A narrow thorax (9%)
         f) Hydrocephalus (9%)
         g) A single umbilical artery (9%)
   c. Early prenatal diagnosis with fetal MRI (Gobbi et al. 2008)
3. Management (Mathews et al. 1998)
   a. Appropriate parental counseling and referral to a center with significant expertise in the management of cloacal exstrophy when prenatal diagnosis is made
   b. Medical stabilization of the infant
      i. Fluid and electrolyte replacement
      ii. Parenteral nutrition
      iii. Moisten the exstrophied bladder and bowel with saline and cover them with a protective plastic dressing
      iv. Daily prophylactic antibiotics
   c. Gender assignment
      i. Evaluation of the genitalia
      ii. Decision limited to the genetic male patients with cloacal exstrophy
         a) Male gender assignment appropriate for male patients with adequate bilateral or unilateral phallic structures
         b) Male neonates with minimal phallic structures: appropriate to raise as female subjects with early excision of the gonads
         c) Appropriate hormonal manipulation to improve psychosexual dysfunction
         d) Improvements in phallic reconstruction eventually allow most genetic male patients to be assigned male gender.
      iii. Initial sexual reassignment to be done in conjunction with extensive family counseling as well as continued counseling for the parents and children
   d. Management of gastrointestinal malformations
      i. Closure of omphalocele
      ii. Combined with gastrointestinal diversion or reconstruction
         a) Ileostomy with resection of the hindgut remnant
         b) Colostomy
   e. Management of genitourinary malformations
      i. Bladder closure
      ii. Initial bladder excision and urinary diversion
      iii. Further augmentation or urinary diversions to achieve continence
   f. Management of CNS malformations
      i. Closure of myelomeningocele
      ii. Cord untethering
      iii. Spinal fusion
      iv. Cranial expansion for craniosynostosis
   g. Management of orthopedic malformations
      i. Manage myelodysplasia
      ii. Pelvic osteotomies
      iii. Various orthopedic devices to assist with ambulation

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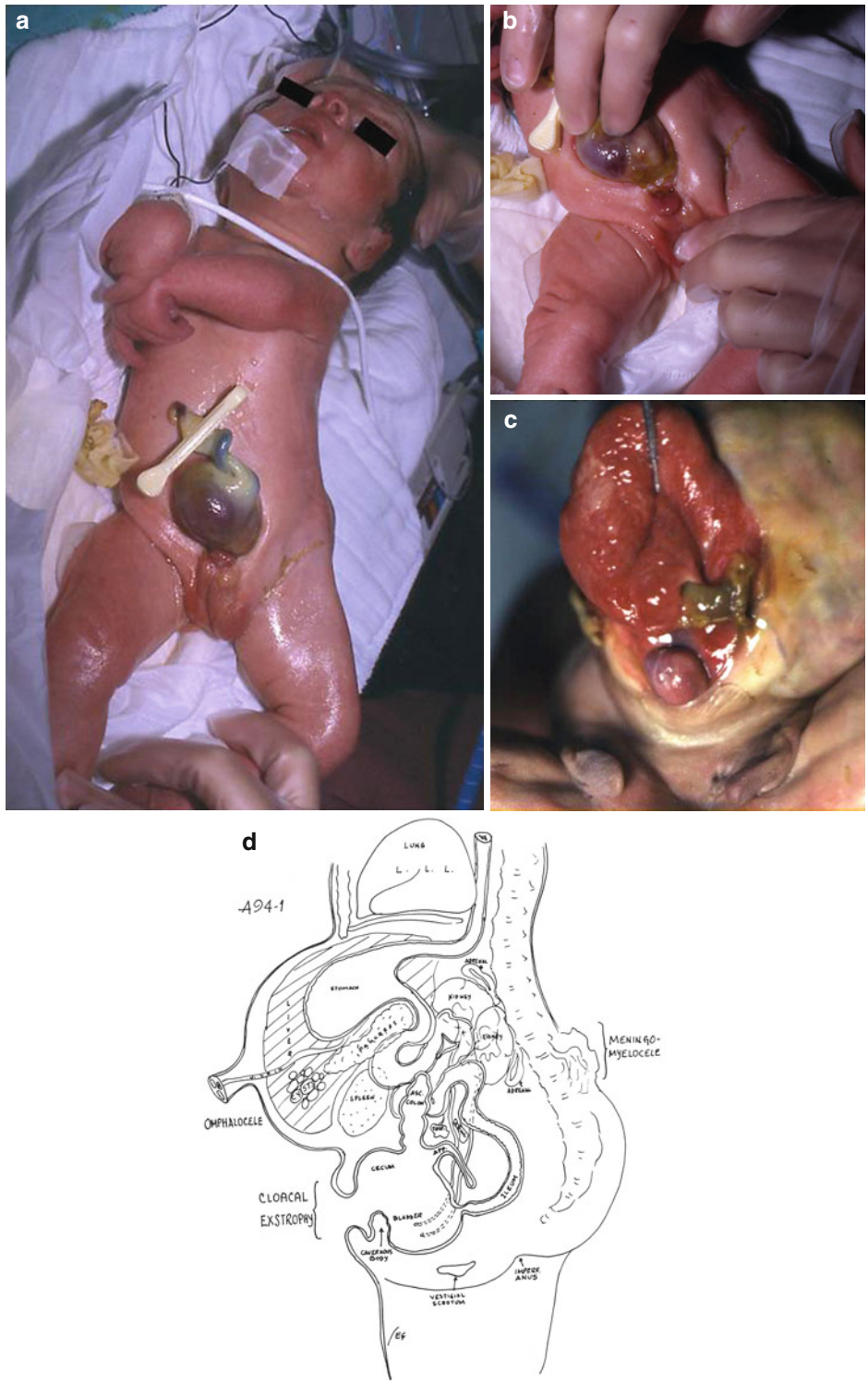

Fig. 1 Two infants (**a–c**) with cloacal exstrophy. The schematic diagram (**d**) illustrates the anatomy of various defects in the second infant (**c**)

Clubfoot

Clubfoot, or talipes equinovarus, is one of the most common congenital deformities affecting the lower limbs in approximately 1–2 in 1,000 live births. The incidence is higher in Hispanics and lower in Asians. Although clubfoot is recognizable at birth, the severity of the deformity can vary from mild to an extremely rigid foot that is resistant to manipulation (Dobbs and Gurnett 2009).

Synonyms and Related Disorders

Talipes equinovarus

Genetics/Basic Defects

1. Pathogenesis
   a. Genetic cause: suggested because it tends to run in families (Lochmiller et al. 1998)
   b. Oligohydramnios: suggested as a cause from early amniocentesis data (CEMAT Group 1998)
   c. Osseous deformities (Shapiro and Glimcher 1979), muscle abnormalities (Herceg et al. 2006), and arrested fetal development (Fukuhara et al. 1994): hypothesized to play a role in pathogenesis
2. Etiology (Dobbs and Gurnett 2009)
   a. Most commonly as an isolated birth defect and considered idiopathic (Wynne-Davies 1964): various theories on etiologies include:
      i. Vascular deficiencies (Hootnick et al. 1982)
      ii. Environmental factors
         a) Early amniocentesis (<13 weeks gestation): associated with an increased risk in talipes equinovarus (an uncommon risk factor), compared to midgestational amniocentesis or chorionic villus sampling (Philip et al. 2004)
         b) Partially associated with amniotic fluid leakage: suggesting that oligohydramnios occurring at a critical gestational period may be detrimental to foot development (Tredwell et al. 2001)
         c) Environmental exposure to cigarette smoke in utero: an independent risk factor (Honein et al. 2000)
      iii. In utero positioning (Dunn 1972)
      iv. Abnormal muscle insertions (Bonnell and Cruess 1969)
   b. Genetic factors suggested by:
      i. Thirty-three percent concordance of identical twins and the fact that nearly 25% of all cases are familial (Lochmiller et al. 1998)
      ii. Differences in clubfoot prevalence across ethnic populations with the lowest prevalence in Chinese (0.39 cases per 1,000 live births) and the highest in Hawaiians and Maoris (seven per 1,000) (Beals 1978; Chung et al. 1969)
   c. Multifactorial and possibly polygenic causation suggested (Lochmiller et al. 1998; Wynne-Davies 1972)
   d. Prevalence of additional congenital anomalies
      i. Chromosomal abnormalities (e.g., trisomy 18 syndrome) in patients with clubfoot (24–50%) (Bakalis et al. 2002; Gurnett et al. 2008)
      ii. Distal arthrogryposis
      iii. Myelomeningocele

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e. Recent identification of a rare mutation in the transcription factor PITX1 in a large family with idiopathic clubfoot: importance of genes involved in early limb development (Gurnett et al. 2008)
   i. *PITX1*: the first gene implicated in clubfoot that explains the specific involvement of the foot, since *PITX1* is expressed nearly exclusively in the hindlimb and is responsible for rapid evolutionary changes in pelvic morphology in lower vertebrates (Shapiro et al. 2004).
   ii. Specific involvement of the foot also appears to exclude many of the skeletal muscle contractile genes that are responsible for distal arthrogryposis (Sung et al. 2003a, b; Toydemir et al. 2006; Veugelers et al. 2004) in the causation of idiopathic clubfoot, as mutations in these genes cause both upper and lower extremity involvement and were not identified in idiopathic clubfoot patients (Gurnett et al. 2009).

3. Multifactorial inheritance
   a. Most infants with clubfoot (idiopathic congenital clubfoot) have no identifiable genetic, cytogenetic, syndromal, or extrinsic cause. The idiopathic congenital clubfoot is primarily caused by a multifactorial inheritance.
   b. The observed percentages of talipes equinovarus in relatives of an affected child are consistent with a multifactorial mode of inheritance (Wynne-Davies 1965, 1972)
      i. Monozygotic twins with about 32.5% rate of concordance (both twins affected with clubfoot)
      ii. First degree relatives (parents and siblings) occurrence rate
         a) 2.14%
         b) About 17 times as high as the population rate
      iii. Second degree relatives (aunts and uncles) occur
         a) 0.61%
         b) About six times as high as the population rate
      iv. Third degree relatives (cousins)
         a) 0.2%
         b) Near the incidence in the general population
4. Part of a genetic syndrome
   a. An autosomal recessive inheritance of clubfoot: for example,
      i. Diastrophic dwarfism
      ii. Larsen syndrome
      iii. Smith-Lemli-Opitz syndrome
   b. An autosomal dominant inheritance of clubfoot: for example,
      i. Distal arthrogryposis type 2A (Whistling-face syndrome)
      ii. Distal arthrogryposis type 1
      iii. Freeman-Sheldon syndrome
   c. An X-linked recessive inheritance of clubfoot: for example, Pierre-Robin syndrome
   d. Other syndromic clubfoot: for example,
      i. Meningomyelocele/spina bifida
      ii. Sacral agenesis
      iii. Constriction band syndrome
      iv. Congenital myopathy
5. Part of a cytogenetic abnormality: Numerous cytogenetic abnormalities produce individuals with multiple anomalies including clubfoot
6. Extrinsic causes
   a. Teratogenic agents
      i. Sodium aminopterin
      ii. Position in utero at the time of d-tubocurarine paralysis
   b. Loss of amniotic fluid during gestation
   c. Mechanical forces or positional influence (restriction of fetal foot movement by the uterus)
   d. Drugs

Clinical Features

1. Bilateral in about 50% of cases
2. Three major components of talipes equinovarus
   a. Equinus (limitation of extension) of the ankle and subtalar joint
   b. Hindfoot and midfoot varus
   c. Forefoot adduction
3. Evaluation of the foot, ankle, and leg
   a. "Down and in" appearance
   b. Shorter and wider than the normal foot
   c. Flexible, softer heel due to hypoplastic calcaneus
   d. Concave medial border
   e. Transverse plantar creases or clefts at the midfoot and at the posterior part of the ankle
   f. Highly convex lateral border

g. Internally rotated heel making the soles of the feet facing each other in cases of bilateral deformities
h. Internal rotation of the leg
i. Variable rigidity of the foot
j. Calf and foot atrophy (more obvious in older child than in infant)
k. Mild hypoplasia of the tibia, fibula, and bones of the foot
l. Pronounced tightness of the Achilles tendon with very little dorsiflexion
m. Range of motion of the joints

4. Idiopathic clubfoot
   a. An isolated deformity of the foot and leg
      i. Identifiable in utero
      ii. Consists of four components
         a) Equinus
         b) Hindfoot varus
         c) Forefoot adductus
         d) Cavus
   b. When untreated, children with clubfoot walk on the sides and/or tops of their feet, resulting in (Dobbs and Gurnett 2009):
      i. Callus formation
      ii. Potential skin and bone infections
      iii. Inability to wear standard shoes
      iv. Substantial limitations in mobility and employment opportunities
   c. By far the most common form
   d. Occurring more common in males than in females (2 ~ 2.5:1)
   e. Normal upper limbs
   f. Associated features
      i. Joint laxity
      ii. Congenital dislocation of the hip
      iii. Tibial torsion
      iv. Ray anomalies of the foot (oligodactyly)
      v. Absence of some tarsal bones
      vi. A history of other foot anomalies in the family
5. Various associated anomalies in syndromic talipes equinovarus

Diagnostic Investigations

1. Plain radiography
   a. Limitations
      i. Risk of ionizing radiation
      ii. Proper positioning difficult
      iii. Lack of ossification in some involved bones
         a) Only talus, calcaneus, and metatarsals are ossified in neonates
         b) Cuboid ossification at 6 months
         c) Cuneiforms ossification at 1 year
         d) Navicular ossification after 3 years
   b. Assessment
      i. Hindfoot equinus (plantar flexion of the anterior calcaneus)
      ii. Hindfoot varus (calcaneus rotated around the talus into a varus, i.e., toward midline, position)
      iii. Forefoot varus (increased forefoot supination on dorsoplantar view)
   c. Common measurements
      i. Anteroposterior talocalcaneal angle (typically $<20^\circ$ in a clubfoot)
      ii. Talar-first metatarsal angle
         a) Up to about 30° of valgus in a normal foot
         b) Mild-to-severe varus in a clubfoot
      iii. Medial displacement of the cuboid ossification center on the axis of the calcaneus representing either of the following:
         a) Angular deformity of the calcaneus
         b) Medial subluxation of the cuboid on the calcaneus
2. CT scan
   a. Limitations
      i. Risk of ionizing radiation
      ii. Lack of ossification of the tarsal bones
      iii. Susceptible to motion artifact
   b. Advantage: better assessment of complex 3-dimensional deformity by 3-dimensional reconstructions
3. MRI
   a. Limitations
      i. Need for patient sedation
      ii. Loss of signal caused by ferromagnetic effects of fixation devices
   b. Advantages
      i. Capability of multiplanar imaging
      ii. Excellent depiction of following:
         a) Ossific nuclei
         b) Cartilaginous anlage
         c) Surrounding soft-tissue structures
   c. Findings
      i. Plantar flexion
      ii. Varus angular deformity of the talus, calcaneus, and cuboid

Genetic Counseling

1. Recurrence risk: depends on underline etiology
   a. Patient's sib
      i. Multifactorial trait: approximately 2.1% (first degree relatives)
      ii. Autosomal recessive: 25%
      iii. Autosomal dominant: not increased unless a parent is affected
      iv. X-linked recessive: 50% of male sibs affected if the mother is a carrier
      v. Chromosomal: increased risk, especially a parent is a translocation carrier
   b. Patient's offspring
      i. Multifactorial: approximately 2.1%
      ii. Autosomal recessive: not increased unless the spouse is also a carrier
      iii. Autosomal dominant: 50%
      iv. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal.
      v. Chromosomal: increased risk
2. Prenatal diagnosis
   a. Ultrasonography: Wide variation in the accuracy of ultrasonography
      i. Isolated clubfoot
         a) Better prognosis especially detected in the 3rd trimester of pregnancy
         b) Poor correlation between the prenatal appearance of the foot on ultrasound findings and the severity of the talipes at birth
      ii. Complex clubfoot: associated with syndromic, neuromuscular, or chromosomal conditions
3. Management
   a. Traditional nonoperative approach
      i. Appropriate initial management for all children with clubfoot
      ii. Splintage begins at 2–3 days after birth
      iii. Order of correction
         a) Forefoot adduction
         b) Forefoot supination
         c) Gentle correction of equinus
      iv. Two methods most widely performed and with highest reported long-term success rates
         a) Kite and Lovell method
         b) Ponseti method
      v. "Montpellier" method: remains popular in France
   b. Ponseti method: currently widely utilized with high success rate in treating clubfoot
      i. Goal
         a) To reduce or eliminate deformity (equinus, hindfoot varus, forefoot adductus, and cavus)
         b) To attain functional, pain-free, plantigrade foot with good mobility and without calluses, and without need to wear modified shoes
      ii. Techniques
         a) Serial manipulation
         b) A specific technique of cast application
         c) Possible percutaneous Achilles tenotomy
      iii. Significant risk factors for the recurrence of clubfoot deformity after correction with the Ponseti method
         a) Noncompliance of the parents
         b) Lower educational level of the parents
      iv. Outcome
         a) Appears to be effective
         b) Requires only a reasonable amount of time out of the lives of the patient and his or her parents
         c) Frequently include some minimal invasive surgery
   c. Kite and Lovell method
      a) Starting with stretching of the foot through longitudinal traction applied to the foot
      b) Less often requires minimally invasive surgery
      c) More time-consuming
   d. "Montpellier" method
      i. Require fairly extensive physical therapy
      ii. Demand substantial parental time and attention
      iii. Long-term results yet to be confirmed
   e. Operative approach
      i. Should be considered only after a suitable trial of manipulating the foot and holding it in a suitable cast or other device has failed
      ii. Operative treatment
         a) Incisions
         b) Medial plantar release
         c) Posterior release
         d) Lateral release
         e) Reduction and fixation
         f) Intraoperative assessment
         g) Wound closure

h) Revision surgery
i) Postoperative evaluation

iii. Treatment of residual deformity
a) Residual forefoot adduction
b) Residual cavus
c) Angulation of the heel for residual varus or valgus
d) Dynamic forefoot supination
e) Residual toeing-in
f) Dorsal bunion (a painful swelling of the bursa of the first joint of the big toe)
g) Overcorrected foot
h) Skin problems

f. Complications of treatment
i. Failure to correct (undercorrection) resulting from:
a) Selection of inappropriate procedure
b) Inadequate performance of an appropriate procedure

ii. Overcorrection resulting from:
a) Selection of an inappropriate procedure
b) Overzealous release of appropriate structures
c) Inappropriate release of normal structures

iii. Recurrence of deformity

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Fig. 1 Bilateral talipes equinovarus in an infant

Fig. 3 Bilateral talipes equinovarus in a fetus with trisomy 18 syndrome

Fig. 2 Bilateral talipes equinovarus in an infant with Smith-Lemli-Opitz syndrome

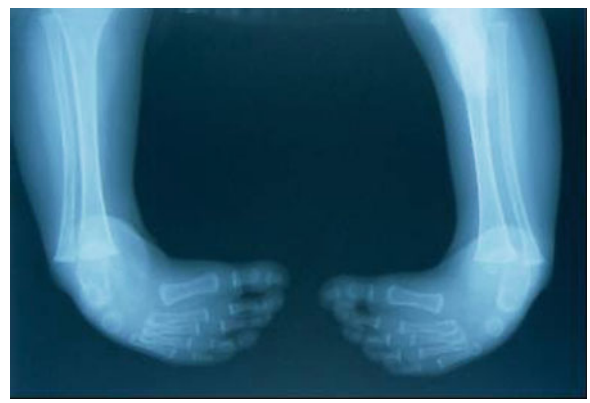

Fig. 4 Radiograph of talipes equinovarus in another infant

Collodion Baby

Collodion baby is a descriptive term for infants born encased in a membrane-like thick scale resembling oiled parchment or collodion. The presence of a collodion membrane at birth represents a defect in skin barrier function and is usually the initial presentation of a congenital ichthyosiform disorder, most often autosomal recessive congenital ichthyosis (ARCI). Thus, neonates born with the features of collodion baby subsequently develop lamellar ichthyosis (LI), nonbullous congenital ichthyosiform erythroderma (NCIE), or other forms of ichthyosis (Akiyama 2006). However, in 10% of neonates spontaneous healing occurs (Raghunath et al. 2003). Collodion baby is a rare congenital condition accounting for 1 in 50,000–1 in 100,000 deliveries.

Synonyms and Related Disorders

Collodion fetus; Ichthyosis congenita; Lamellar exfoliation of newborn; Lamellar ichthyosis

Genetics/Basic Defects

1. Etiology (Taïeb and Labrèze 2002)
   a. The presence of a collodion membrane at birth (Hackett et al. 2010)
      i. Represents a defect in skin barrier function
      ii. Usually the initial presentation of a congenital ichthyosiform disorder, most often autosomal recessive congenital ichthyosis
   b. Common severe phenotype (not associated with noncutaneous features)
      i. Autosomal recessive nonbullous congenital erythrodermic ichthyosis (50% of cases) including harlequin fetus. Harlequin ichthyosis represents the most severe end of the phenotypic spectrum
      ii. Autosomal recessive lamellar ichthyosis (10%) with mutations in the gene for keratinocyte transglutaminase (*TGM1*) on chromosome 14q11 in many patients
      iii. Mapping of a second locus for lamellar ichthyosis to chromosome 2q33-q35 (Permentier et al. 1996)
      iv. Rare reports of autosomal dominant lamellar ichthyosis
      v. Other clinically indistinguishable cases linked to chromosomes 3 and 19
   c. Common milder phenotypes
      i. Mild form of ichthyosis vulgaris (10%)
      ii. Recovery without sequelae: self-healing collodion babies: descried in a minority of collodion babies (10%)
         a) Two self-healing collodion baby siblings observed to have compound heterozygous transglutaminase 1 mutations G278R and D490G (Raghunath et al. 2003)
         b) An acral self-healing collodion baby caused by a new *TGM1* mutation (Mazereeuw-Hautier et al. 2009)
         c) Genotypic heterogeneity of *TGM1* mutations: can lead to nonbullous congenital ichthyosiform erythroderma, self-healing collodion baby (localized or generalized), lamellar ichthyosis, and bathing suit ichthyosis (Petit et al. 1997; Oji et al. 2006; Arita et al. 2007; Hackett et al. 2010)

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   d. Associated congenital ichthyosis
      i. Trichothiodystrophy
      ii. Poorly documented true collodion membrane
         a) Sjögren–Larsson syndrome (ichthyosis, spastic paraplegia, mental retardation, and retinopathy with abnormal levels of fatty aldehyde dehydrogenase activity in cultured fibroblasts)
         b) Netherton syndrome
         c) Gaucher disease type II
         d) Congenital hypothyroidism
         e) Conradi syndrome
         f) Dorfman Chanarin syndrome
         g) Ketoadipiaciduria
         h) Koraxitrachitic syndrome
         i) Ichthyosis variegata
         j) Palmoplantar keratoderma with anogenital leukokeratosis
2. Genes known to be associated with autosomal recessive congenital ichthyosis (ARCI) (Bale and Richard 2009; Hackett et al. 2010)
   a. *TGM1*: Mutations in *TGM1* account for 50–60% of all ARCI and 90% or more of severe LI
   b. *ALOXE3* and *ALOX12B* genes: Mutations in the two *ALOX* genes are present in an estimated 10% of individuals with NCIE or intermediate LI/NCIE phenotypes
   c. *NIPAL4* (*ICHTHYIN*): *NIPAL4* mutations appear to be less common
   d. *ABCA12*: The vast majority of individuals with harlequin ichthyosis and a few individuals with LI have mutations in *ABCA12*, including partial-gene deletions
   e. *CYP4F22*
   f. At least one gene remains unknown
3. Pathogenesis (Akiyama 1999)
   a. Pathogenesis not yet clarified
   b. The term "collodion baby" is considered a descriptive term for infants born encased in membrane-like thick scale and includes several heterogeneous conditions
   c. Several disorders of cornification showing this phenotype at birth
   d. A mutation of keratinocyte transglutaminase may play a role in lamellar ichthyosis, although lamellar ichthyosis is still considered genetically heterogeneous.
   e. Keratinocytes lacking specific transglutaminase will not cause cross-linked envelopes

Clinical features

1. Major clinical features (Sybert 1997)
   a. Newborn covered with a taut, shiny membrane resembling plastic wrap
   b. The membrane often fissured and cracked at birth
   c. Lamellar exfoliation cracks and peels over the course of several weeks to reveal underlying normal skin or skin with mild scaling that goes on to resolve
   d. Red/ivory-colored (erythematous) underlying skin
   e. Persistence of mild ichthyosis in some patients
   f. Ectropion (eversion of the eyelids)
   g. Eclabium (eversion of the lips)
   h. Crumpled pinnae
   i. Resolved tapered fingertips and partially flexed hands with shedding of the encasing membrane
2. Minor clinical features
   a. Secondary skin infections in the cracks and fissures
   b. Scarring in the areas of deep fissuring
3. Complications
   a. Difficulties in temperature regulation (hypothermia)
   b. Increased insensible water loss predisposing to hypernatremic dehydration
   c. Secondary infections from gram-positive organisms and *Candida albicans*
   d. Septicemia
   e. Pneumonia secondary to aspiration of squamous material in the amniotic fluid
   f. Respiratory difficulty due to restricted chest wall movement
   g. Possible loss of vision caused by corneal damage
   h. Constrictive bands of the extremities resulting in vascular compromise and edema (Van Gysel et al. 2002; Roberts and Adelson 2010)
4. Prognosis
   a. Long-term prognosis difficult to address at birth
   b. Infrequently, a collodion baby may have normal skin after exfoliation of the membranes

Diagnostic Investigations

1. Skin biopsy
   a. Transglutaminase assay
   b. Conventional and electron microscopy
      i. Hyperkeratosis with thick compact cornified layer (orthokeratotic stratum corneum)
      ii. Aberrant keratinized/cornified cells
      iii. Irregularly convoluted horny cells and numerous intercellular Odland bodies (lamellar granules) and nuclear debris in distal layer of the stratum corneum
2. Molecular genetic analysis
   a. *TGM1* sequence analysis: identification of mutation of keratinocyte transglutaminase 1 gene for severe form of autosomal recessive lamellar ichthyosis and self-healing collodion baby
   b. *TGM1* mutations include missense, nonsense, and splice site
   c. Carrier testing available to at-risk family members on a clinical basis once the mutation in *TGM1* has been identified in the proband
   d. Other gene mutations
3. Studies for other associated conditions
   a. Polarized light examination of hair and eye brows
      i. Trichothiodystrophy
      ii. Netherton syndrome
   b. Leukocyte lipid inclusions
      i. Dorfman Chanarin syndrome
      ii. Neonatal Gaucher disease
   c. Thyroid hormone level: congenital hypothyroidism
   d. Skeletal study: Conradi syndrome
   e. Neurosensory evaluation

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal recessive inheritance: 25% recurrence risk
      ii. Autosomal dominant inheritance: not increased unless a parent is affected
   b. Patient's offspring
      i. Autosomal recessive inheritance: not increased unless the spouse is a carrier or affected
      ii. Autosomal dominant inheritance: 50%
2. Prenatal diagnosis: direct mutation analysis of the keratinocyte transglutaminase 1 gene on fetal DNA obtained from amniocentesis or CVS for severe form of autosomal recessive lamellar ichthyosis, provided the mutation in *TGM1* or other disease-causing mutation has been identified in the proband
3. Management: requiring intensive care (Shareef et al. 2000)
   a. Maintain skin integrity
      i. Assess open skin lesions
      ii. Minimal handling with precaution
      iii. Prevent secondary infection and avoid prophylactic use of antibiotics
   b. Maintain body temperature
      i. Avoid radiant heat
      ii. Use humidified incubator for dehydration and hypothermia
      iii. Pre-warm all linen used to absorb weeping
   c. Ophthalmological management of ectropion important for the prevention of conjunctivitis and keratitis
   d. Sedation with opioids indicated for severe pain
   e. Petrolatum-based creams/ointments to keep the skin soft, supple, and hydrated
   f. Retinoids in case of delayed shedding of the collodion membrane beyond 3 weeks
   g. Use keratolytics agents (e.g., alpha hydroxy acid preparations) or urea preparations to promote peeling and thinning of the stratum corneum as the child becomes older
   h. Release of collodion membrane on digits, when necessary, to maintain circulation and on the thorax for adequate respiration

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Fig. 1 (**a**–**c**) A collodion baby wrapped with a taut, shinny membrane over the whole body, red underlying skin, ectropion, crumpled pinnae, and partially flexed hands by encasing membrane

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) refers to a family of inherited disorders of adrenal steroidogenesis. The common functional defect in each disorder is impaired cortisol secretion, resulting in hypersecretion of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) and consequent hyperplasia of the adrenal glands (Antal and Zhou 2009).

More than 90% of cases of CAH are caused by a defect in the enzyme 21-hydroxylase. Four other enzyme deficiencies in the steroid biosynthesis pathway, along with one cholesterol transport protein defect, account for the remaining cases. Depending on the severity of the enzyme deficiency, 21-hydroxylase deficiency is defined as classic (severe form) or nonclassic (mild form). Approximately, 75% of patients who have the classic form also have salt wasting due to inadequate aldosterone production, further subdividing the classification into classic simple virilizing and classic salt-wasting forms. This chapter will discuss 21-hydroxylase deficiency in detail with a brief discussion of the other forms of CAH.

21-hydroxylase deficiency is the most common type of congenital adrenal hyperplasia (CAH). The incidence of classic 21-hydroxylase deficiency is estimated to be 1/12,000–1/15,000 births. The nonclassical form of the disease, also called "late-onset" CAH, occurs in approximately 1 in 1,000 of the general population depending on the ethnic group and in up to 6% of hirsute women (Deneux et al. 2001).

Synonyms and Related Disorders

11-beta hydroxylase deficiency; 17-alpha-hydroxylase deficiency; 21-hydroxylase deficiency; 3-beta-hydroxysteroid dehydrogenase deficiency; Lipoid congenital adrenal hyperplasia

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Biochemical and molecular basis
   a. Deficient 21-hydroxylase activity : the most common form (>90% of cases) of CAH
   b. Caused by mutations of *CYP21* (*CYP21A2*) gene, mapped on the short arm of chromosome 6 (6p21.3): present in duplicate
   c. A highly homologous pseudogene (*CYP21P*)
      i. Located in the same chromosomal region as the active gene
      ii. Severe mutations of the pseudogene incompatible with coding for a functional enzyme
   d. About 95% of mutant alleles generated by recombination events between *CYP21* and *CYP21P* (Forest et al. 1998)
   e. Relatively common exchange of genetic material between these two homologous genes, the major reason for the high incidence of 21-hydroxylase deficiency compared to other forms of CAH

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3. Pathophysiology (New 2002)
   a. Classic form of 21-hydroxylase deficiency
      i. Prenatal exposure to potent androgens (testosterone and delta4-androstenedione) at critical stages (8–12 weeks) of sexual differentiation resulting in virilization of the external genitalia in genetic females, resulting in varying degrees of genital ambiguity (female pseudohermaphroditism) at birth
      ii. Subdivision of classic form
         a) Simple virilizing form (about 25%)
         b) Salt-wasting form (>75%) in which aldosterone production is inadequate and at risk of life-threatening salt-wasting crises
   b. Nonclassic "late onset" form of 21-hydroxylase deficiency
      i. Has only moderate enzyme deficiency
      ii. Present postnatally with signs of hyperandrogenism
      iii. Females with the nonclassic form: not virilized at birth
4. CAH due to 21-hydroxylase deficiency
   a. 21-hydroxylase
      i. A microsomal cytochrome P450 enzyme
      ii. Required to convert:
         a) 17-hydroxy-progesterone to 11-deoxycortisol
         b) Progesterone to deoxycorticosterone
   b. 21-hydroxylase deficiency
      i. Impairs the metabolism of cholesterol to cortisol, generating excessive level of 17-hydroxyprogesterone
      ii. Produces androstenedione and other androgens from the precursor (17-hydroxyprogesterone) via an alternative metabolic pathway
      iii. Aldosterone deficiency
         a) Inability to synthesize adequate amounts of aldosterone due to severely impaired 21-hydroxylation of progesterone in about 75% of patients
         b) Resulting in sodium loss via the kidney, colon, and sweat glands and excrete potassium from the renal tubules
   c. Cortisol deficiency
      i. Glucocorticoids
         a) Increase cardiac contractility
         b) Increase cardiac output
         c) Increase cardiac and vasculature sensitivity to the pressor effects of catecholamines and other pressor hormone
      ii. Absence of glucocorticoids
         a) Decrease in cardiac output
         b) Decrease in glomerular filtration leading to an inability to excrete free water and consequently to hyponatremia
   d. Shock and severe hyponatremia much more likely in 21-hydroxylase deficiency in which both cortisol and aldosterone biosynthesis are affected
5. Phenotype-genotype correlations (White 2001)
   a. Mutations in CYP21, such as deletions, frameshifts, or nonsense mutations
      i. Totally ablate enzyme activity
      ii. Most often associated with salt-wasting
   b. Mutations mainly consisting of the missense mutation Ile172Asn (Il72N)
      i. Yielding enzymes with 1–2% normal activity
      ii. Carried predominantly by patients with simple virilizing disease
   c. Mutations such as Val281Leu (V281L) and Pro30Leu (P30L)
      i. Producing enzymes with 20–60% of normal activity
      ii. Most often associated with the nonclassical disorder
   d. Two different CYP21 mutations
      i. Producing compound heterozygotes
      ii. Most often with a phenotype compatible with that of the less severe gene defects
   e. All patients homozygous or compound heterozygous for large deletions or gene conversions have a salt-wasting classic form.
6. Characteristics of other forms of CAH (Antal and Zhou 2009)
   a. 11-Beta Hydroxylase deficiency
      i. Incidence: 1:100,000
      ii. Gene involved: *CYP11B1*
      iii. Chromosome location: 8q24.3
   b. 17-alpha-hydroxylase deficiency
      i. Incidence: rare
      ii. Gene involved: *CYP17*
      iii. Chromosome location: 10q24.3
   c. 3-beta-hydroxysteroid Dehydrogenase deficiency
      i. Incidence: rare
      ii. Gene involved: *HSD3B2*
      iii. Chromosome location: 1p13.1

d. Lipoid CAH
   i. Incidence: rare
   ii. Gene involved: steroidogenic acute regulatory protein (*StAR*)
   iii. Chromosome location: 8p11.2

Clinical Features

1. Typical signs and symptoms of acute adrenal crisis (Antal and Zhou 2009)
   a. Decreased activity/fatigue
   b. Altered sensorium/unresponsiveness
   c. Poor feeding/weak suck
   d. Dry mucous membranes
   e. Hyperpigmentation
   f. Abdominal pain
   g. Vomiting
   h. Hyponatremia
   i. Hyperkalemia
   j. Hypoglycemia
   k. Metabolic acidosis
   l. Hypothermia
   m. Hypotension
   n. Dehydration
   o. Lack of weight gain
2. Classic CAH phenotype (New 2002; White 2001)
   a. Simple virilizing form (about 25% of patients)
   b. Salt-wasting form (>75% of patients)
      i. Adrenal crises present at 1–4 weeks of age in severely affected patients
         a) Severe dehydration
         b) Hypotension
         c) Severe hyponatremia, hyperkalemia, and hyperreninemia
         d) Progressing to adrenal crisis (azotemia, vascular collapse, hypovolemic shock, and death) if adequate medical care is not provided
         e) Affected infant boys who are not detected in a newborn screening program are at high risk of a salt-wasting crisis since their normal genitalia fail to alert physicians to the diagnosis of congenital adrenal hyperplasia.
      ii. Non-specific symptoms
         a) Poor appetite/feeding
         b) Vomiting
         c) Hypotension
         d) Lethargy
         e) Failure to gain weight (weight loss)
      iii. Improved sodium balance and more efficient aldosterone synthesis with age in patients known to have severe slat-wasting episodes in infancy and early childhood
      iv. Siblings may be discordant for salt wasting
      v. The degree of salt wasting may vary in individuals carrying identical mutations.
      vi. Patients with 3β-hydroxysteroid hydrogenase deficiency, aldosterone synthase deficiency, or lipoid hyperplasia
         a) Unable to synthesize aldosterone
         b) May present with salt-wasting crises
   c. Children with classic CAH
      i. Lack of sufficient amounts of cortisol to mount a stress response and frequently succumb to minor illnesses
      ii. Premature closure of the epiphyses resulting in short stature even though these children grow at an accelerated rate when young
   d. Growth disturbances
      i. Accelerated skeletal maturation in untreated patients due to high levels of androgen
      ii. Growth retardation in patients treated with excessive doses of glucocorticoids
      iii. Final height, despite careful monitoring and good patient compliance, usually averaging one to two standard deviations below the population mean or the target height based on parental heights
   e. Reproductive problems in affected females (White 2001)
      i. Ambiguous genitalia typically present in the neonatal period
         a) Clitoromegaly (mild)
         b) With or without partial fusion of the labioscrotal folds (intermediate)
         c) Complete fusion of the labioscrotal folds with the appearance of a penile urethra (severe)
      ii. Internal genitalia
         a) Normal ovaries, fallopian tubes, and uteri
         b) Normal upper third of the vagina but urogenital sinus may be present distally with one opening on the perineum
      iii. Signs of androgen excess in affected females without glucocorticoid replacement therapy (New 2002)

a) Clitoral enlargement
b) Excessive linear growth
c) Advanced bone age
d) Acne
e) Early onset of pubic and axillary hair
f) Hirsutism
g) Male pattern baldness
h) Menstrual abnormalities
i) Reduced fertility

iv. Adolescence (White 2001)
a) Late menarche in inadequately treated girls
b) Sonographic finding of multiple ovarian cysts similar to patients with polycystic ovarian syndrome
c) Anovulation
d) Irregular bleeding
e) Hyperandrogenic symptoms

v. Pregnancy and live-birth rates
a) Severely reduced in salt-wasting patients
b) Mildly reduced in simple virilizing patients
c) Normal in nonclassical patients

vi. Factors suggested responsible for the impaired fertility (Stikkelbroeek et al. 2003)
a) Adrenal overproduction of androgens and progestins (17-hydroxyprogesterone, progesterone, and androstenedione)
b) Ovarian hyperandrogenism
c) Polycystic ovary syndrome
d) Ovarian adrenal rest tumors
e) Neuroendocrine factors
f) Genital surgery
g) Psychosocial factors (delayed psychosexual development, reduced sexual activity, low maternal feelings)

vii. No evidence of an excess of congenital malformations in offspring of women with 21-hydroxylase deficiency (White 2001)

viii. Other types of congenital adrenal hyperplasia (White 2001)
a) 11β-hydroxylase deficiency: similar to 21-hydroxylase deficiency
b) 17α-hydroxylase deficiency: remains sexually infantile due to inability to synthesize sex hormones unless supplemented with estrogen
c) 3β-hydroxysteroid hydrogenase deficiency: slightly virilized due to high levels of dehydroepiandrosterone

f. Reproductive function and problems in affected males (New 2002; White 2001)
i. Signs of androgen excess in affected males without glucocorticoid replacement therapy
a) Penile enlargement
b) Small testes
c) Excessive linear growth
d) Advanced bone age
e) Acne
f) Early onset of pubic and axillary hair

ii. Ability to father children

iii. Testicular adrenal rests
a) Most often benign
b) Manifest as testicular enlargement
c) Seen most often in inadequately treated patients, particularly those with the salt-wasting form of 21-hydroxylase deficiency

iv. Other types of congenital adrenal hyperplasia
a) Men with 11β-hydroxylase deficiency: similar to those with 21-hydroxylase deficiency
b) Genetic males with 3β-hydroxysteroid hydrogenase deficiency, 17α-hydroxylase deficiency, or lipoid hyperplasia: usually raised as females and castrated during or before adolescence to prevent malignant transformation of abdominal testes

g. Effects on gender role, sexual orientation, and identity (White 2001)
i. Gender role
a) Referring to gender-stereotyped behaviors such as choice of play toys by young children
b) Girls with 21-hydroxylase deficiency may show low interest in maternal behavior, extending from lack of doll play in early childhood to lack of interest in childrearing in women.

ii. Sexual orientation
a) Referring to homosexual versus heterosexual preferences
b) Heterosexuality in most adult women with 21-hydroxylase deficiency

c) Homosexuality or bisexuality or increased tendency to homo-erotic fantasies in a small but significant proportion in women with 21-hydroxylase deficiency

iii. Gender identity
a) Referring to self-identification as male or female
b) Self-reassignment to the male sex is unusual in women with 21-hydroxylase deficiency
c) Severely virilized females are more likely to be raised as males in cultures that value boys more highly and/or in third world countries in which the diagnosis is likely to be delayed.

3. Nonclassic CAH phenotype (White 2001)
a. Having only moderate enzyme deficiency
b. Nonambiguous external genitalia, with normal or mild clitoromegaly, in females affected with mild, nonclassical form of 21-hydroxylase deficiency
c. Signs of androgen excess
i. Wide spectrum of symptoms and signs
ii. Asymptomatic in many affected individuals
iii. Children: premature pubarche
iv. Young women
a) Severe cystic acne
b) Hirsutism
c) Oligomenorrhea
d. Signs and symptoms suggesting mild CAH (Deaton et al. 1999)
i. Children
a) Moderate to severe recurrent sinus or pulmonary infections
b) Severe acne
c) Hyperpigmentation, especially of the genitalia
d) Tall for age
e) Early onset of puberty
ii. Adults
a) Childhood history as described above
b) Syncope or near-syncope
c) Shortened stature compared with either parent
d) Hypotension (21-hydroxylase deficiency)
e) Hypertension (11β-hydroxylase deficiency)
iii. Women
a) Clitoromegaly
b) Poorly developed labia
c) Premature adrenarche
d) Hirsutism
e) Menstrual disturbances
f) Infertility
g) Polycystic ovary syndrome

4. Clinical characteristics of other forms of CAH (Antal and Zhou 2009)
a. 11-Beta Hydroxylase deficiency
i. Ambiguous genitalia in females
ii. Rare adrenal crisis
b. 17-alpha-hydroxylase deficiency
i. Ambiguous genitalia in males
ii. No adrenal crisis
c. 3-beta-hydroxysteroid Dehydrogenase deficiency
i. Ambiguous genitalia in males
ii. Adrenal crisis present
d. Lipoid CAH
i. Ambiguous genitalia in males
ii. Severe adrenal crisis

Diagnostic Investigations

1. Newborn screening (New 2002; White 2001, 2009)
a. Objectives
i. Detect a common and potentially fatal childhood disease (classic form of CAH)
ii. Prevent serious morbidity and mortality by early recognition and treatment
iii. Prevent incorrect male sex assignment of affected female infants with ambiguous genitalia
iv. Detect most, but not all, cases of the nonclassic form of 21-hydroxylase deficiency
b. Filter-paper blood spot sample (White 2001)
i. Markedly elevated 17-hydroxyprogesterone by radioimmunoassay
ii. False positives
a) Samples taken in the first 24 h of life (elevated in all infants)
b) Variation of weight adjusted cutoff values among newborn screening programs
c) Infants with low birth weight or prematurity
c. Diagnosis is based on elevated levels of 17-hydroxyprogesterone, the preferred substrate for steroid 21-hydroxylase

d. Initial testing usually involves dissociation-enhanced lanthanide fluorescence immunoassay that has a low positive predictive value (about 1%), leading to many follow-up evaluations that have negative results
e. Second level of screening based on detection of actual mutations on DNA extracted from the same dried blood spots or liquid chromatography followed by tandem mass spectrometry
f. Main benefits of newborn screening
   i. Reduced morbidity and mortality
   ii. Reduced time to diagnosis of infants with 21-hydroxylase deficiency
   iii. Infants ascertained through screening
      a) Less severe hyponatremia
      b) Tend to be hospitalized for shorter periods of time

2. Diagnosis of CAH
   a. Female neonates
      i. With genital ambiguity
         a) Genital ambiguity highly distressing to the family
         b) Require urgent expert medical attention
         c) Need immediate comprehensive evaluation by a multidisciplinary team including specialists from pediatric endocrinology, psychosocial services, pediatric surgery/urology, and genetics
      ii. With or without salt loss
      iii. Presence of elevated concentration of serum 17-hydroxyprogesterone
         a) Only diagnostic of CAH when measured after the 3rd day of life
         b) Presence of relatively high concentrations in the immediate neonatal period in normal infants
      iv. Normal internal female genitalia on pelvic ultrasonography
      v. Normal female karyotype (46,XX)
   b. Male neonates
      i. Salt-losing crises
      ii. Presence of elevated 17-hydroxyprogesterone concentration
3. Clinical chemistry
   a. Important initial laboratory evaluation for patients suspected of experiencing adrenal crisis due to 21-hydroxylase deficiency (Antal and Zhou 2009)
      i. Glucose/dextrose stick at bedside
      ii. Chem-20 (including electrolytes and liver function panel): critical to assure that the potassium concentration is obtained from a nonhemolyzed sample to minimize the likelihood of a falsely elevated potassium value
      iii. Arterial blood gas/serum pH
      iv. Cortisol
      v. ACTH
      vi. 17-OHP
      vii. Pelvic ultrasonography
      viii. Karyotype
   b. ACTH stimulation test: necessary to evaluate adrenal function and differentiate among the various potential enzymatic defects (Antal and Zhou 2009)
   c. Comparison of baseline and cortrosyn-stimulated serum concentrations of the steroid precursor 17-hydroxyprogesterone (nonclassical)
   d. Increased serum levels of progesterone, 17-hydroxyprogesterone, and androstenedione in affected males and females with classic 21-hydroxylase deficiency
   e. Elevated serum levels of testosterone and adrenal androgen precursors in affected girls
   f. Salt losers
      i. Low serum bicarbonates, sodium, and chloride levels
      ii. Elevated levels of serum potassium and serum urea nitrogen
      iii. Hyponatremia and hyperkalemia usually not present before 7 days of age
      iv. Inappropriately increased urine sodium levels
      v. Elevated plasma rennin levels
      vi. Serum aldosterone level inappropriately low for the rennin level
4. Karyotyping or fluorescence in situ hybridization for sex chromosome material
   a. 46,XX in females with 21-hydroxylase deficiency
   b. 46,XY in males with 21-hydroxylase deficiency
5. Annual bone age radiography
6. Careful monitoring of linear growth
7. Transabdominal pelvic sonography
   a. Perform in patients with CAH undergoing vaginal reconstruction
   b. Provide adequate information about the anatomy of the vagina and urogenital sinus

c. Demonstrate presence or absence of a uterus or associated renal anomalies
8. Urogenitogram helpful to define the anatomy of the internal genitalia
9. Adrenal ultrasonography to detect enlarged, lobulated adrenals with stippled echogenicity invariably associated with CAH
10. Sonography or MRI for testicular adrenal rest tumors
11. Carrier detection (New 2002)
    a. Carriers: asymptomatic individuals who have one normal allele and one mutant allele
    b. ACTH stimulation test
        i. Resulting in slightly elevated serum concentrations of deoxycortisol and 17-hydroxyprogesterone
        ii. Overlap in serum concentration of 17-hydroxyprogesterone between carriers and noncarriers
        iii. No longer the preferred method of carrier detection
    c. Molecular genetic testing
        i. Molecular genetic testing of the *CYP21A2* gene available to at-risk relatives, given that the disease-causing mutation(s) have been identified in the proband
        ii. The preferred method of carrier detection
12. Molecular genetic testing (New 2002)
    a. Molecular genetic analysis for *CYP21A2* gene for a panel of 9 common mutations and gene deletions detect about 90–95% of disease-causing alleles in affected individuals and carriers.
    b. Complete gene sequencing detects more rare alleles in affected individuals in whom the panel of nine mutations and deletions reveals only one or neither disease-causing allele
    c. Applications
        i. Primarily used in genetic counseling for carrier detection of at-risk relatives and for prenatal diagnosis
        ii. Can be used for diagnosis in newborns with slight to moderate elevations of 17-hydroxyprogesterone
13. Laboratory characteristics of other forms of CAH (Antal and Zhou 2009)
    a. 11-Beta Hydroxylase deficiency
        i. Glucocorticoid values; decreased
        ii. Mineralocorticoid values: elevated
        iii. Androgens: elevated
        iv. Sodium concentrations: elevated
        v. Potassium concentrations: decreased
        vi. Elevated metabolites
            a) Deoxycorticosterone (DOC)
            b) 11-deoxycortisol
    b. 17-alpha-hydroxylase deficiency
        i. Glucocorticoid values: decreased
        ii. Mineralocorticoid values: elevated
        iii. Androgens: decreased
        iv. Sodium concentrations: increased
        v. Potassium concentrations: decreased
        vi. Elevated metabolites
            a) Deoxycorticosterone
            b) Corticosterone
    c. 3-beta-hydroxysteroid Dehydrogenase deficiency
        i. Glucocorticoid values: decreased
        ii. Mineralocorticoid values: decreased
        iii. Androgens
            a) Elevated in females
            b) Decreased in males
        iv. Sodium concentrations: decreased
        v. Potassium concentrations: elevated
        vi. Elevated metabolites
            a) Dehydroepiandrosterone (DHEA)
            b) 17-hydroxypregnenolone
    d. Lipoid CAH
        i. Glucocorticoid values: decreased
        ii. Mineralocorticoid values: decreased
        iii. Androgens: decreased
        iv. Sodium concentrations: decreased
        v. Potassium concentrations: elevated
        vi. Elevated metabolites: none

Genetic Counseling

1. Recurrence risk
    a. Genetic counseling according to autosomal recessive inheritance
        i. Most parents: heterozygotes with one normal allele and one mutated allele.
        ii. One percentage of probands having only one parent who is heterozygous since 1% of mutations occur de novo
        iii. In some instances, a parent, who was previously not known to be affected, was found to have the nonclassic form of 21-hydroxylase deficiency.

b. Patient's sib
   i. When the parents of a proband are both obligate heterozygotes
      a) Twenty-five percent risk of inheriting both altered alleles and being affected
      b) Fifty percent risk of inheriting one altered allele and being an unaffected carrier
      c) Twenty-five percent risk of inheriting both normal allele and being unaffected
      d) Two-third chance of unaffected sibs of a proband being a carrier
   ii. When a parent of a proband has 21-hydroxylase deficiency and the other is heterozygous
      a) Fifty percent risk of inheriting both mutant alleles and being affected
      b) Fifty percent risk of inheriting one mutant allele and being a carrier
c. Patient's offspring for a woman with classic 21-hydroxylase deficiency
   i. When the spouse status is unknown (Lo and Grumbach 2001)
      a) Risk of having an infant with the same disorder: approximately 1 in 120 births
      b) Risk of having an affected female infant: approximately 1 in 240 births
      c) Risk figures are based on an estimated 1 in 60 incidence of heterozygous individuals with a *CYP21* mutation, derived from newborn screening data
   ii. When the spouse is not a carrier or not affected: risk is not increased
   iii. Appropriate to offer molecular genetic testing of the *CYP21A2* gene to the spouse given the high carrier rate for 21-hydroxylase deficiency
d. Patient's offspring for a woman with nonclassic CAH and are compound heterozygotes with one severe *CYP21A2* mutation: Risk of having an affected infant with classic CAH is 1 in 4 pregnancies (or 1 in 8 pregnancies for an affected female infant) when the spouse is a known carrier of the severe form of *CYP21A2* deficiency.

2. Prenatal diagnosis
   a. Determination of amniotic fluid (AF) hormone levels
      i. Elevated 17α-hydroxyprogesterone
      ii. Elevated androstenedione
   b. Human leukocyte antigen (HLA) typing on cultured chorionic villus cells and cultured AF cells
      i. Basis for prenatal diagnosis: the gene for 21-hydroxylase has been linked to the HLA system on chromosome 6
      ii. HLA type
         a) Fetus with an HLA type identical to that of the proband with 21-hydroxylase deficiency predicted to be affected
         b) Fetus sharing 1 parental haplotype with the proband predicted to be a heterozygous carrier
         c) Fetus with both haplotypes different from the index case predicted to be homozygous normal
   c. Molecular DNA diagnosis
      i. Molecular genetic testing of the proband and both parents should be undertaken prior to conception:
         a) To identify the two disease-causing mutations
         b) To confirm both parents are carriers
      ii. Analysis of both parents
         a) To determine the phase of different mutations (whether they lie on the same or opposite alleles)
         b) To distinguish homozygotes and hemizygotes (individuals who have a mutation on one chromosome and a deletion on the other)
      iii. De novo mutations, found in patients with CAH but not in parents, observed in 1% of disease-causing CYP21B mutations
      iv. Before 10 weeks of gestation and prior to any prenatal testing, administer dexamethasone to the pregnant mother to suppress excess fetal adrenal androgen secretion and to prevent virilization of an affected female
      v. Obtain fetal cells to determine fetal sex by chromosome analysis or FISH using Y-chromosome specific probes
         a) CVS in the 10th–12th week of gestation (preferable because of early result)
         b) Amniocentesis at 16–18 weeks of gestation
      vi. If the fetus is a female and if the two *CYP21A2* disease-causing mutations have been identified in the proband:

a) Perform molecular genetic testing to determine whether the fetus has inherited both disease-causing alleles
b) Female fetus known to have 21-hydroxylase deficiency by DNA analysis or having an indeterminant status: continue dexamethasone treatment to term

vii. If the fetus is a male or unaffected female by DNA analysis: discontinue dexamethasone treatment

3. Management (White 2001)
   a. Replacement with glucocorticoids (hydrocortisone, prednisone, dexamethasone)
      i. Indicated in all patients with classic and symptomatic nonclassical patients with 21-hydroxylase deficiency
      ii. To suppress the excessive secretion of CRH and ACTH by the hypothalamus and pituitary
      iii. To reduce the abnormal blood levels of adrenal sex steroids
      iv. Situations in which increase hydrocortisone dose is needed in patients with classic 21-hydroxylase deficiency
         a) Febrile illness
         b) Surgery under general anesthesia
      v. Increase doe of hydrocortisone or prednisone in pregnancy due to pregnancy-induced alterations in steroid metabolism and clearance
      vi. Glucocorticoid replacement also required in patients with CAH caused by other enzymatic deficiencies
   b. Mineralocorticoid replacement
      i. Mineralocorticoid (fludrohydrocortisone) and sodium chloride supplements required in infants with the salt-wasting form of 21-hydroxylase deficiency
      ii. Treat patients with simple virilizing form of the disease by fludrohydrocortisone to aid in adrenocortical suppression and reduce the dose of glucocorticoid required to maintain acceptable 17-hydroxyprogesterone levels
      iii. Signs of overtreatment with mineralocorticoid and sodium replacement
         a) Hypertension
         b) Tachycardia
         c) Suppressed plasma rennin activity
      iv. Other indications of fludrohydrocortisone replacement
         a) 3β-hydroxysteroid hydrogenase deficiency
         b) Aldosterone synthase deficiency
         c) Lipoid hyperplasia
   c. Other pharmacological approaches
      i. A novel 4-drug regimen for 21-hydroxylase deficiency
         a) Consisting of flutamide (an androgen receptor blocking drug), testolactone (an aromatase inhibitor), and low dose of hydrocortisone and fludrocortisone
         b) Benefit: produce less bone age advancement and attain more appropriate linear growth velocity than standard treatment
         c) Side effect: occurrence of central precocious puberty requiring treatment with gonadotrophin releasing hormone analog
      ii. Experimental treatment with carbenoxolone, an inhibitor of 11β-hydroxysteroid dehydrogenase
   d. Corrective surgery
      i. Decision about surgery
         a) Made by the parents, together with the clinical team
         b) After disclosure of all relevant clinical information and all available options
         c) Obtain informed consent
      ii. Objectives
         a) Genital appearance compatible with gender
         b) Unobstructed urinary emptying without incontinence or infections
         c) Good adult sexual and reproductive function
      iii. Clitoroplasty, rather than clitoridectomy, done in infancy
      iv. Vaginal reconstruction
         a) Often postponed until the age of expected sexual activity
         b) Single-stage corrective surgery in children
   e. Adrenalectomy
      i. Questionable therapeutic alternative
      ii. Likely to be used, if at all, in patients with severe 21-hydroxylase deficiency refractory to standard medical management

f. Management of testicular adrenal rests
   i. Effective adrenal suppression with dexamethasone since many of these tumors are ACTH-responsive
   ii. Testis-sparing surgery for cases unresponsive to dexamethasone after imaging the tumor by sonography and/or MRI
g. Management of adolescence with classical and nonclassical CAH (Clayton et al. 2002)
   i. Psychological assessment and support of the patient
   ii. Counseling
      a) Sexual function
      b) Future surgeries
      c) Gender role
      d) Issues related to living with a chronic disorder
      e) Low risk of women with CAH or nonclassic CAH having an affected fetus
h. Management of pregnancy in women with classic 21-hydroxylase deficiency (Lo and Grumbach 2001)
   i. Factors contributing to lower fertility rates
      a) Masculinization of the external genitalia
      b) An inadequate introitus
      c) Factors relating to genital reconstructive surgery (poor surgical repair, vaginal stenosis, and clitoral dysfunction)
      d) Hormonal factors (increased levels of adrenal androgens and progestational steroid, and ovarian hyperandrogenism)
   ii. Recent improvement of fertility prognosis
      a) Earlier detection and treatment of 21-hydroxylase deficiency
      b) Surgical advances in genital reconstruction
      c) Higher patient compliance rates
   iii. Preconception issues for all women with classic 21-hydroxylase deficiency who desire pregnancy
      a) Need for glucocorticoid treatment
      b) Careful endocrine monitoring throughout gestation
      c) Ovulation induction with clomiphene citrate or gonadotropin therapy or in vitro fertilization for patients who do not achieve normal ovulatory cycles and fertility despite effective glucocorticoid therapy
      d) Most pregnancies are successful in carrying to term with a healthy outcome.
      e) Preconceptional counseling about the risk of having a child affected with 21-hydroxylase deficiency
   iv. Gestational management (Lo Lo and Grumbach 2001)
      a) Regular assessment of maternal clinical status, serum electrolytes, and circulating adrenal androgen levels during gestation to determine the need for increased glucocorticoid or mineralocorticoid therapy
      b) Signs of adrenal steroid insufficiency (excessive nausea, slat craving, and poor weight gain)
      c) Monitor hypertension and fluid retention in patients receiving mineralocorticoid therapy, particularly in the third trimester
   v. Labor and delivery (Lo and Grumbach 2001)
      a) Require stress doses of glucocorticoid therapy during labor and delivery
      b) Elective cesarean section considered for pregnant women with virilizing CAH, for cephalopelvic disproportion due to android pelvic characteristics and especially for those who have had reconstructive surgery of the external genitalia
   vi. Evaluation of the infant (Lo and Grumbach 2001)
      a) Clinical signs of adrenal suppression (hypotension, hypoglycemia), particularly in cases in which dexamethasone was administered during pregnancy
      b) Sign of ambiguous external genitalia
      c) Female pseudohermaphroditism secondary to either maternal hyperandrogenism or fetal 21-hydroxylase deficiency (if the father is a carrier)
i. Prenatal therapy
   i. Inclusion criteria (Clayton et al. 2002)
      a) A previously affected sibling or first-degree relative with known mutations causing classic CAH, proven by DNA analysis
      b) Reasonable expectation that the father is the same as the father of the proband
      c) Availability of rapid, high-quality genetic analysis
      d) Therapy started less than 9 weeks after the last menstrual period

e) No plans for therapeutic abortion
f) Reasonable expectation of patient compliance

ii. Dexamethasone
a) No salt-retaining activity
b) Not significantly metabolized by placental 11β-hydroxysteroid dehydrogenase
c) Able to cross the placenta

iii. Administer oral dexamethasone to the mother in pregnancies at risk for a female child affected with virilizing adrenal hyperplasia
a) To suppress fetal adrenal androgen production, beginning after conception and before the 7–8th week of gestation, to prevent ambiguity of the external genitalia in the female fetus with classic CAH
b) To prevent progression of virilization on therapy after 7–8th week of gestation
c) Chromosome analysis from fetal cells obtained from either CVS at 10–12 weeks of gestation or amniocentesis at 14–18 weeks of gestation
d) If the fetus is a female, additional molecular genetic testing is performed on the sample to determine if she has 21-hydroxylase deficiency (Antal and Zhou 2009)
e) If the fetus is affected, maternal dexamethasone administration is continued to term; if not, it can be discontinued

iv. Outcome of prenatally treated females (American Academy of Pediatrics 2000)
a) Approximately 70% born with normal or only slightly virilized genitalia with clitoromegaly, partial labial fusion, or both
b) Approximately 30% born with marked genital virilization

v. Disadvantage: 7 out of 8 fetuses unnecessarily treated since CAH is inherited as an autosomal recessive disease and only affected girls benefit from the treatment

vi. Prompt discontinuation of dexamethasone therapy to minimize potential risks of glucocorticoid toxicity if (White 2001):
a) Male sex determination by prenatal genetic diagnosis
b) *CYP21* genotype indicating that the fetus is unaffected

vii. Refer patient to centers with expertise in the prenatal management of pregnancies at risk for CAH.

viii. Long-term follow-up studies still needed for prenatally treated children

ix. Side effects of women treated to term (10%)
a) Features of Cushing syndrome (excessive weight gain, severe striae, hypertension, hyperglycemia)
b) Resolved when the treatment is discontinued

x. Side effects of women treated for a shorter time (10–20%)
a) Edema
b) Gastrointestinal upset
c) Mood fluctuations
d) Acne
e) Hirsutism

xi. Similar therapeutic approaches: effective in families at risk for 11β-hydroxylase deficiency, in which affected female fetuses may also suffer severe prenatal virilization

xii. Prenatal therapy not appropriate for nonclassic CAH

xiii. Parents of affected girls
a) Many opting for prenatal medical treatment because of severe psychological impact of ambiguous genitalia on the child and on the family
b) Obtain informed consent as to the potential fetal and maternal risks, some of which may yet to be recognized

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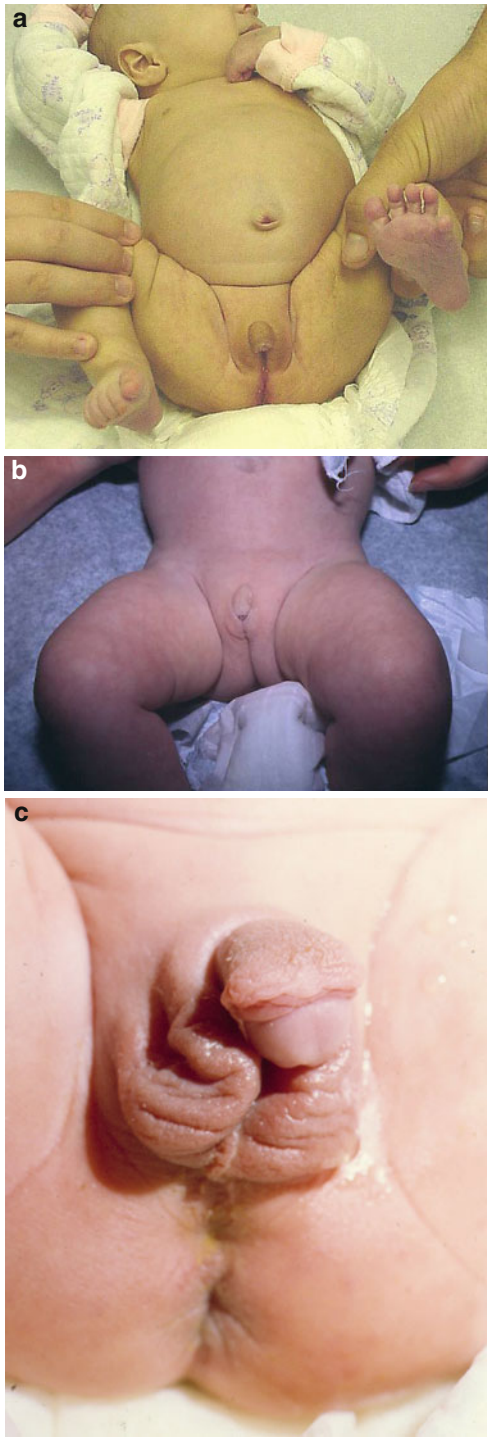

Fig. 1 (**a**–**c**) Female infants (46,XX) with classic form of CAH showing varying degree of virilization

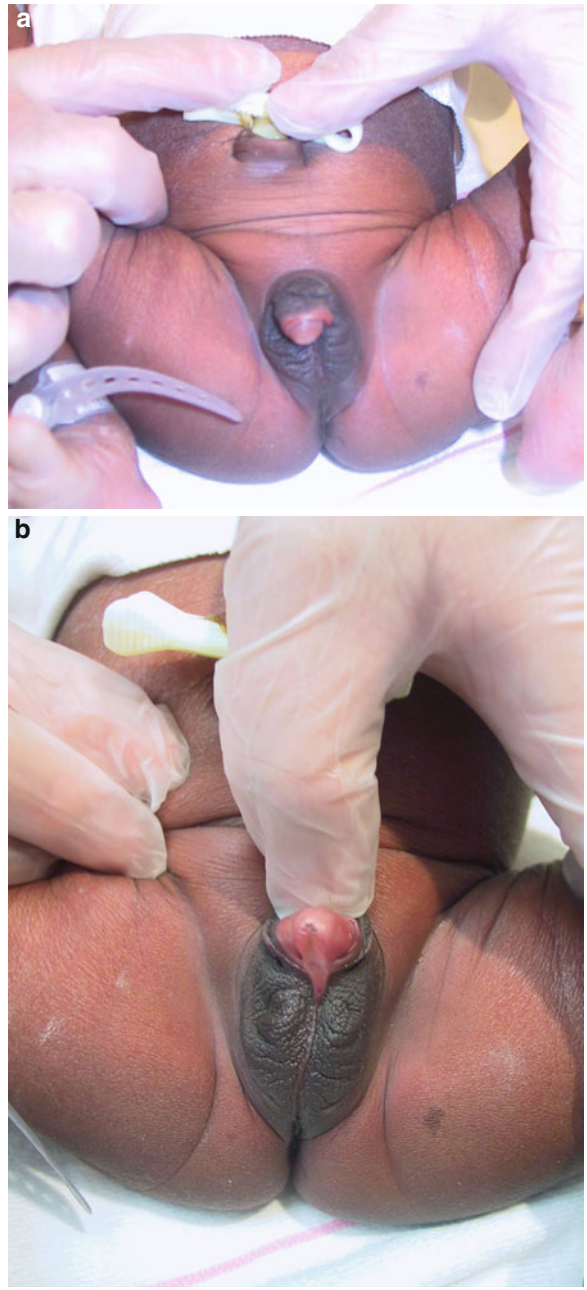

Fig. 2 (**a**, **b**) A newborn with congenital adrenal hyperplasia showing ambiguous genitalia. Newborn screening from filter paper showed total 17OHP of >240 ng/mL (normal <33). A pair of intron 2 mutations were detected by PCR

Congenital Cutis Laxa

Congenital cutis laxa is a rare inherited connective tissue disorder manifested by inelastic, loose, pendulous skin, giving the appearance of premature aging (Andiran et al. 2002).

Synonyms and Related Disorders

Cutis laxa, Debre type; Cutis laxa with growth and developmental delay

Genetics/Basic Defects

1. Genetic heterogeneity
   a. Autosomal recessive cutis laxa, a genetically heterogeneous condition: the most common type
      i. Type I autosomal recessive cutis laxa: less frequent than type II
      ii. Type IIA autosomal recessive cutis laxa (cutis laxa, Debre type; cutis laxa with growth and developmental delay; cutis laxa with or without congenital disorder of glycosylation)
      iii. Type IIB: cutis laxa with progeroid features
   b. Autosomal dominant cutis laxa
   c. X-liked recessive cutis laxa
      i. Previously called occipital horn syndrome
      ii. At present, best termed as Ehlers–Danlos syndrome type IX
2. Biochemical and molecular defects (Loeys et al. 2002)
   a. Autosomal recessive cutis laxa type I: Molecular studies in a large consanguineous Turkish family demonstrated the presence of a homozygous missense mutation (T998C) in the fibulin-5 (*FBLN5*) gene, resulting in a serine-to-proline (S227P) substitution in the fourth calcium-binding epidermal growth factor–like domain of fibulin-5 protein
   b. Type IIA autosomal recessive cutis laxa
      i. Caused by mutation in the ATPase, H + transporting, lysosomal, V0 subunit A2 gene (ATP6V0A2)
      ii. A combined disorder of N- and O-linked glycosylation has been described in children with congenital cutis laxa in association with severe central nervous system involvement, brain migration defects, seizures, and hearing loss (Morava et al. 2008).
      iii. Type IIB: caused by mutation in the *PYCR1* gene
   c. Autosomal dominant cutis laxa
      i. Can be caused by mutations in the elastin gene
      ii. Molecular heterogeneity cannot be excluded
   d. X-linked recessive cutis laxa (Byers et al. 1980; Gorlin and Cohen 1990)
      i. Caused by mutations in the *ATP7A* gene
      ii. Characterized by diminished activity of lysyl oxidase in the skin from affected males
      iii. Reduced serum copper and ceruloplasmin in affected males, suggesting that the lysyl oxidase deficiency may be secondary to a defect in copper metabolism
      iv. Now known to be allelic to Menkes disease

Clinical Features

1. Autosomal recessive cutis laxa (Gorlin 1990)
   a. More common than the autosomal dominant form

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b. Autosomal recessive cutis laxa type I
   i. The poorest prognosis
   ii. Pulmonary emphysema
   iii. Umbilical and inguinal hernias
   iv. Gastrointestinal and vesicourinary tract diverticuli
c. Autosomal recessive cutis laxa type II, also called cutis laxa with joint laxity and developmental delay
d. Characteristic facies
   i. Appearing aged due to accentuation of skin folds
   ii. Downward slanting palpebral fissures
   iii. Blepharochalasis and, at times, ectropion, adding to the aged appearance
   iv. A broad flat nose
   v. Sagging cheeks
   vi. Long upper lip
   vii. Short columella
   viii. Large ears
e. Skin
   i. Prominent skin folds (loose skin) around the knees, abdomen, and thighs
   ii. No hyperelasticity, fragility, or difficulty in wound healing
f. Skeletal muscular abnormalities
   i. Dislocation of the hips
   ii. Joint hyperextensibility
   iii. Hernia
   iv. Osteoporosis
g. Cardiopulmonary abnormalities
   i. Severe pulmonary emphysema resulting from generalized elastolysis
      a) Tachypnea
      b) Pneumonitis
      c) Airway obstruction
      d) Severe hypoxia
      e) Respiratory failure
   ii. Cardiac abnormalities
      a) Right ventricular enlargement
      b) Cor pulmonale
      c) Bundle branch block
      d) Pulmonary artery hypoplasia and stenosis
      e) Dilated and tortuous carotid, vertebral, and pulmonary arteries
      f) Aortic aneurysm
h. Other abnormalities
   i. Hernias
      a) Inguinal
      b) Diaphragmatic
      c) Ventral
      d) Inguinal
   ii. Hollow viscus (pharynx, esophagus, and rectum) diverticula
   iii. Oral abnormalities
      a) Deep and resonant voice secondary to lax vocal cords
      b) Loose oral and pharyngeal mucosa
   iv. Genitourinary abnormalities
      a) Bladder diverticula
      b) Vaginal prolapse
   v. Dental caries
i. A shorter life span

2. Autosomal dominant cutis laxa
   a. Less common than the autosomal recessive form
   b. Cutaneous laxity
   c. Clinical features presenting in infancy (Andiran et al. 2002)
      i. Intrauterine growth retardation
      ii. Delayed fontanelle closure
      iii. Ligamental laxity
      iv. Episodes of edema may precede the skin changes, usually within the first 2 months of life.
      v. Aging appearance by the end of the second year
      vi. Pulmonary emphysema common due to a loss of elastic tissue in the lungs
   d. Skin changes presenting in adulthood
      i. Usually no internal defects
      ii. Having a normal life expectancy
   e. Aging appearance
      i. Drooping of eyelids
      ii. Sagging facial skin
      iii. Accentuation of the nasolabial and other facial folds
      iv. Often hooked nose with everted nostrils
      v. Long philtrum
   f. Few complications
      i. Hoarseness
      ii. Pulmonary artery stenosis

iii. Mitral valve prolapse
iv. Hernia
v. Bronchiectasis
vi. Joint dislocations
vii. Tortuosity and dilatation of carotid arteries and aorta
viii. Dilatation of sinuses of Valsalva
ix. Coarctation of the aorta

g. Normal life span

3. X-linked recessive cutis laxa (Brown et al. 1982)
   a. Long and thin face, neck, and trunk
   b. Mild hyperelastic (but not lax) and bruisable skin with resultant atrophic scars
   c. Musculoskeletal abnormalities
      i. Inferior cranial spurs (occipital horns)
         a) A constant feature
         b) May be palpated
         c) May become larger with age
         d) May represent ectopic bone formation within the trapezius and sternocleidomastoid aponeuroses
      ii. Skeletal dysplasia most prominent at the wrists and elbows
      iii. Limitation of extension of the elbows, shoulders, knees
      iv. Hypermobility of the finger joints
      v. Pes planus
      vi. Genu valga
      vii. Pectus excavatum or carinatum (40%)
   d. Obstructive uropathy secondary to bladder diverticula with bladder neck obstruction (60–70%)
   e. Various hernias (hiatal, femoral, and inguinal) (35%)
   f. Chronic diarrhea (40%)
4. Differential diagnosis
   a. Wrinkling skin syndrome
      i. A rare autosomal recessive disorder of the connective tissue
      ii. Wrinkled skin over abdomen and on the dorsum of the hands and feet
      iii. Poor skin elasticity in affected areas
      iv. Increased palmar and plantar creases
      v. A prominent venous pattern on the chest
      vi. Mental retardation
      vii. Microcephaly
      viii. Hypotonia
      ix. Musculoskeletal abnormalities
   b. De Barsy syndrome (Andiran et al. 2002; Gorlin 1990)
      i. Cutis laxa (wrinkled atrophic skin)
      ii. Retarded psychomotor development
      iii. Corneal clouding due to degeneration of the tunica elastica of the cornea
      iv. Intrauterine growth retardation
      v. Pseudoathetoid movement
      vi. Muscular hypotonia
      vii. Hypermobility of small joints
   c. Costello syndrome (Davies and Hughes 1994)
      i. Nasal papillomata
      ii. Coarse facies
      iii. Mental retardation
      iv. Growth retardation
      v. Cutis laxa
   d. SCARF syndrome (Koppe et al. 1989)
      i. An X-linked recessive disorder
      ii. Skeletal abnormalities
         a) Craniostenosis
         b) Enamel hypoplasia, hypocalcification of the teeth
         c) Short sternum
         d) Pectus carinatum
         e) Abnormally shaped vertebrae
         f) Abnormal modeling of long tubular bones
      iii. Cutaneous abnormalities
         a) Cutis laxa
         b) Wide-spaced nipples
         c) Diastasis recti
         d) Umbilical hernia
      iv. Ambiguous genitalia
         a) Micropenis
         b) Perineal hypospadias
      v. Retardation: mild to moderate psychomotor retardation
      vi. Facial abnormalities
         a) Multiple hair whorls
         b) Epicanthal folds
         c) Ptosis
         d) High and broad nasal root
         e) Low-set and posteriorly rotated ears
         f) Small chin

Diagnostic Investigations

1. Radiography
   a. Autosomal recessive cutis laxa
      i. Presence of a variety of hernias
         a) Femoral
         b) Inguinal
         c) Obturator
         d) Hiatal
      ii. Eventrations of the diaphragm
      iii. Rectal and uterine prolapse
      iv. Common intrathoracic abnormalities
         a) Hyperexpansion of the lungs
         b) Emphysema which may lead to cor pulmonale and death in childhood
         c) Upper airway obstruction caused by excessively lax vocal cords, leading to congestive heart failure
         d) Frequent peripheral pulmonary artery stenosis and aortic dilatation
      v. Diverticula involving the entire bowel but no functional significance
      vi. Diverticula of the urinary tract predisposing to infection or causing obstruction
      vii. Arteriographic changes
         a) Peripheral pulmonary stenosis
         b) Dilatation and tortuosity of the aorta
         c) A peculiar corkscrew appearance of the peripheral systemic arteries, similar to the arterial changes seen in Menkes syndrome
   b. X-linked recessive cutis laxa (Gorlin 1990)
      i. Occipital exostosis (horns) symmetrically located on each side of the foramen magnum
      ii. Short clavicles with a widened medullary cavity
      iii. Hammer-shaped distal extremities
      iv. Focal hyperostosis of the femora at sites of tendon and ligament insertion
      v. Carpal fusion involving capitate-hamate and trapezium-trapezoid coalescence (over 50%)
      vi. Deformation of humerus, radius, ulna, tibia, fibula (90%)
      vii. Osteoporosis (70%)
      viii. Narrowing of rib cage (65%)
      ix. Dislocation of radial head (40%)
      x. Mild platyspondyly
      xi. Coxa valga
      xii. Flattening of acetabular roofs
2. Histopathological abnormality: fragmentation and paucity of elastic fibers in the skin
3. X-linked cutis laxa
   a. Non-molecular testing
      i. Low serum copper concentration
      ii. Low serum ceruloplasmin concentration
      iii. Copper transport studies in cultured fibroblasts: impaired cellular copper exodus demonstrated by increased cellular copper retention in pulse-chase experiments with radiolabeled copper
      iv. Plasma and CSF catecholamine analysis: abnormal levels reflecting partial deficiency of dopamine-beta-hydroxylase, a copper-dependent enzyme critical for catecholamine biosynthesis
      v. Low activity of a copper-dependent enzyme, lysyl oxidase
   b. Molecular genetic testing
      i. Mutation analysis: multiplex PCR analysis, available on a clinical basis, to detect large *ATP7A* deletions
      ii. Sequence analysis: direct sequence analysis of the *ATP7A* coding region and flanking intron sequences, available on a clinical basis
      iii. Mutation scanning: heteroduplex analysis, available on a clinical basis, to detect small mutations

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal recessive cutis laxa: 25%
      ii. Autosomal dominant cutis laxa: not increased unless a parent is affected
      iii. X-linked recessive cutis laxa:
         a) When the mother is a carrier: 50% risk of brother will be affected and 50% of sisters carriers
         b) When mother is not a carrier: the recurrence risk is low but greater than that for the general population because the risk of germline mosaicism in mother is not known.

   b. Patient's offspring
      i. Autosomal recessive cutis laxa: not increased unless the spouse is a carrier or affected
      ii. Autosomal dominant cutis laxa: 50%
      iii. X-linked recessive cutis laxa: Males with occipital horn syndrome will pass the disease-causing gene to all of their daughters and none of their sons.
2. Prenatal diagnosis
   a. DNA-based analysis on fetal DNA obtained from amniocentesis or CVS for the previously characterized disease-causing mutation
   b. Fetal sex determination for X-linked recessive cutis laxa (occipital horn syndrome)
3. Management (Nahas et al. 1999; Strohecker 1995)
   a. Supportive therapy: antibiotic prophylaxis for bladder infection
   b. Surgery for bladder diverticula
   c. Plastic surgery to improve aging appearance
      i. Serial excisions of the skin
      ii. Blepharoplasty
      iii. Rhytidectomy
      iv. Rhinoplasty
      v. Shortening of the upper lip
      vi. Earlobe reduction
      vii. Neck lift
      viii. Correction of lower eyelid laxity, epiphora, and upper eyelid ptosis

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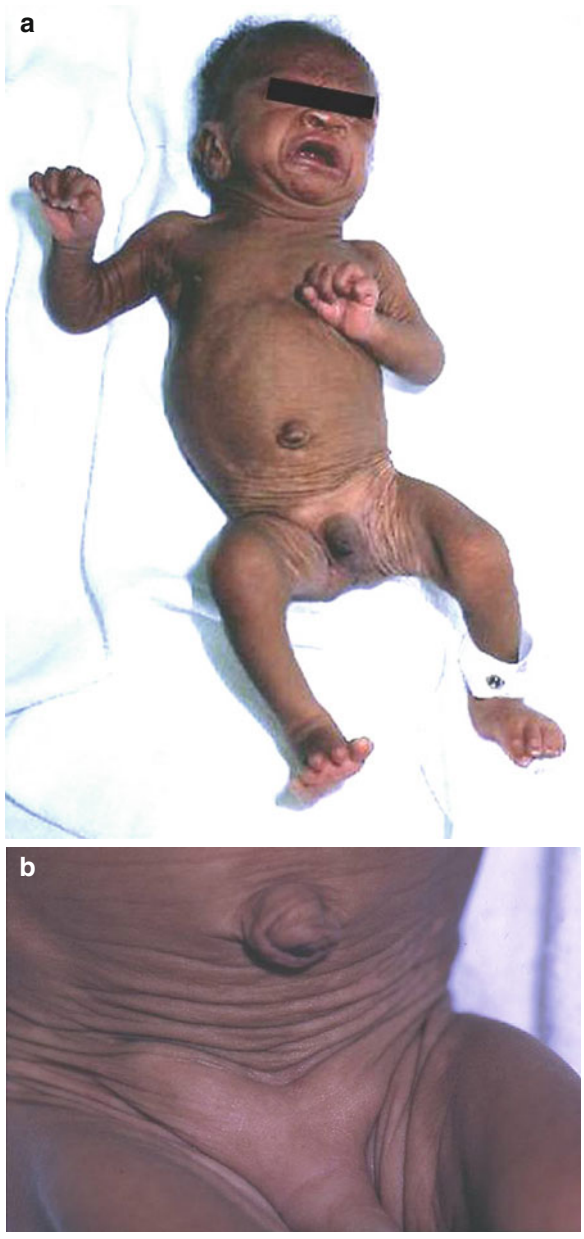

Fig. 1 (**a**, **b**) An infant with cutis laxa showing redundancy of skin folds and bilateral hernias

Fig. 2 A young girl with cutis laxa showing redundancy of the skin folds, short columella, long philtrum, and sagging of the lower chin and prominent loose skin folds of the trunk

Fig. 3 (**a**, **b**) A 10-year-old girl with cutis laxa showing redundancy of the skin, sagging of the upper lids, short columella, long philtrum, and sagging skin folds over trunk

Congenital Cytomegalovirus Infection

Congenital cytomegalovirus infection is the most common congenital infection in neonates in the USA, affecting approximately 0.5–1.5% of all live births and 30,000–40,000 newborns annually. Congenital infections result from transplacental transmission of cytomegalovirus (CMV).

Synonyms and Related Disorders

Intrauterine cytomegalovirus infection of fetus

Genetics/Basic Defects

1. Human cytomegalovirus
   a. A DNA virus belonging to the herpesvirus group (herpes simplex, varicella zoster, Epstein–Barr) (Brown and Abernathy 1998; Kuhlmann and Autry 2001)
   b. Ability of the virus (Pass 2002)
      i. To destroy host cells (lytic infection)
      ii. To infect a wide range of cells and tissues
      iii. To evade and interfere with host defense mechanisms
      iv. To persist indefinitely in the host
      v. To infect and destroy cells during productive infection (with release of progeny virus)
2. Transmission of CMV (Kuhlmann and Autry 2001)
   a. Horizontal transmission: Close intimate contact with another person shedding the virus in body fluids (saliva, blood, cervical secretions, semen, urine, or respiratory droplets)
   b. Vertical transmission: from mother to infant
      i. In utero by transplacental passage of maternal blood-borne virus
      ii. At birth by passage through an infected maternal genital tract
      iii. Postnatally by ingestion of CMV-positive human milk from seropositive mothers
   c. Infected organ or bone marrow transplantation
   d. Infected blood transfusion from CMV-seropositive donors
3. Primary sources of CMV infection for women of childbearing age
   a. Young children
   b. Sexual contacts
4. Types of CMV infection (Kuhlmann and Autry 2001)
   a. Primary (first experience)
   b. Secondary (recurrent)
      i. Reactivation of the original endogenous CMV
      ii. Reinfection with a new strain of CMV
   c. Latent infection: sites at kidney, bone marrow, monocytes
5. The most common vertically transmitted viral infection from mother to fetus in pregnancy (Kuhlman 2001)
   a. Recurrent infection: 1% risk of vertical transmission
   b. Primary infection: 1–4% risk of vertical transmission
6. Symptomatic congenital infections observed primarily among women undergoing a primary infection
7. Greatest risk occurring with infection during the first 22 weeks of gestation

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8. Congenitally infected newborns: may shed the virus for many years
9. Perinatal CMV infection acquired during birth or from mother's milk: not associated with newborn illness or CNS sequelae, except perhaps in very preterm newborns who have very low levels of passively acquired CMV antibody at the time of infection

Clinical Features

1. Symptomatic at birth in 5–10% of congenital CMV infections (Enders et al. 2001)
   a. Approximately 20% of these will die
   b. Ninety percent of survivors will develop major neurological sequelae
2. Asymptomatic or "silent" congenital infections at birth in vast majority (85–90%) of cases. 10–15% of the asymptomatic newborns will be afflicted by late sequelae such as mental retardation, deafness or hearing defects, usually during the first 2 years of life. (Enders et al. 2001)
3. Non-neurologic symptoms at birth
   a. Petechiae (most common non-neurologic symptom)
   b. Thrombocytopenia
   c. Purpura
   d. Ecchymoses
   e. Splenomegaly
   f. Hepatomegaly
   g. Jaundice
   h. Intrauterine growth retardation
   i. Chorioretinitis
   j. Pneumonitis
   k. Anemia
   l. Nonimmune hydrops
4. Neurologic symptoms at birth
   a. Hypotonia
   b. Lethargy
   c. Jitteriness
   d. Split sutures
   e. Immature primitive reflexes
   f. Feeding difficulties
   g. Microcephaly: the most specific predictor of mental retardation and major motor disability
   h. Seizures
5. Eye manifestations (Metz 2001)
   a. Chorioretinitis resulting in a chorioretinal scar
   b. Corneal opacities
   c. Bilateral anterior polar cataracts
   d. Optic nerve hypoplasia and optic nerve coloboma
   e. Cyclopia and anophthalmia
6. Later neurologic symptoms
   a. Sensorineural hearing loss
   b. Learning disability
   c. Mental retardation
   d. Cerebral palsy
7. Prognosis
   a. Neonatal clinical abnormalities expected to resolve spontaneously within weeks, except for those involving the CNS and hearing
   b. A leading cause of mental retardation and sensory impairment (50–90% of symptomatic newborns) and sensorineural hearing loss (7–15% of asymptomatic infants)
   c. An important cause of cerebral palsy and retinal damage
8. Long-term sequelae of congenital cytomegalovirus infection in children with and without symptoms at birth (Sharon and Schleiss 2007; Schleiss 2008)
   a. Overall incidence
      i. Symptomatic: 50–90%
      ii. Asymptomatic: 10–15%
   b. Hearing loss
      i. Symptomatic: 50–60%
      ii. Asymptomatic: 7–15%
   c. Cognitive deficits
      i. Symptomatic: 50–70%
      ii. Asymptomatic: ~4%
   d. Microcephaly
      i. Symptomatic: 35–40%
      ii. Asymptomatic: ~2%
   e. Ocular abnormalities
      i. Symptomatic: 25–50%
      ii. Asymptomatic: ~3%
   f. Seizures
      i. Symptomatic: 15–20%
      ii. Asymptomatic: ~1%
   g. Mild to moderate motor deficits
      i. Symptomatic: 25–30%
      ii. Asymptomatic: <1%
   h. Severe motor deficits
      i. Symptomatic: 15–25%
      ii. Asymptomatic: <1%
9. Maternal primary CMV infection
   a. Asymptomatic: vast majority of pregnant women

   b. Symptomatic (mononucleosis-like syndrome) in approximately 10% of infected pregnant patients
      i. Fever
      ii. Fatigue/malaise
      iii. Myalgia
      iv. Pharyngitis
      v. Cough
      vi. Nausea
      vii. Headache

Diagnostic Investigations

1. Children with symptomatic congenital CMV infection (Pass 2002)
   a. Cytomegalic inclusion bodies in the urine
   b. Elevated alanine aminotransferase (ALT >80 IU/mL)
   c. Thrombocytopenia (<100,000/mcL)
   d. Conjugated hyperbilirubinemia (direct bilirubin >2 mg/dL)
   e. Anemia
   f. Elevated CSF protein (>120 mg/dL)
   g. Abnormal CT scan (most common neurologic sign and the most sensitive predictor for mental retardation)
      i. White matter lucencies
      ii. Ventriculomegaly
      iii. Intracranial calcifications (usually periventricular)
      iv. Destructive encephalopathy
      v. Brain atrophy
      vi. Neuronal migration disorders
2. Evidence of infection with CMV (Kuhlman 2001)
   a. Fourfold rise in anti-CMV IgG titers
   b. Seroconversion from negative to positive
   c. Sensitivity of the CMV IgM assays (50–90%). The IgM titers may not become positive during acute infection.
3. Viral isolation (Kuhlman 2001)
   a. The most sensitive method to diagnose CMV infection
   b. Culture of CMV from virtually all body fluids, including saliva and urine of the newborn, semen, and cervicovaginal secretions
   c. Detection of CMV within the first 3 weeks of life: considered proof of congenital CMV infection
4. Identification of CMV DNA through PCR (sensitivity of 75–100%)
5. Newborn screening for congenital cytomegalovirus infection (Bale 2010)
   a. Universal screening methods by using polymerase chain reaction (PCR) analysis of newborn dried blood spots (Boppana et al. 2010)
   b. Cytomegalovirus infection
      i. Accounts for as much or more disability over the past 50 years than was associated with congenital rubella syndrome
      ii. Represents the most common nongenetic cause of permanent hearing loss among children in the USA
   c. The most effective strategy for reducing CMV-induced sensorineural hearing loss, as well as for eliminating CMV-associated neurodevelopmental disability, will not be universal screening but prevention of congenital CMV infection (Pass et al. 2009).

Genetic Counseling

1. Recurrence risk
   a. Preconceptional immunity to CMV provides substantial protection against intrauterine transmission and severe fetal infection.
   b. Presence of maternal humoral antibody: conferring no fetal protection in subsequent reinfection or reactivation
2. Prenatal diagnosis
   a. Prenatal ultrasonography
      i. Intrauterine growth retardation
      ii. Microcephaly
      iii. Ventriculomegaly
      iv. Periventricular calcifications
      v. Intrahepatic calcifications
      vi. Nonimmune hydrops
      vii. Fetal Ascites
      viii. Pericardial effusion
      ix. Hepatosplenomegaly
      x. Echogenic bowel
      xi. Cardiomegaly
      xii. Oligohydramnios
      xiii. Placentomegaly
   b. Prenatal diagnosis of congenital CMV infection by combined detection of CMV-DNA and CMV-IgM in fetal blood or by combined testing of AF

and fetal blood for CMV-DNA and IgM antibodies (sensitivity of 100%) (Enders et al. 2001)

c. Negative results of CMV culture or PCR in the amniotic fluid cannot formally exclude intrauterine infection (Bodéus et al. 1999).

d. Prenatal diagnosis of CMV infection remains a "long-standing problem still seeking a solution" as long as no assistance (treatment or prevention) can be offered to the pregnant women.

3. Management

a. Prevention

i. Complicated because both primary and secondary maternal infections give rise to disease in the offspring and absence of characteristic symptoms in CMV-infected mothers excludes clinical recognition of at-risk pregnancies.

ii. Routine screening of pregnant patients for CMV status: not currently recommended because no effective antiviral therapy is available during gestation and also there is no means to predict the outcome in an infected fetus

iii. Risk to CMV infection for women in high-risk environments (day-care centers, nurseries, elementary schools, or health care facilities)

iv. Strict hygiene practices for seronegative women to reduce the risk for the infection

b. Prospects of intervention (Cheeran et al. 2009)

i. Antiviral drugs (Ganciclovir, Valganciclovir, Foscarnet, Cidofovir, CMV immune globulin) are available for treatment of congenital CMV infection, and there is evidence that therapy ameliorates the severity of one of the CNS complications of infection, sensorineural hearing loss. Long-term neurodevelopmental follow-up studies should further clarify the value of antiviral therapy in congenitally infected infants.

ii. Uncontrolled studies of therapy in utero with CMV immune globulin have suggested an impact on neuropathogenesis, and controlled trials should be conducted with pregnant women.

iii. CMV vaccines may hold the greatest promise in reducing the neurodevelopmental consequences of congenital infection, although the immune correlates of protection of the fetus remain incompletely defined.

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Fig. 1 (**a**, **b**) A neonate with blue berry muffin skin lesions (generalized purpura) due to cytomegalovirus infection. He died 20 h after birth. CMV inclusions were noted in kidneys, lungs, liver, pancreas, thyroid, brain and eyes, and also in the urine. Photomicrograph of the kidney shows many tubular epithelial cells containing large cytomegalic inclusion bodies

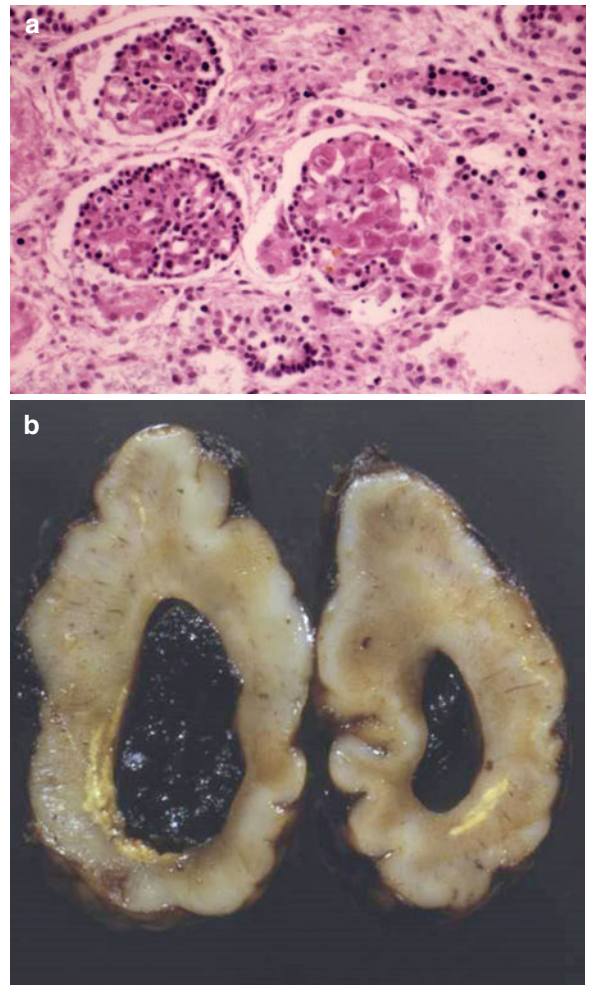

Fig. 2 (**a**, **b**) Photomicrograph of the kidney (macerated fetus, 16 weeks gestation). Even though the tissue is macerated, many cytomegalic inclusion bodies are demonstrable. Coronal section of the brain (frontal lobe) showing ventricular hemorrhage and focal encephalomalacia (chalky white discoloration) due to cytomegalovirus infection

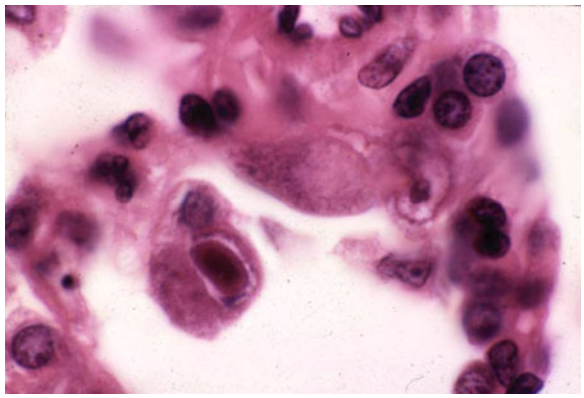

Fig. 3 Photomicrograph of premature lung of a different patient showing a single large cytomegalic inclusion body

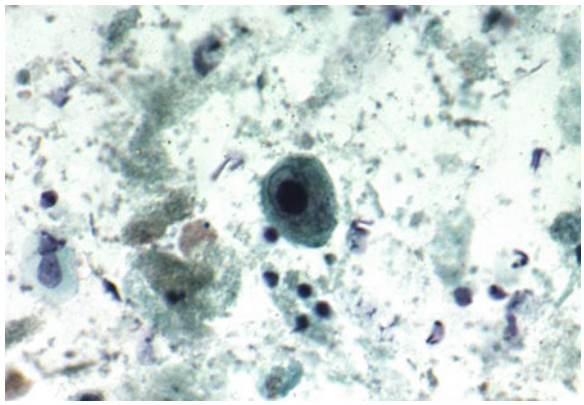

Fig. 4 One cytomegalic inclusion body in the urine sediment in another patient

Fig. 5 A macerated stillborn with hydrops fetalis from congenital CMV infection

Fig. 6 (**a**, **b**) An infant with CNS involvement and chorioretinitis from congenital CMV infection

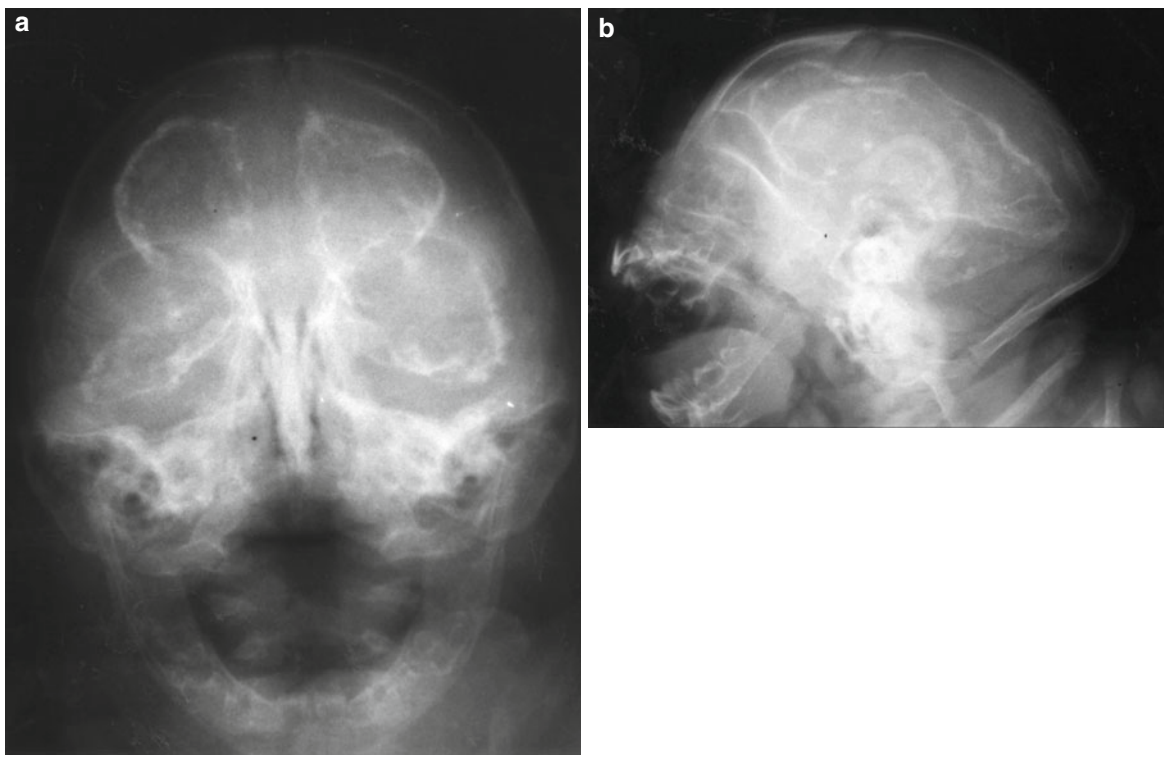

Fig. 7 (**a**, **b**) Skull radiographs of another patient with congenital CMV infection showing microcephaly and typical intracranial ventricular subependymal calcifications

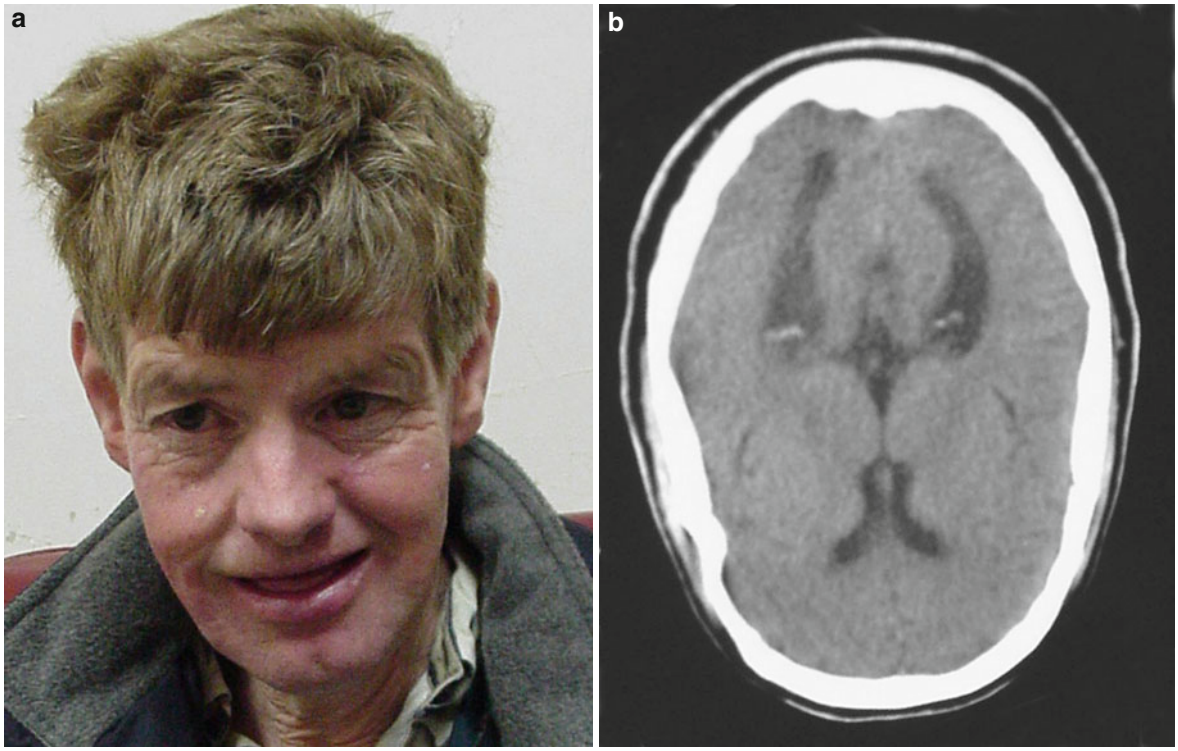

Fig. 8 (**a**, **b**) An adult with congenital CMV infection showing mental retardation and intracranial calcifications by CT scan

Congenital Generalized Lipodystrophy

Congenital generalized lipodystrophy (CGL), also called Berardinelli–Seip syndrome (BSCL) (Berardinelli 1954; Seip and Tryqstad 1963), is an extremely rare genetic disorder characterized by extreme paucity of adipose tissue from birth, extreme insulin resistance, hypertriglyceridemia, hepatic steatosis, and early onset of diabetes (Agarwal et al. 2002). Its prevalence is estimated to be 1 in 200,000 (Portugal) to 1 in 12 million people (USA) (Mandal et al. 2006).

Synonyms and Related Disorders

Berardinelli–Seip congenital lipodystrophy

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Garg 2004)
2. Existence of two loci in a gene for congenital generalized lipodystrophy (Berardinelli–Seip congenital lipodystrophy)
   a. Berardinelli–Seip congenital lipodystrophy 1 (BSCL1)
      i. Identification of the aberrant gene, 1-acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2*) in patients from several pedigrees in which the lipodystrophy was linked to chromosome 9q34
      ii. Several homozygous or compound heterozygous mutations in the *AGPAT2* gene identified in affected patients
      iii. *AGPAT2* (1-acylglycerol-3-phosphate O-acyltransferase 2)
         a) Encodes the enzyme AGPAT2 that is responsible for the production of an important intermediate in the synthesis of triglycerides or fat
         b) Mutations of *AGPAT2*: may cause CGL by inhibiting the fat synthesis and storage in adipocytes (fat cells)
   b. Berardinelli–Seip congenital lipodystrophy 2 (BSCL2)
      i. Identification of another disease locus (*BSCL2*) which is mapped to chromosome 11q13
      ii. Identification of mutations of *BSCL2* gene in all families linked to 11q13
      iii. *BSCL2* (*Seipin*) gene
         a) Highly expressive in the brain and testis
         b) Encodes a protein whose function remains unknown
   c. Berardinelli–Seip congenital lipodystrophy X (BSCLX): specific genetic locus has not been identified (Van Maldergem et al. 2002)
3. Several other genes are responsible for different types of inherited lipodystrophies:
   a. Lamin A/C (*LMNA*) gene in familial partial lipodystrophy Dunnigan variety (autosomal dominant familial partial lipodystrophy) mapped to 1q21-22
   b. *PPAR-γ* (peroxisome proliferator-activated receptor-γ) gene in autosomal dominant familial partial lipodystrophy

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4. Cause
   a. CGL is caused by mutations in *BSCL2*, *AGPAT2*, and other as yet unmapped genes.
   b. This genetic heterogeneity is also accompanied by phenotypic heterogeneity.
5. Proposed pathogenesis: Genetic defect results in poor growth and development of metabolically active adipose tissue with preservation of mechanical disposition of the adipose tissue (Garg et al. 1999; Premkumar et al. 2002)

Clinical Features

1. BSCL1 (Garg 2000, 2004; Kobashi et al. 2007)
   a. Prevalent in African-Americans
   b. Less severe
   c. Usually comes to clinical attention in the second or third decade of life
   d. Demonstrates marked lack of metabolically active adipose tissue in subcutaneous tissues, muscles, bone marrow, and intra-abdominal and intrathoracic regions
   e. Normal intelligence
2. BSCL2
   a. Slightly more common than BSCL1 worldwide
   b. More severe
   c. Onset in the neonatal period or early
   d. Demonstrates marked lack of metabolically active adipose tissue in subcutaneous tissues, muscles, bone marrow, and intra-abdominal and intrathoracic regions
   e. In addition, characterized by a paucity of adipose tissue from anatomical areas in which it serves a mechanical function such as the palms, soles, orbits, scalp, and periarticular regions (Simha and Garg 2003)
3. BSCLX (Van Maldergem et al. 2002)
   a. A very rare type
   b. Tends to be severely affected
   c. Comes to clinical attention in early infancy
4. Extreme paucity (near complete absence) of adipose tissue from birth, resulting in a generalized muscular appearance (an essential diagnostic criterion)
5. Characteristic features during early childhood
   a. Accelerated linear growth
   b. Voracious appetite
   c. Increased basal metabolic rate (hypermetabolism)
   d. Advanced bone age
6. Acanthosis nigricans (dark velvety pigmentation of the skin)
   a. Common occurrence
   b. Usually appears by age 8
   c. May be widespread, involving the neck, axillae, groin, and trunk
   d. Can eventually cause skin tag formation
7. Umbilical hernia: common
8. Hepatosplenomegaly
   a. Almost universal presence of hepatomegaly from fatty liver, ultimately leading to cirrhosis
   b. Splenomegaly common
9. Acromegaloid appearance
   a. Enlarged hands and feet
   b. Prominent mandible
10. Premature thelarche and adrenarche
11. Affected women (Garg et al. 1999)
   a. Virilization (clitoromegaly and hirsutism)
   b. Oligo-amenorrhea
   c. Polycystic ovaries in postpubertal female patients
   d. Successful pregnancy rare
12. Affected males with normal reproductive potential
13. Multiple focal lytic lesions in the appendicular bones in postpubertal patients
14. Severe fasting and postprandial hyperinsulinemia and marked hypertriglyceridemia resulting in chylomicronemia, eruptive xanthomas, acute pancreatitis and predisposing to premature atherosclerosis
15. Abnormal glucose intolerance and diabetes mellitus develop during puberty or early adolescence. Diabetic nephropathy and nephropathy may develop during adulthood
16. Rare hypertrophic cardiomyopathy
17. Mental retardation in a few patients
18. Clinical diagnosis criteria (Van Maldergem 2010): three major criteria or two major criteria plus two or more minor criteria make a diagnosis of BSCL very likely
   a. Major criteria
      i. Lipoatrophy affecting the trunk, limbs, and face
         a) Generalized lipodystrophy: apparent at birth.

b) In some individuals, the face may be normal at birth with lipoatrophy becoming apparent during the first months of life.
c) Lipoatrophy gives an athletic appearance, especially because skeletal muscle hypertrophy is also present.

ii. Acromegaloid features:
a) Gigantism
b) Muscular hypertrophy
c) Advanced bone age
d) Prognathism
e) Prominent orbital ridges
f) Enlarged hands and feet
g) Clitoromegaly
h) Enlarged external genitalia in the male

iii. Hepatomegaly
a) Secondary to fatty liver early on
b) Progresses to cirrhosis late in the disease course

iv. Elevated serum concentration of triglycerides
a) Serum concentration of triglycerides can be elevated up to 80 g/L.
b) Sometimes associated with hypercholesterolemia.

v. Insulin resistance
a) Elevated serum concentrations of insulin and C-peptide may occur starting in the first years of life.
b) Overt clinical diabetes mellitus usually develops during the second decade.
c) Its early clinical expression is acanthosis nigricans of the groin, neck, and axillae, which may have, in some cases, a verrucous appearance.

b. Minor criteria
i. Hypertrophic cardiomyopathy: may be present in infancy or develop later in life
ii. Psychomotor retardation: mild (IQ: 50–70), moderate (IQ: 35–50)
a) Mild-to-moderate intellectual impairment observed in approximately 80% of individuals with mutations in *BSCL2*
b) Intellectual impairment observed in only 10% of individuals with mutations in *AGPAT2*

iii. Hirsutism
a) Manifests with low frontal and posterior hairline
b) Apparently independent of hormonal stimulation

iv. Precocious puberty in females: In a series of 75 individuals with BSCL, three females underwent puberty before age 7 years (Van Maldergem et al. 2002)

v. Bone cysts
a) Occur in 8–20% of affected individuals and have a polycystic appearance in X-rays
b) Located in the epiphyseal and metaphyseal regions of the long bones: often diagnosed during the second decade
c) Are mostly observed in individuals with mutations in *AGPAT2*

vi. Phlebomegaly: Prominence of the veins of the lower and upper limbs is observed, in part because of the lack of subcutaneous fat

19. Differential diagnosis with other genetic lipodystrophy (Agarwal and Garg 2006)
a. Other autosomal recessive lipodystrophies
i. Lipodystrophy associated with mandibuloacral dysplasia: characterized by hypoplasia of the mandible and clavicles and by acro-osteolysis (resorption of terminal phalanges) and other features (Simha and Garg 2002)
a) Partial lipodystrophy (type A pattern): *LMNA* (lamin A/C) mutations
b) Generalized lipodystrophy (type B pattern): *ZMPSTE24* (zinc metalloproteinase) mutations
c) Other varieties

ii. Lipodystrophy associated with SHORT (*s*hort stature, *h*yperextensibility of joints and/or inguinal hernia, *o*cular depression, *R*ieger anomaly, and teething delay) syndrome: characterized by defects in multiple organs and loss of adipose tissue

iii. Lipodystrophy associated with neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome) (Pivnick et al. 2000)

b. Autosomal dominant lipodystrophies
i. Familial partial lipodystrophy (FPL): characterized by variable loss of body fat from

the extremities as well as from the trunk. The diagnosis is made easily in women but is difficult in men because even many normal men appear muscular. The diagnosis can be suspected in nonobese patients with early onset of diabetes and hypertriglyceridemia, particularly if they have marked loss of fat from the extremities and hips.
   a) Dunnigan variety (FPLD): LMNA (lamin A/C) mutations
   b) FPL associated with *PPARG* (peroxismal proliferator-activated receptor γ) mutations
   c) FPL associated with AKT2 (v-AKT murine thymoma oncogene homolog 2) mutations
   d) Other varieties
ii. Lipodystrophy associated with SHORT syndrome.
iii. Lipodystrophy associated with Hutchinson–Gilford progeria syndrome.
   a) Progressive and generalized loss of body fat during childhood resulting in severe lipodystrophy with increasing age.
   b) Most patients have a de novo synonymous heterozygous Gly608Gly mutation in the *LMNA* gene of paternal origin (Eriksson et al. 2003; De Sandre-Giovannoli et al. 2003).
iv. Puberty-onset generalized lipodystrophy due to *LMNA* mutations.
   a) Puberty-onset of generalized lipodystrophy
   b) Diabetes
   c) Progeroid features
   d) Reported to have novel missense mutations in *LMNA* (Caux et al. 2003)

Diagnostic Investigations

1. Clinical laboratory workup
   a. Marked insulin resistance
   b. Severe hyperinsulinemia
   c. Nonketotic insulin-resistant diabetes mellitus
   d. Hypertriglyceridemia with low serum high-density lipoprotein (HDL) and cholesterol concentration
   e. Chylomicronemia
   f. Markedly low plasma leptin levels
2. MRI (confirmatory) and necropsy (Garg et al. 1999)
   a. An extreme paucity of subcutaneous and intermuscular fat
      i. Intraabdominal sites (omental, mesenteric, and retroperitoneal areas)
      ii. Thoracic cavity (retrosternal, epicardial, and superior mediastinal areas)
      iii. Bone marrow
      iv. Parathyroid glands
   b. In contrast, a peculiar distribution of normal amounts of adipose tissue over whole body
      i. Orbits
      ii. Crista galli
      iii. Palms
      iv. Soles
      v. Scalp
      vi. Perineum
      vii. Vulva
      viii. Epidural area
      ix. Pericalyceal regions of the kidney
      x. Periarticular regions (knee, hip, shoulder, elbow, wrist, and ankle joints)
      xi. Some fat localizes in breasts, tongue, and buccal region
3. Skeletal radiography: Multiple focal lytic lesions appear in appendicular skeletons after puberty
4. Echocardiography to detect hypertrophic cardiomyopathy
5. Molecular genetic analysis of mutations in *BSCL2* (*Seipin*) gene and *AGPAT2* gene

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis (Van Maldergem 2010)
   a. Possible for pregnancy at risk for BSCL caused by *BSCL2* of *AGPAT2* mutations by analysis of fetal cell DNA obtained from amniocentesis or CVS, provided both disease-causing alleles of an affected family member must be identified previously.

   b. Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified.
3. Management (Agarwal and Garg 2006)
   a. Cosmetic management
      i. Facial reconstruction with free flaps, transposition of facial muscle, and silicone or other implants in the cheeks
      ii. Liposuction or lipectomy for removal of excessive facial or neck fat
      iii. Etretinate and fish oil may improve acanthosis in some patients
   b. Diet
      i. Avoidance of weight gain to reduce the risk of developing diabetes and dyslipidemia
      ii. Need sufficient energy to allow for growth and maturation in childhood
      iii. Low-fat diet for extreme hypertriglyceridemia to minimize chylomicron formation
      iv. Reduction in saturated fat and cholesterol intake to reduce LDL or non-HDL cholesterol levels reduces atherosclerosis risk
   c. Hypoglycemic drugs
      i. Require rigorous glycemic control by oral hypoglycemic drugs and/or insulin therapy
      ii. Require large dose of insulin to control hyperglycemia and prevent long-term complications of diabetes, such as nephropathy, retinopathy, neuropathy, and possibly atherosclerosis
   d. Lipid-lowering drugs
      i. Fibrates and, if needed, n-3 polyunsaturated fatty acids
      ii. Avoid estrogens for oral contraception or postmenopausal hormone replacement therapy in women because it can accentuate hypertriglyceridemia
   e. Clinical trial of adipocytes hormone leptin-replacement therapy has shown a marked reduction in the blood glucose and lipids and reverse hepatic steatosis, allowing discontinuation of several medications (Oral et al. 2002)
   f. Elucidation of the pathways underlying genetic lipodystrophies is expected to help in developing innovative therapeutic strategies for treating diabetes, hyperlipidemia, hepatic steatosis, and other metabolic complications

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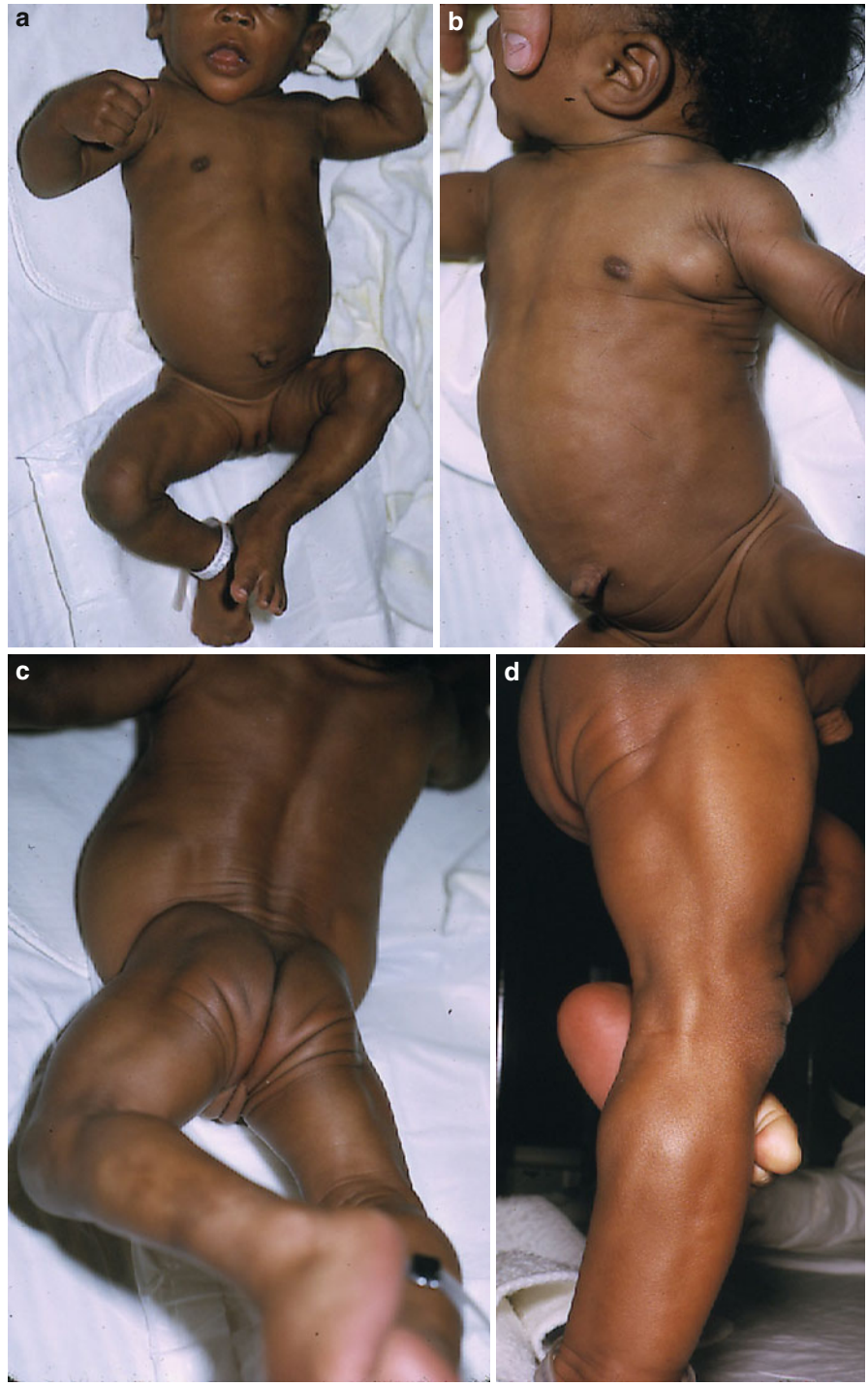

Fig. 1 (**a**–**d**) An infant with congenital generalized lipodystrophy showing extreme paucity (near complete absence) of adipose tissue from birth, resulting in a generalized prominent muscular appearance

Congenital Hemihyperplasia

In 1822, Meckel first described congenital hemihypertrophy. Hemihypertrophy, also called hemihyperplasia, is defined as asymmetric body overgrowth of one or more body parts. The overgrowth may involve an entire half of the body, a single limb, and one side of the face or combinations thereof. There may be accompanying asymmetric visceromegaly. Hemihyperplasia can be isolated or can occur as part of a syndrome.

Synonyms and Related Disorders

Congenital hemihypertrophy

Genetics/Basic Defects

1. The asymmetric overgrowth, traditionally termed "hemihypertrophy," is more accurately referred to as hemihyperplasia, since the pathologic growth process involves an abnormal proliferation of cells (hemihyperplasia), rather than an increase in the size of existing cells (hemihypertrophy)
2. Isolated hemihyperplasia (IHH)
   a. Usually isolated: estimated prevalence as 1 in 13,200 to1 in 86,000 live births
   b. Familial occurrence
3. Part of well-defined syndrome
   a. Beckwith–Wiedemann syndrome
   b. Proteus syndrome
   c. Russell–Silver syndrome
   d. Neurofibromatosis type I (NF I)
   e. Klippel–Trénaunay–Weber syndrome
   f. McCune–Albright syndrome

Clinical Features

1. Clinical characteristics of isolated hemihyperplasia
   a. Birth incidence: 1:86,000 live births
   b. Females outnumber males two to one
   c. Increased birth weight (mean 3.8 kg)
   d. Diagnosis by exclusion
   e. Variable degree of asymmetry (mild cases are easily overlooked)
   f. Asymmetry becoming more pronounced or less noticeable with age with predominance of right-sided overgrowth
   g. Involves a discrepancy in both length and circumference of the affected limb in comparison to the contralateral side
   h. Observation of the enlargement of one kidney, adrenal, testis, or ovary with medullary sponge kidney, often an attendant finding
   i. Nervous system accompaniments: include unilateral peripheral nerve enlargement, sciatica, and hemimegalencephaly with frequent mental retardation
   j. Facial involvement may be present (cheek, lip, nasal, external ear, palpebral fissure, tongue, maxillary, mandibular, palatal, and/or tooth asymmetry)
   k. Natural history of IHH: varies markedly
      i. Average life span.
      ii. Prognoses for long-term survival may be modified by serious associated anomalies.
      iii. Leg length discrepancy may lead to pelvic tilt and scoliosis.
      iv. Renal function may be impaired by medullary sponge kidney.
   l. Predisposition to neoplasia (cancer) in isolated hemihyperplasia: well known

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i. An overall incidence of 5.9%
ii. Embryonal neoplasms: similar to those noted in other overgrowth disorders
a) Wilms tumor: Hemihypertrophy occurs in approximately 3% of Wilms tumor cases
b) Adrenal cell carcinomas
c) Hepatoblastoma
d) Leiomyosarcoma

2. Malformation syndromes associated with hemihyperplasia
a. Beckwith–Wiedemann syndrome
i. Omphalocele
ii. Hypoglycemia
iii. Generalized overgrowth
iv. Macroglossia
v. Visceromegaly
vi. Ear lobe pits and creases
vii. Predisposition to neoplasia
viii. Inheritance: heterogeneous (autosomal dominant, autosomal recessive, dup 11)
b. Neurofibromatosis
i. Café-au-lait spots
ii. Hypopigmented patches
iii. Axillary freckling
iv. Neurofibromas
v. Iris Lisch nodules
vi. Macrocephaly
vii. Scoliosis
viii. Hypertension
ix. CNS tumors
x. Inheritance (autosomal dominant)
c. Klippel–Trénaunay–Weber syndrome
i. Hemangiomata
ii. Lymphatic anomalies
iii. Poly/syndactyly
iv. Oligodactyly
v. Macrocephaly
vi. Glaucoma
vii. Cataracts
viii. Inheritance (unknown; sporadic)
d. Proteus syndrome
i. Lipomata
ii. Hemangiomata
iii. Macrocephaly
iv. Scoliosis
v. Macrodactyly
vi. Gyriform changes on soles of feet
vii. Inheritance (unknown, sporadic)
e. McCune–Albright syndrome
i. Fibrous dysplasia of bones
ii. Irregular hyperpigmentation
iii. Precocious puberty
iv. Hyperthyroidism
v. Hyperparathyroidism
vi. Other endocrinopathies
vii. Inheritance (unknown; sporadic; female predominance)
f. Epidermal nevus
i. Epidermal nevi
ii. Pigmentary changes
iii. Mental deficiency
iv. Seizures
v. CNS malformations
vi. Kyphoscoliosis
vii. Potential for malignancy
viii. Inheritance (heterogenous; usually sporadic but autosomal dominant and recessive inheritance described)
g. Triploid/diploid mixoploidy
i. Large placenta with hydatidiform changes
ii. Incomplete calvarial ossification
iii. Microretrognathia
iv. Microphthalmia
v. Colobomata
vi. Cataracts
vii. Irregular skin pigmentation
viii. Syndactyly
ix. Chromosomal diploid/triploid mosaicism (may be found only in fibroblasts)
h. Langer–Giedion syndrome
i. Multiple exostoses
ii. Unusual facies with bulbous nose
iii. Long simple philtrum
iv. Microcephaly
v. Loose skin in infancy
vi. Sparse scalp hair
vii. Deafness
viii. Inheritance (heterogenous; chromosome anomaly del(8)(q23q24); autosomal dominant)
i. Multiple exostoses
i. Juxtaepiphyseal exostoses
ii. Forearm bowing
iii. Short stature
iv. Malignant transformation (sarcoma) in adulthood
v. Inheritance (autosomal dominant)

   j. Mafucci syndrome
      i. Enchondromata
      ii. Hemangiomata (especially phlebectasia)
      iii. Bowing of long bones
      iv. Chondrosarcoma
      v. Inheritance (unknown; sporadic)
   k. Osteochondromatosis (Ollier disease)
      i. Bilateral, asymmetric endochondromata
      ii. Fractures
      iii. Chondrosarcoma
      iv. Inheritance (unknown; sporadic)
3. Extent of involvement
   a. Range from enlargement of a single digit to an entire half of the body
   b. Segmental, unilateral, or crossed (affecting different anatomic areas on either side of the body)
   c. System involvement
      i. A single system
         a) Muscular
         b) Vascular
         c) Skeletal
         d) Nervous
      ii. Combination of all systems
   d. Total hemihypertrophy
      i. Right side more affected than the left
      ii. Males appear to be affected more frequently
   e. Associated anomalies found in about 50% of affected individuals
   f. Onset and course of asymmetry
      i. Almost always evident at birth
      ii. May be accentuated at puberty
      iii. Appears to be constant once developed
4. Facial involvement
   a. Involvement of the face only
   b. Unilateral facial enlargement accompanied by enlargement of the complete half of the body
   c. Variable degree of involvement
5. Skin and skin appendages
   a. Involved side
      i. Thicker with increased function of the sebaceous and sweat glands
      ii. Pigmentation as well as early development of varicose veins or a medusa-like plexus of veins in the lower abdomen and groin area
      iii. Supernumerary nipples as well as an enlarged breast
      iv. Thicker and coarser hair
      v. Abnormal nail growth
   b. Either involved or contralateral side: Telangiectasia and increased numbers of nevi
6. Skeletal system
   a. Unilaterally enlarged bones
   b. Other lesions
      i. Macrodactyly
      ii. Polydactyly
      iii. Syndactyly
      iv. Lobster claw deformity
      v. Scoliosis
      vi. Tilting of the pelvis
      vii. Club foot
7. Central nervous system
   a. Mental retardation in 15–20% of affected individuals
   b. Sciatica probably resulting from pelvic tilt
   c. Dilatation of the anterior basal cisterna
   d. Dilatation of the pupil on the affected side
8. Genitourinary system
   a. Kidney and adrenal: most frequently enlarged on the involved side
   b. Other anomalies
      i. Hypospadias
      ii. Cryptorchidism
      iii. Elevated level of urinary gonadotropin and short stature
      iv. Adrenogenital syndrome
      v. Embryonal tumors
      vi. Wilms tumor
      vii. Adrenal cortical carcinoma
9. Enlarged oral lesions on the involved side
   a. Enlarged and thickened tongue
   b. Oral soft and hard tissues such as lips, uvula, maxilla, mandible, tongue, alveolar process, and some teeth

Diagnostic Investigations

1. Radiographic studies of hemihypertrophy
2. Abdominal ultrasound for visceromegaly
3. Brain MRI for hemihyperplasia
4. Chromosome analysis, UPD analysis, or gene mutation studies depending on the types of the malformation syndromes

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Isolated case: a low recurrence risk
      ii. Familial case: Recurrence risk depends on mode of transmission
         a) Autosomal dominant: a low recurrence risk if parents are normal
         b) Autosomal recessive: a 25% risk
         c) Imprinting mechanism such as in Beckwith–Wiedemann syndrome
   b. Patient's offspring
      i. Isolated case: a low recurrence risk
      ii. Autosomal dominant: a 50% risk
      iii. Autosomal recessive: recurrence risk does not increase unless the spouse is a carrier or affected
2. Prenatal diagnosis
   a. Prenatal ultrasound/radiography for fetal hemihyperplasia
   b. Chromosome analysis from amniocentesis or CVS for triploidy or mixoploidy
3. Management
   a. Screening abdominal ultrasounds every 3–6 months to monitor Wilms tumor development in patients with idiopathic hemihypertrophy
   b. Orthopedic management for hemihypertrophy
   c. Management for neoplasm

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Fig. 1 (**a**–**c**) A girl with hemihypertrophy of the right side of the body

Fig. 2 (**a**–**d**) A 7-year-old girl with hemihypertrophy of the right upper extremity. The radiograph of the forearms and hands showed osseous and soft tissue hypertrophy. She is otherwise normal

Fig. 3 (**a**–**c**) A 6-year-old girl with hemihypertrophy of the right upper and lower extremities. She also had talipes equinovarus (corrected) and abnormal pigmentation on the back

Fig. 4 A 60-year-old female was evaluated for mental retardation associated with left hemihypertrophy

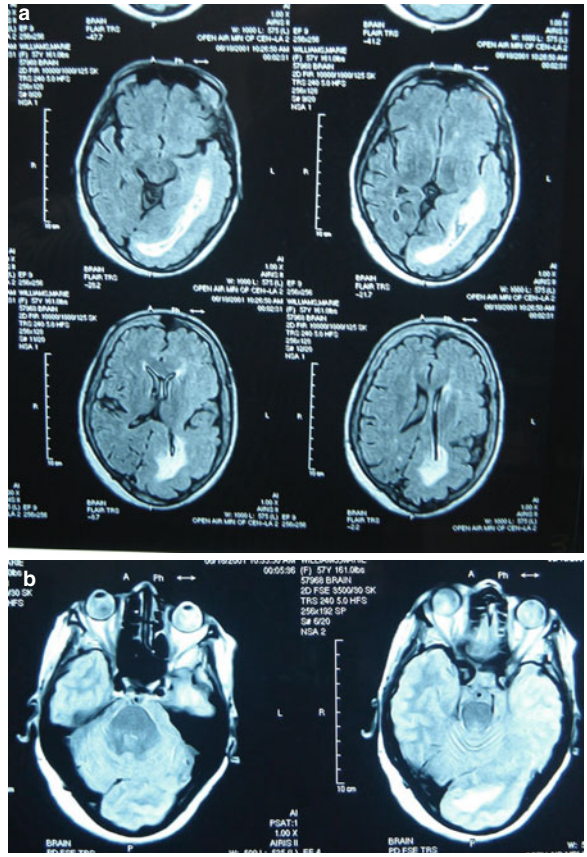

Fig. 5 (**a**, **b**) The patient's MRI of the brain showed cerebral asymmetry with left temporal, occipital, and parietal lobe hypertrophy associated with areas of macrogyria and lissencephaly, consistent with a congenital neuronal migration abnormality

Congenital Hydrocephalus

Congenital hydrocephalus is one of the most common CNS congenital anomalies. The incidence of congenital hydrocephalus is estimated as 3 per 1,000 live births. Hydrocephalus is defined as an increase in the cerebral spinal fluid (CSF) volume within the ventricular system independent of the actual head circumference.

Genetics/Basic Defects

1. Physiology of CSF production and absorption
   a. Production of CSF: by choroid plexus of lateral ventricles
   b. Pathway of CSF flow
      i. From lateral ventricles to third ventricle through foramen of Monro
      ii. From third ventricle to fourth ventricle through aqueduct of Sylvius
      iii. Out of the ventricular system: from fourth ventricle to spinal subarachnoid spaces through foramen of Magendie or to the basal cisterns through two lateral foramina of Luschka
   c. Site of CSF resorption into venous system: primarily through superior sagittal sinus via arachnoid granulations
2. Types and causes of hydrocephalus
   a. Overproduction of CSF: usually caused by choroid plexus tumors (very rare)
   b. Noncommunicating hydrocephalus
      i. Mechanical obstruction within the ventricular system causing impaired CSF absorption
         a) Foramen of Monro
         b) Aqueduct of Sylvius
         c) The fourth ventricle and its outlet channels
      ii. Causes
         a) Tumors
         b) Cysts
         c) Inflammatory scarring
         d) Intraventricular hemorrhage
         e) Rarely genetic disorders
   c. Communicating hydrocephalus
      i. Obstruction distally at the arachnoid granulations causing impaired absorption into blood stream
      ii. Causes
         a) Meningitis
         b) Trauma
         c) Intraventricular hemorrhage
3. Etiology of congenital hydrocephalus
   a. Tumors blocking CSF pathway
      i. Benign tumors such as choroid plexus papilloma
      ii. Malignant tumors
   b. CNS malformations/syndromes
      i. Congenital atresia of the foramina of Monro, Magendie, or Luschka
      ii. Dandy–Walker syndrome
         a) Atresia of the foramina of the fourth ventricle
         b) Dilation of fourth ventricle
         c) Extreme dolichocephaly
         d) Sac formation at the caudal end of the cerebellum filling the posterior cranial fossa
      iii. Aqueductal stenosis
      iv. X-linked hydrocephalus: Bickers–Adams syndrome characterized by:
         a) Stenosis of the aqueduct of Sylvius
         b) Severe mental retardation

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c) An adduction-flexion deformity of the thumb
v. Chiari II malformation
vi. Cerebellar agenesis
vii. Neural tube defects
a) Meningomyelocele
b) Encephalocele
viii. Other Mendelian conditions with congenital hydrocephalus
a) Walker–Warburg syndrome
b) Hydrolethalus syndrome
c) Meckel syndrome
d) Smith–Lemli–Opitz syndrome
c. Chromosome abnormalities
i. Trisomy 13
ii. Trisomy 18
iii. Trisomy 9 and 9p (mosaic)
iv. Triploidy
v. Other aneuploidies
d. Skeletal dysplasias
i. Achondroplasia
ii. Craniosynostosis syndromes such as Crouzon syndrome or Apert syndrome
iii. Fanconi anemia
iv. Hurler or Hunter syndromes
e. Infections
i. Congenital CMV infection
ii. Congenital toxoplasmosis
iii. Congenital rubella infections
iv. Congenital syphilis
v. Meningitis
vi. Ventriculitis
vii. Abscess
f. Vascular malformation
g. In utero intraventricular hemorrhage
h. Birth trauma
i. Destructive lesions
i. Hydranencephaly
ii. Porencephaly
iii. Perinatal leukomalacia
4. Familial (X-linked) aqueductal stenosis (HSAS: hydrocephalus-stenosis of the aqueduct of Sylvius sequence)
a. X-linked recessive inheritance.
b. Linked to chromosome Xq28.
c. Mutations in *L1-CAM*, the major gene for X-linked hydrocephalus (accounting for 7–27% of all male cases).
d. *L1-CAM*, a neuronal surface glycoprotein, has been implicated in neuronal migration and axon fasciculation.
5. Traits known to be due to allelic mutations of *L1-CAM*
a. HSAS
b. MASA
i. Mental retardation
ii. Aphasia
iii. Shuffling gait
iv. Adducted thumbs
c. SP1 (complicated spastic paraparesis, type 1)
d. MR-CT (mental retardation–clasped thumbs)
e. ACC-DCC (agenesis or dysgenesis of the corpus callosum)
6. Pathogenesis of hydrocephalus-induced brain dysfunction: complex
a. Chronic ischemia in white matter related to changes in intracranial pressure and in the vasculature
b. Physical damage to periventricular axons with disconnection of neurons
c. Alterations in the extracellular chemical environment of neurons

Clinical Features

1. Children <2 years
a. Relatively benign course because infants can expand their cranium
b. Early signs
i. Increased head circumference (macrocephaly)
ii. Full anterior fontanelle
iii. Split cranial sutures
iv. Prominent scalp veins
v. Poor feeding
vi. Vomiting
vii. Irritability
viii. Reduced activity
ix. Delay or loss of developmental milestones
x. Hypertonia
xi. Hyperreflexia
c. Late signs
i. Lethargy
ii. Sixth cranial nerve palsy
iii. Limitation of upgaze resulting in a chronic downward deviation of the eyes (sunsetting sign)

2. Children >2 years
   a. Symptoms and signs more related to increased intracranial pressure due to inability of cranium to expand sufficiently to offset the mounting volume of CSF
   b. Headaches
   c. Nausea
   d. Vomiting
   e. Lethargy
   f. Loss of milestones
   g. School performance and behavioral change
   h. Sunsetting of the eyes
   i. Sixth cranial nerve palsy
   j. Papilledema
3. Natural history of untreated childhood hydrocephalus: poor. Handicaps resulting directly from hydrocephalus include the following:
   a. Disturbances in motor abilities, particularly gait
   b. Impaired cognitive development
   c. Hypothalamic dysfunction with delayed growth and short stature
4. X-linked neurological syndromes
   a. HSAS (*h*ydrocephalus-*s*tenosis of the *a*queduct of *S*ylvius sequence)
      i. Hydrocephalus
      ii. Macrocephaly
      iii. Adducted thumbs
      iv. Spasticity
      v. Agenesis of the corpus callosum
      vi. Mental retardation
   b. MASA syndrome
      i. *M*ental retardation
      ii. *A*phasia
      iii. *S*huffling gait
      iv. *A*dducted thumbs
      v. Hydrocephalus

Diagnostic Investigations

1. Fundoscopic examination
   a. Bilateral papilledema secondary to high intracranial pressure
   b. Normal finding in some cases of acute hydrocephalus
2. Lumbar puncture for measuring intracranial pressure
   a. Avoid if an increase in intracranial pressure is suspected due to obstruction since relief of pressure may cause herniation of the brainstem
   b. Perform only after imaging studies ruling out an obstruction
3. TORCH titers on the infant and mother if intrauterine infection is suspected
4. Chromosome analysis in cases of associated multiple congenital anomalies
5. Cranial sonography (provided anterior fontanelle is still open)
   a. Ventriculomegaly
   b. Intraventricular hemorrhage
6. CT scans
   a. Ventriculomegaly
   b. Cerebral edema
   c. Mass lesions
      i. Colloid cyst of the third ventricle
      ii. Thalamic tumor
      iii. Pontine tumor
7. MRI
   a. Ventriculomegaly
   b. Mass lesions
   c. Associated brain anomalies
      i. Agenesis of the corpus callosum
      ii. Chiari malformations
      iii. Disorders of neuronal migration
      iv. Vascular malformations
8. Molecular genetic diagnosis to identify *L1CAM* mutations, identified in 22.4% (15/67) of sporadic cases of clinically or prenatally suspected L1-disease

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Sporadic: low (4%)
      ii. Multifactorial trait (e.g., neural tube defect or in female infants with congenital hydrocephalus due to stenosis of the aqueduct of Sylvius): low recurrence risk (5%) for subsequent sibling; 10% risk if there are two affected siblings
      iii. Autosomal recessive traits (e.g., Dandy–Walker syndrome): 25% affected; 50% carriers; 25% normal

iv. X-linked hydrocephalus: 50% of brothers affected and 50% of sisters carriers if the mother is a carrier; negligible in males with "sporadic" hydrocephalus representing a new X-linked mutation

b. Patient's offspring
   i. Sporadic: low (4%)
   ii. Multifactorial trait: 3–4.5% recurrence risk
   iii. Autosomal recessive traits: not increased unless the spouse is a carrier or affected
   iv. X-linked hydrocephalus: All daughters will be carriers in case of an affected father

2. Prenatal diagnosis
   a. Ultrasonography
      i. Fetal ventriculomegaly
      ii. Additional CNS malformations
      iii. Extracerebral malformations
   b. Sonographic findings in HSAS or MASA syndromes
      i. Male fetus
      ii. Hydrocephalus
      iii. Hypoplasia or agenesis of the corpus callosum
      iv. Bilateral adducted thumbs
   c. Amniocentesis
      i. Alpha-fetoprotein and cholinesterase determination from amniotic fluid for neural tube defects
      ii. Chromosome analysis for suspected chromosomal disorder
   d. Molecular genetic diagnosis
      i. DNA diagnosis often requested in families with "isolated" hydrocephalus case due to high rate of *de novo* mutations, small family size, and the improved sensitivity of prenatal ultrasound scanning
      ii. Molecular diagnosis of prenatally suspected L1 spectrum disorders, even in cases without positive family history
3. Management (Hamid and Newfield 2001; Kestle 2003)
   a. Folic acid intake before and during the first trimester reduces the incidence of neural tube defects, thereby the incidence of hydrocephalus
   b. Shunting CSF from the ventricles
      i. Ventriculoperitoneal shunting (VP) devices with pressure-controlled valves under the scalp close to the burr hole
      ii. Ventriculopleural shunt
      iii. Ventriculoatrial shunt
      iv. Frontal or parietal ventriculostomy
      v. Does not completely reverse the pathologic alterations in the brain and, unfortunately, treatment by shunting is associated with frequent complications
   c. Major complication associated with shunt treatment: 81% of children with shunts suffer at least one and usually several malfunctions necessitating hospitalization
      i. Shunt obstruction
      ii. Valve malfunction
      iii. Disconnection
      iv. Hematoma
      v. Overdrainage
      vi. Outgrown shunt
      vii. Shunt fracture
      viii. Shunt-related infections, most often caused by staphylococcus aureus, with unexplained fever or frank meningitis
      ix. Signs of increased intracranial pressure with headache, lethargy, and vomiting
      x. Abdominal complications
         a) Peritonitis
         b) Perforation of an abdominal organ
         c) Peritoneal cysts
         d) Development of hydroceles in boys
      xi. Seizures
      xii. Allergic reaction to material
   d. A trial of in utero ventriculo-amniotic shunt for treating congenital hydrocephalus (Al-Anazi et al. 2008)

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Fig. 1 A child with hydrocephalus which was shunted

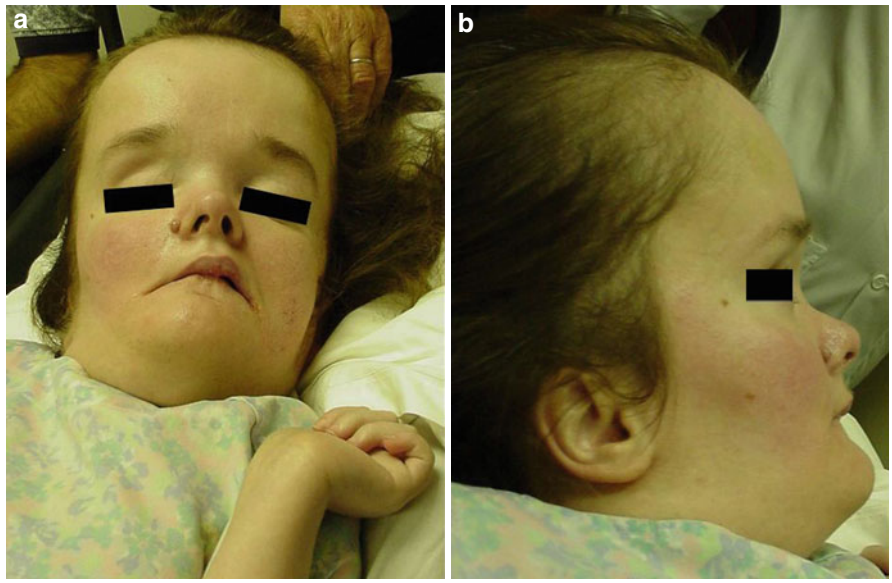

Fig. 2 (**a**, **b**) An adult with severe congenital hydrocephalus and mental retardation

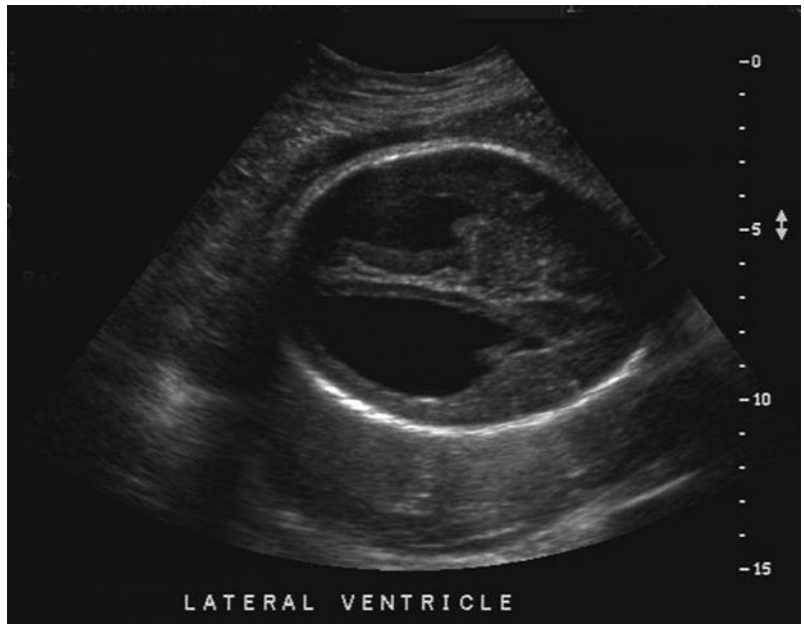

Fig. 3 Prenatal ultrasound at 33 weeks showing markedly dilated lateral ventricles

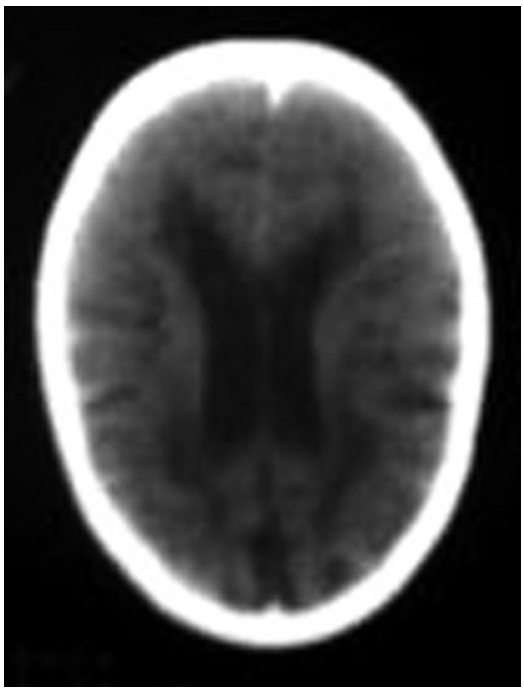

Fig. 4 CT scan of the head of a patient showing ventriculomegaly with congenital hydrocephalus

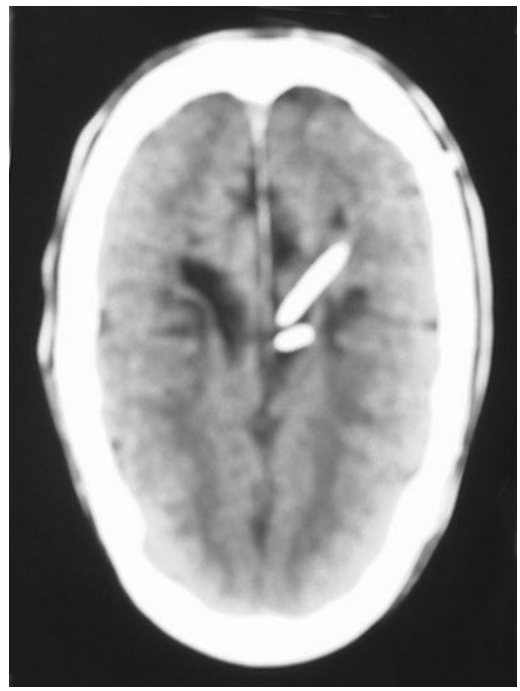

Fig. 5 CT scan of the head of a patient after ventriculoperitoneal shunt

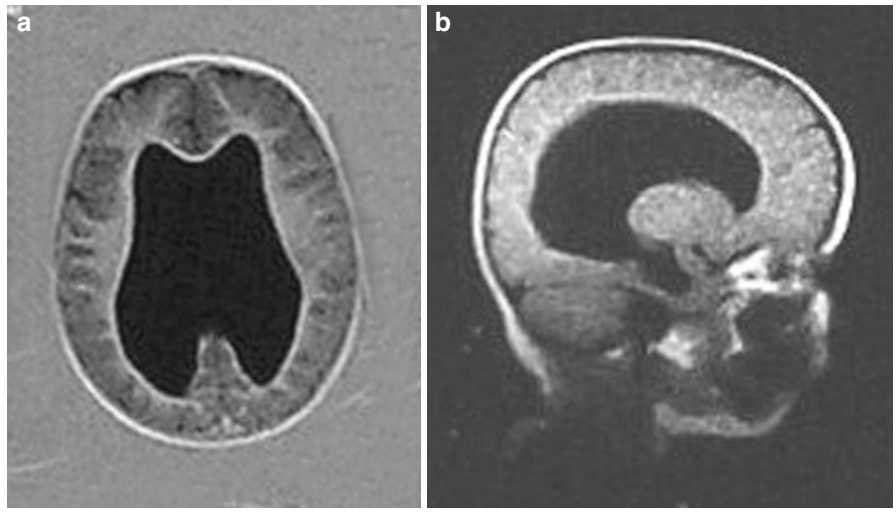

Fig. 6 (**a**, **b**) MRI of the brain of a patient showing hydrocephalus due to aqueduct stenosis

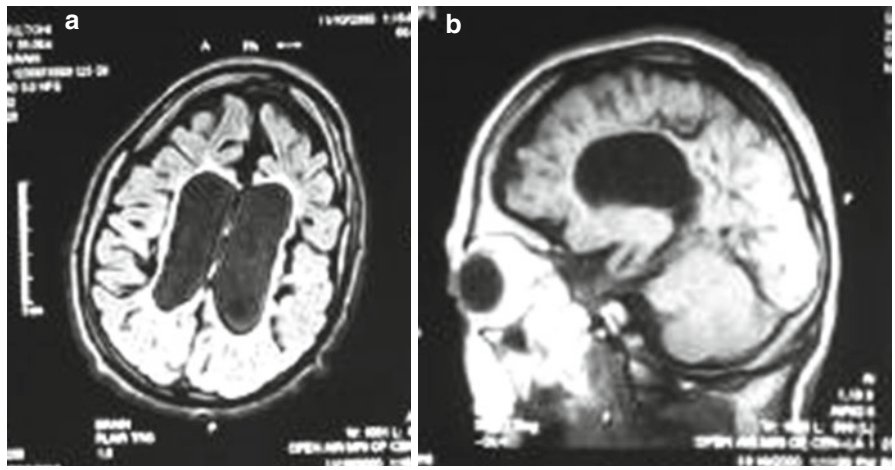

Fig. 7 (**a**, **b**) CT scans of the brain of a patient showing dilatation of the lateral ventricles with stretching of corpus callosum and cortical atrophy

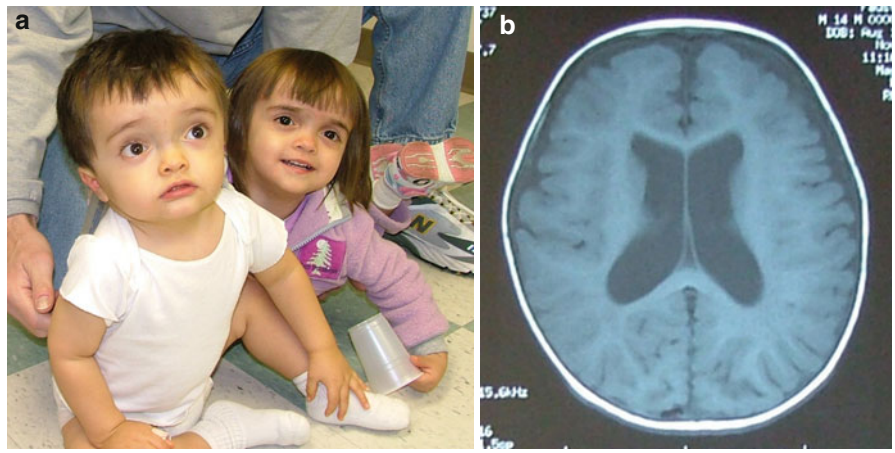

Fig. 8 (**a**, **b**) A brother (16 months) and a sister (29 months) with benign familial hydrocephalus. A MRI of the brain of the brother showed mild ventriculomegaly

Congenital Hypothyroidism

All forms of congenital hypothyroidism occur in 1 in 4,000 live births worldwide. The dysgenetic form affects twice as many females as males. It is the most prevalent congenital endocrine disease. The incidence is approximately 1 in 32,000 in Blacks and 1 in 2,000 in Hispanics.

Synonyms and Related Disorders

Ectopic thyroid gland; Thyroid agenesis; Thyroid dysgenesis; Thyroid hypoplasia; Thyrotropin resistance

Genetics/Basic Defects

1. Inheritance (Ambrugger et al. 2001)
   a. Thyroid dysgenesis
      i. The most frequent cause of congenital hypothyroidism (85% of cases)
      ii. Morphological classification
         a) Ectopic thyroid gland: the most frequent malformation, observed most frequently at the base of the tongue
         b) Athyreosis (absence of any detectable thyroid tissue)
         c) Hypoplasia (partially absent thyroid)
      iii. Sporadic in most cases
      iv. Genetic factors contributing to the development of thyroid dysgenesis in 2% of cases with a positive familial history
      v. Molecular defects clarified only in few cases of thyroid dysgenesis (Grüters et al. 2002)
         a) TSH-receptor gene (thyroid hypoplasia, "apparent athyrosis")
         b) Transcription factors: Thyroid-specific transcription factor-1 (TTF-1) (hypothyroidism, chorea, choreoathetosis, respiratory distress), TTF-2 (thyroid hypoplasia, cleft palate, choanal atresia, curly hair, developmental delay), PAX-8 (thyroid hypoplasia, ectopy)
         c) NKX2A (athyrosis, hypoplasia, normally developed gland, choreoathetosis, pulmonary problems, mental retardation, pituitary abnormalities)
   b. Autosomal recessive defects of thyroid hormone biosynthesis with identification of the following candidate genes for congenital hypothyroidism
      i. Thyroid peroxidase (*TPO*) gene
         a) A hemoprotein responsible for tyrosine iodination and coupling
         b) Intriguing role of *TPO* mutations in the development of thyroid tumor
      ii. Sodium-iodide symporter (*NIS*) gene
      iii. Thyroglobulin (*TG*) gene
      iv. Pendrin (*PDS*) gene (Pendred syndrome)
      v. Thyroid oxidase 2 (*THOX2*) gene (Pfarr et al. 2006)
   c. Autosomal dominant transmission of congenital hypoplasia due to loss-of-function mutation of PAX-8 (Vilain et al. 2001)
2. Etiology of thyroidal congenital hypothyroidism (De Vijlder 2003)
   a. Disorders in development of the thyroid gland (85% of cases with congenital hypothyroidism)
      i. Absent thyroid
      ii. Under-development with migration failure
      iii. Under-development with normal migration

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   b. Disorders in thyroid hormone synthesis (10–20%)
      i. TSH hypo-responsiveness (TSH-receptor abnormalities)
      ii. Defects in iodide transport from circulation into the thyroid cells
      iii. Defects in iodide transport from the thyroid cell to the follicular lumen, often combined with inner ear deafness (Pendred syndrome, sensorineural hearing loss, and goiter)
      iv. Defects in the synthesis of hydrogen peroxide
      v. Defects in the oxidation of iodide, iodination, and iodothyronine synthesis
      vi. Defects in processes involved in the synthesis or degradation of thyroglobulin
      vii. Defects in iodine recycling
3. Etiology of central (hypothalamic or pituitary) congenital hypothyroidism
   a. Disorders in development and/or function of the hypothalamus
   b. Disorders in development and/or function of the pituitary glands
   c. Disorders in development and/or function of the hypothalamus and pituitary glands
4. Transient form of primary congenital hypothyroidism (Moreno et al. 2002)
   a. Occurs in 5–10% of infants detected by newborn screening
   b. Represents about 5% of cases with congenital hypothyroidism
   c. Etiology
      i. Mothers with chronic autoimmune thyroiditis: transplacental passage of maternal TSH-receptor blocking antibodies leading to inhibition of TSH action on the infant's thyroid gland until the maternal antibodies disappear
      ii. Antithyroid drugs taken by pregnant women with thyroid autoimmune disease
      iii. Maternal dietary iodide deficiency
      iv. Maternal dietary goitrogen ingestion
      v. Exposure to excess iodine in the perinatal period
         a) Use of iodinated disinfectants
         b) Use of contrast agents
5. Down syndrome: Congenital hypothyroidism occurs approximately 28 times more common among infants with Down syndrome than in the general population with an incidence of 1% detected by newborn screening
6. Pathogenesis of mental retardation in congenital hypothyroidism: due to the central role of thyroid hormones in brain development, which takes place during fetal life and early postnatal life up to the second or third year of age (DeLange 1997)

Clinical Features

1. Most newborn are asymptomatic (Beltroy et al. 2003)
2. Severe dysgenetic and athyrotic hypothyroidism
   a. Early symptoms
      i. Feeding problems
      ii. Constipation
      iii. Growth failure
      iv. Hoarse cry
   b. Signs and symptoms in infants and toddlers
      i. Delayed linear growth
      ii. Hypotonia
      iii. Decreased activity
      iv. Lethargy
      v. Prolonged jaundice
      vi. Bradycardia
      vii. Hypothermia
      viii. Cold to touch
      ix. Dry/puffy/thick skin
      x. Sparse hair
      xi. Characteristic craniofacial appearance
         a) Coarse facial feature
         b) Puffy eyes
         c) Myxedematous facies
         d) Large fontanelles
         e) A broad, flat nose
         f) Pseudohypertelorism
         g) Large, protruding tongue
      xii. Delayed tooth eruption
      xiii. Occasional cardiomegaly
      xiv. Protuberant abdomen with umbilical hernia
      xv. Constipation
      xvi. Poor nail growth
      xvii. Delayed return of the deep tendon reflexes
      xviii. Irreversible growth failure and mental retardation

Diagnostic Investigations

1. Newborn screening: Ideally universal screening at 3–4 days of age should be done for detecting CH. Abnormal values on screening (T4 < 6.5 ug/dL, TSH > 20mu/L) should be confirmed by a venous sample (using age appropriate cutoffs) before initiating treatment
   a. Successful identification of infants with congenital hypothyroidism
   b. Enables early diagnosis and treatment of infants and prevention of mental retardation
   c. Newborn screening measures either TSH or T_4 in neonatal blood placed on filter paper
   d. Confirmation with a serum sample if the filter paper result is abnormal
      i. Primary congenital hypothyroidism
         a) Low serum T_4 levels
         b) Elevated serum TSH
      ii. Hypopituitary hypothyroidism
         a) Low total T_4 levels
         b) Low or normal TSH
      iii. Thyroxine-binding globulin (TBG) deficiency
         a) Low total T_4 but normal serum-free T_4 levels
         b) Normal TSH
   e. Screening programs for congenital hypothyroidism in premature newborns (Kugelman et al. 2009)
      i. Sick premature infants may display transient hypothyroxinemia secondary to immaturity of the hypothalamic-pituitary axis.
      ii. Therefore, early screening programs of such infants may be misleading.
      iii. Recommendations
         a) Screening programs should report thyroid stimulating hormone (TSH) as well as thyroxin (T4) levels in premature infants, which will allow the treating physicians to be aware of possible abnormality that needs to be followed.
         b) Sick premature infants and other populations at risk should undergo a full serum thyroid function evaluation including free T4 and TSH beyond the screening program at discharge or at 30 days of age, whichever comes first.
         c) Physicians should use their clinical judgment and experience even in the face of normal newborn thyroid screening test and reevaluate for hypothyroidism when there is a clinical suspicion.
   f. Pendred syndrome (Banghova et al. 2008)
      i. An autosomal recessive disorder characterized by sensorineural hearing loss and thyroid dyshormonogenesis
      ii. Caused by mutations in the *PDS/SLC26A4* gene
      iii. Present from birth
      iv. Can be diagnosed by newborn screening
2. Laboratory diagnosis
   a. Thyroid function tests
      i. Elevated serum TSH
      ii. Low serum T_4 levels
   b. Determine antithyroglobulin and antithyroid peroxidase antibodies if indicated
   c. Determine TBG levels for suspected TBG deficiency
3. Radiography for bone age
4. Ultrasonography, considered as the best noninvasive method for the anatomical assessment of the thyroid gland
5. Radionuclide scan (thyroid scintigraphy) using ^{99m}Tc or ^{123}I (DeLange 1997)
   a. To demonstrate the presence of ectopic thyroid tissue or thyroid aplasia
   b. Iodide transport defect
      i. Low or absent uptake of ^{123}I
      ii. Response to therapeutic doses of potassium iodide
   c. Defective organification of iodide
      i. Rapid uptake of ^{123}I
      ii. Marked decrease in thyroid radioactivity when perchlorate or thiocyanate is administered 2 h after administering radioiodine
      iii. Occasional sensorineural hearing loss (Pendred syndrome)
   d. Iodotyrosine-coupling defect
      i. Rapid uptake of ^{123}I
      ii. No discharge by perchlorate
      iii. Very high thyroid gland content of monoiodotyrosine (MIT) and diiodotyrosine (DIT)
      iv. Virtually undetectable T_4 and T_3
      v. Adequately iodinated thyroglobulin

e. Defects in thyroglobulin gene expression and thyroglobulin secretion
   i. Elevated uptake of ^{123}I
   ii. No discharge by perchlorate
   iii. Abnormal serum iodoproteins
   iv. Elevated protein-bound/T_4 iodine ratio
   v. Low or borderline serum thyroglobulin
f. Iodotyrosine deiodinase defect
   i. Rapid uptake and turnover of ^{123}I
   ii. Elevated serum and urinary iodotyrosines (MIT, DIT)
   iii. Response to iodine supplementation
6. Intelligence quotient (IQ) measurement for testing neuropsychological progress and outcome
7. Molecular genetic diagnosis by sequencing of select exons to identify mutations

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Sporadic cases: low recurrence risk
      ii. Autosomal recessive inheritance: 25%
      iii. Autosomal dominant inheritance: low recurrence risk unless a parent is affected
   b. Patient's offspring
      i. Sporadic cases: low recurrence risk
      ii. Autosomal recessive inheritance: low recurrence risk unless the spouse carries the recessive gene
      iii. Autosomal dominant inheritance: 50%
2. Prenatal diagnosis
   a. Ultrasonography and percutaneous fetal blood sampling
      i. Detection of fetal goiter
         a) A rare yet potentially dangerous condition
         b) A large goiter may cause hyperextension of the neck of the fetus caused by a large goiter, resulting in malpresentation and complicating labor and delivery
         c) Possibility of compressing the trachea and asphyxiating the neonate after birth
      ii. Fetal blood sample
         a) Elevated TSH
         b) Low T4
   b. Amniocentesis
      i. Determination of TSH concentration (markedly elevated TSH level) in amniotic fluid in the second trimester for the offspring of a couple both known to have an iodide (iodothyronine synthesis) enzymatic organification defect
      ii. Affected fetus with markedly increased TSH level in the amniotic fluid sample for the trimester
   c. Molecular genetic diagnosis possible by sequencing of select exons on fetal DNA for previously identified mutations in a research laboratory
3. Management
   a. Sodium L-thyroxine
      i. The treatment of choice
      ii. Early therapy (within 14 days) with appropriate doses of thyroxine (about 10 μg/kg/day) will prevent any brain damage even in case of evidence of fetal hypothyroidism, since thyroxine of maternal origin will reach and protect the fetus (DeLange 1997)
      iii. Avoid over treatment to prevent the following adverse effects (LaFranchi 1999):
         a) Premature cranial suture fusion
         b) Acceleration of growth and skeletal maturation
         c) Problems with temperament and behavior
   b. X-linked dominant thyroxine-binding globulin deficiency (causing a low total T4 but normal free T4): no need for thyroid hormone replacement
   c. Intrauterine treatment of fetus with a large goiter (Davidson et al. 1991)
      i. Indicated because of the morbidity associated with compression of the trachea and mechanical interferences during delivery
      ii. Intra-amniotic administration of levothyroxine presents the least invasive approach to fetal treatment
         a) Rapid decrease in the fetal goiter size
         b) Normalization of fetal thyroid function
   d. Intrauterine treatment of fetus affected with iodide organification defect with synthroid

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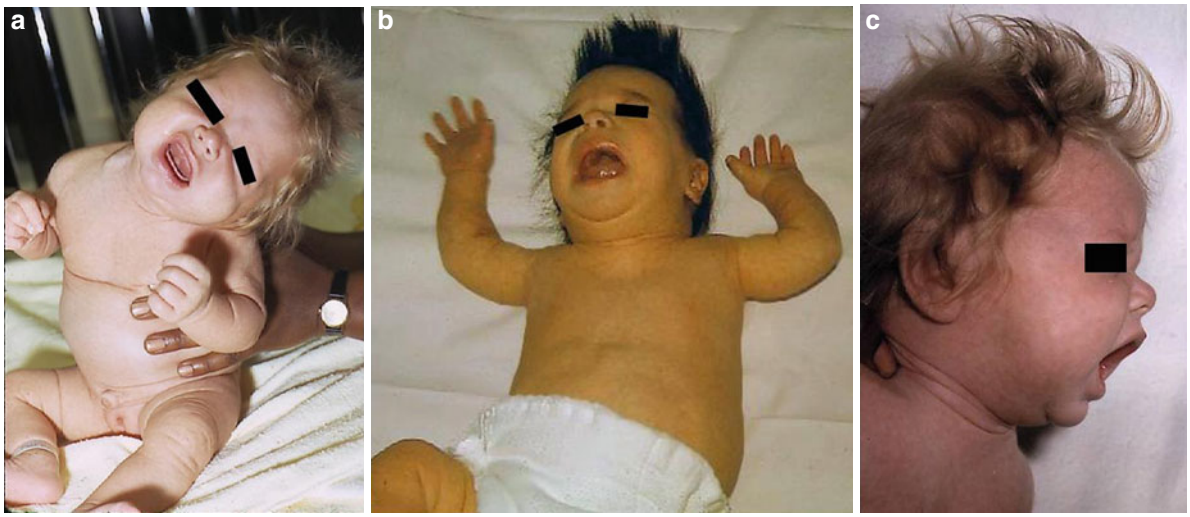

Fig. 1 (**a**–**c**) A neonate with congenital hypothyroidism showing coarse facial features, hypotonia, macroglossia, and umbilical hernia

Fig. 2 A twin affected with congenital hypothyroidism (*left*) shows coarse facial features. The normal co-twin is on the *right*

Congenital Muscular Dystrophy

Congenital muscular dystrophy (CMD) refers to a group of genetic disorders in which weakness and an abnormal muscle biopsy are present at birth.

Synonyms and Related Disorders

Merosin-negative CMD; Merosin-positive CMD with mental retardation and neuronal migration defects (Fukuyama CMD, muscle-eye-brain disease, Walker-Warburg syndrome); Merosin-positive CMD (rigid spine disease, Ullrich disease, pure CMD)

Genetics/Basic Defects

1. Inheritance
   a. Genetic heterogeneity
   b. Most are autosomal recessive (Muntoni and Voit 2004)
2. Caused by genetic defects in proteins of the sarcolemmal membrane or its supporting structures. The proteins may also be expressed in the central nervous system, and many forms of CMD are associated with structural brain and eye anomalies
3. Classification of CMD according to biochemical defect (Cardamone et al. 2008)
   a. Extracellular matrix protein
      i. Merosin (lamin-α2) (*LAMA2*): Merosin-deficient CMD (MDC1A)
         a) Demyelinating neuropathy
         b) White matter signal changes on brain MRI
      ii. Collagen VI (*COL6A1*, *COL6A2*, *COL6A3*): Ullrich CMD, Bethlem CMD
         a) Proximal contractures
         b) Distal hyperextensibility
         c) Sandpaper rash
      iii. Integrin α7 (*ITGA7*): Merosin-positive CMD (mental retardation)
   b. Sarcolemmal protein (Plectin, *PLEC1*): CMD with epidermolysis bullosa (blistering skin rash from birth)
   c. Glycosyltransferases
      i. Fukutin (FCMD): Fukuyama CMD, Walker–Warburg syndrome
         a) Eye and structural brain anomalies
         b) Seizures
         c) Mental retardation
         d) Absent α-dystroglycan on muscle immunocytochemistry
      ii. Protein O-mannose β1.2 (N- acetylglucosaminyltransferase 1 (*POMGnT1*): Muscle-eye-brain disease
         a) Eye and structural brain anomalies
         b) Absent α-dystroglycan on muscle immunocytochemistry
      iii. Protein O-mannosyltransferase 1 (*POMT1*): Walker–Warburg syndrome, Limb-girdle muscular dystrophy, type 2K
         a) Eye and structural brain anomalies
         b) Seizures
         c) Mental retardation
         d) Absent α-dystroglycan on muscle immunocytochemistry
      iv. Protein O-mannosyltransferase 2 (*POMT2*)
         a) Walker–Warburg syndrome: hydrocephalus
         b) Muscle-eye-brain disease: severe structural brain anomalies, absent

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α-dystroglycan on muscle immunocytochemistry
v. Unknown protein: Congenital muscular dystrophy type 1B (muscle hypertrophy, early respiratory failure)
vi. Fukutin-related protein (*FKRP*): Limb-girdle muscular dystrophy type 21, congenital muscular dystrophy type 1C, Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, Walker–Warburg syndrome
a) Duchenne phenocopy
b) Cardiomyopathy
c) Absent α-dystroglycan on muscle immunocytochemistry
vii. LARGE congenital muscular dystrophy (*LARGE*): congenital muscular dystrophy type 1D
a) Severe mental retardation
b) White matter signal changes on brain MRI
viii. SIL1 (*SIL1*): Marinesco–Sjögren syndrome
a) Cerebellar ataxia
b) Congenital cataracts
d. Endoplasmic reticulum protein (Selenoprotein N, *SEPN1*)
i. Rigid spine muscular dystrophy
a) Thin habitus
b) Spinal rigidity
ii. Multicore myopathy: early respiratory failure
iii. Congenital fiber-type disproportion
iv. Myofibrillar myopathy
e. Nuclear envelope protein (Lamin A/C, *LMNA*): variable phenotype
i. Emery–Dreifuss MD
ii. Limb-girdle muscular dystrophy type 1B
iii. Congenital muscular dystrophy
iv. Dilated cardiomyopathy
v. Charcot–Marie–Tooth disease (CMT) type 2B1

Clinical Features

1. Typical features
a. Present in the first year of life
i. Hypotonia and weakness
ii. Respiratory insufficiency
iii. Bulbar dysfunction
iv. Arthrogryposis
b. Hypertrophy of the tongue and limb muscles, scoliosis, and contractures may develop with age
c. Weakness is static or slowly progressive
2. Merosin-negative CMD
a. Demonstrating clinical homogeneity
i. Severe hypotonia
ii. Multiple contractures
iii. Delayed developmental milestones
iv. Normal mentation
v. Variable degrees of central hypomyelination seen on neuroimaging
b. Patients with complete merosin deficiency
i. Typically presenting as floppy infants
ii. May or may not require ventilatory assistance
iii. Most patients stabilize and able to continue developing without mechanical ventilation
iv. Feeding difficulty leading to recurrent aspiration and poor nutrition in some patients
v. The best motor milestone achieved: standing with support
vi. Unable to ambulate
vii. Cognitive development
a) Generally normal
b) Mental retardation in patients with brain anomalies
viii. Epilepsy
c. Patients with partial merosin deficiency
i. Wide clinical spectrum
a) Marked hypotonia at birth, contractures, and severely delayed motor milestones
b) Limb-girdle muscular dystrophy-like presentation in the teen
c) An adult-onset proximal limb-girdle weakness with elevated CK concentration
ii. White matter abnormalities by MRI in all patients with documented merosin gene mutations
3. Merosin-positive CMD
a. Rigid spine disease
i. Onset in infancy
ii. Axial muscle weakness
iii. Early rigidity of the spine
iv. Prominent nasal voice
v. Nocturnal respiratory insufficiency
vi. Early respiratory failure
b. Ullrich disease
i. Proximal contractures
ii. Distal joint laxity

iii. Delayed motor milestones
  a) Ability to walk in some cases
  b) Wheelchair dependent in majority of cases
iv. Normal intelligence

c. Pure CMD
i. Normal intelligence
ii. Normal brain imaging

d. Other merosin-positive CMD

4. Merosin-positive CMD with mental retardation and neuronal migration defects
a. Fukuyama CMD
i. An autosomal recessive disorder
ii. Prevalent in Japan
iii. Early onset (before 9 months)
iv. Muscle weakness
v. Accompanied by joint contractures
vi. Hypotonia/hypokinesia
vii. Severe mental retardation
viii. Epilepsy
ix. Eye anomalies
  a) Myopia
  b) Congenital nystagmus
  c) Cortical blindness
  d) Optic atrophy
  e) Choreoretinal degeneration
x. Brain anomalies (cobblestone lissencephaly; type 2 lissencephaly)
  a) Micropolygyria
  b) Pachygyria
  c) White matter lucency
  d) Minor cerebellar alterations (cortical dysplasia

b. Muscle-eye-brain disease
i. An autosomal recessive disorder
ii. Mimics Walker–Warburg syndrome but overall changes tend to be much milder
iii. Present as a floppy infant with suspected blindness
iv. Severe mental retardation
v. Extensive neuronal migration disorder
  a) Pachygyria and polymicrogyria
  b) Brain stem hypoplasia
  c) Cerebellar dysgenesis
  d) Hydrocephalus
vi. Muscle involvement: typical features of muscular dystrophy with ongoing de- and regeneration
vii. Normal expression of laminin α2

c. Walker–Warburg syndrome
i. An autosomal recessive disorder
ii. Type II lissencephaly
  a) Micropolygyric "cobblestone" cortex
  b) Extensive white matter abnormalities
  c) Hydrocephaly with enlarged ventricles
  d) Brainstem hypoplasia
  e) Hypoplasia of the cerebellum, particularly the cerebellar vermis
iii. Ocular dysgenesis
  a) Megacornea
  b) Buphthalmos
  c) Corneal clouding
  d) Cataracts
  e) Abnormal vitreous
  f) Retinal hypopigmentation
  g) Hypoplasia of the optic nerve
  h) Clinically blind
iv. Muscular dystrophy
  a) Variable in severity: ranges from myopathy with increased variation of fiber size to severe, end-stage muscular dystrophy
  b) Well-preserved expression of laminin α2
v. Complete lack of psychomotor development (severe mental retardation) for those who survive for some years

Diagnostic Investigations

1. Markedly elevated serum creatine kinase (CPK) levels (Caramone et al. 2008).
2. Nerve conduction studies may show demyelinating neuropathy in merosin-deficient CMD (Quijano-Roy et al. 2004).
3. Electromyography (EMG) is myopathic.
4. Muscle biopsy shows typical dystrophic changes (degeneration and regeneration of muscle fibers, and proliferation of fatty and connective tissue).
5. Immunocytochemistry enables analysis of merosin, α-dystroglycan, collagen VI, and other muscle proteins (Jones and North 2003; Muntoni and Voit 2004).
6. Cerebral magnetic resonance imaging (MRI) may show abnormalities of neuronal migration and white matter signal.
a. Pachygyria (with normal cognitive function)
b. Cerebellar hypoplasia (with normal cognitive function but delay of speech development)

c. Cerebellar cysts (in connection with pure CMD)
d. Abnormal white matter signal (in connection with pure CMD of merosin-deficient type)
e. Large lissencephalic changes
f. Hydrocephalus

7. Molecular genetic analyses.
   a. Fukuyama CMD: Sequencing of entire coding region or select exons of *FCMD* gene
   b. Muscle-eye-brain disease: Sequencing of entire coding region or select exons or targeted mutation analysis of *POMGnT1* gene
   c. Walker–Warburg syndrome: Sequencing of entire coding region or select exons or mutation scanning of *POMT1* gene

Genetic Counseling

1. Recurrence risk (Sparks et al. 2011)
   a. Patient's sib
      i. Autosomal recessive: a 25% recurrence risk
      ii. Autosomal dominant (Ullrich congenital muscular dystrophy): a low recurrence risk but greater than that of the general population if both parents are clinically unaffected or if the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, because of the possibility of germline mosaicism
   b. Patient's offspring:
      i. Autosomal recessive
         a) Many individuals not living long enough to reproduce
         b) All offspring are carriers
         c) Recurrence risk to offspring probably less than 1%
      ii. Autosomal dominant: a 50% risk
2. Prenatal diagnosis
   a. Possible for pregnancies at 25% risk for complete merosin deficiency, provided complete merosin deficiency has been documented in the muscle of the proband.
      i. The diagnostic testing must be done on a sample of direct and flesh-frozen chorionic villi obtained at about 10–12 weeks of gestation by immunostaining
      ii. Using molecular testing for mutations that have been previously identified in the proband by CVS or amniocentesis
   b. Prenatal diagnosis by DNA mutation analysis is available for pregnancies at increased risk of Fukuyama MD, muscle-eye-brain disease, Walker–Warburg MD, congenital muscular dystrophy type 1C and 1D, and congenital muscular dystrophy with early spine rigidity by analysis of fetal DNA, obtained by amniocentesis or CVS, provided both disease-causing alleles of an affected family member have been identified.
3. Management (Sparks et al. 2011)
   a. No definitive treatment available
   b. General approaches
      i. Weight control to avoid obesity
      ii. Physical therapy and stretching exercises
         a) To promote mobility
         b) To prevent contractures
      iii. Using mechanical devices to help ambulation and mobility
      iv. Surgical interventions for scoliosis and foot deformity
      v. Medications for seizure control
      vi. Respiratory aids as needed
      vii. Social and emotional support

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Fig. 1 An infant with congenital muscular dystrophy showing hypotonic frog-leg posture, the chest deformity due to weakness of the intercostal muscles, and contractures of joints

Congenital Toxoplasmosis

Acute infection in a pregnant woman with a parasite, *Toxoplasma gondii*, can have serious consequences on the fetus, ranging from fetal loss to severe neurologic or ocular lesions. In other cases, infected newborns are asymptomatic at birth, but are at risk for developing retinal diseases during childhood or adolescence on *Toxoplasma* reactivation (Wallon et al. 2004). In the United States, the incidence of congenital toxoplasmosis is estimated to be 1 in 1,000 to 1 in 10,000 births and approximately 400–4,000 cases of congenital toxoplasmosis occur each year.

Synonyms and Related Disorders

Toxoplasma gondii infection in pregnancy

Genetics/Basic Defects

1. *Toxoplasma gondii* (Beasley and Egerman 1998)
   a. A protozoan parasite
   b. The causative agent of toxoplasmosis, a common infection throughout the world with estimated one billion people infected worldwide
   c. Life cycle: exists in three forms
      i. The oocysts, or soil form
      ii. The tachyzoite, or active infectious form
      iii. The tissue cyst, or latent form
2. Hosts
   a. Cats
      i. The primary host
      ii. Maintain the intestinal–epithelial sexual cycle of *Toxoplasma* development with the production of oocysts
   b. All other animals (humans, birds, rodents, and domestic animals)
      i. The intermediate or secondary hosts
      ii. Have an extraintestinal asexual cycle with resultant parasitemia and the production of tissue cysts
3. Routes by which *Toxoplasma* is transmitted to humans
   a. Principal routes
      i. Acquired
         a) Ingestion of raw or inadequately cooked infected meat (beef, pork, or lamb)
         b) Not washing hands thoroughly after handling raw meat or gardening
         c) Ingestion of oocysts, an environmentally resistant form of the organism that cats pass in their feces and human exposure to cat litter or contaminated soil (from gardening or unwashed fruits or vegetables)
      ii. Congenital: transplacental infection of unborn fetus by the newly infected mother
   b. Rare routes
      i. Blood and blood product transfusion
      ii. Organ transplant
      iii. Laboratory accident
   c. No evidence of direct human-to-human transmission other than from mother to fetus
4. Seventy percent of the obstetric population with negative antibodies: at risk for transmission to the fetus
5. Congenital toxoplasmosis usually occurs as a result of primary maternal infection
6. Maternal–fetal transmission rate depends on gestational age at the time of maternal infection
   a. Less than five percent before fifth week of gestation

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   b. Twenty-five percent in the first trimester
   c. Seventy-five percent in the third trimester
   d. Greater than ninety percent in the last few weeks of pregnancy
7. Severity of the fetal infection inversely related to gestational age: The earlier infections being the most severe
8. Untreated maternal infections: About 50% of cases transmit to the fetus
9. An immunocompetent woman previously infected is considered immune and will not transmit *T. gondii* to her offspring. *Toxoplasma* infection leads to life-long immunity with the presence of *T. gondii*-specific IgG antibodies. Acute toxoplasmosis in the adult is often asymptomatic and usually does not result in complications
10. Reactivation can occur in immunocompromised pregnant woman (i.e., HIV) leading to parasitemia and fetal infection

Clinical Features

1. Unpredictable manifestations in the fetus and in the newborn
2. Maternal infections
   a. Generally asymptomatic in immunocompetent mothers
   b. Subtle symptoms in about 15–20% of infected mothers
      i. Cervical lymphadenopathy: the most common clinical manifestation
      ii. Fatigue
      iii. Flu-like symptoms
   c. In immunocompromised mothers
      i. Chorioretinitis
      ii. Encephalitis
      iii. Pneumonitis
      iv. Myocarditis
   d. Maternal infections early in pregnancy
      i. Less likely to be transmitted to the fetus than infections later in pregnancy
      ii. More likely to be severe than later infections
3. Fetal infections
   a. Usually resulting from a primary maternal infection with risk of developing congenital abnormalities. Reactivation of *T gondii* in an immunocompromised patient can render the fetus susceptible to infection.
   b. Infectivity: The incidence and severity of the fetal infection depend on the gestational age at the time of the maternal infection. The later the gestation, the higher the infectivity. However, the postnatal sequelae are severer when infection occurs early in gestation.
4. Natural history of congenital toxoplasmosis
   a. Free of symptoms at birth in vast majority of cases with congenital infection (70–90% of cases)
   b. About 15% of the infected children with signs or symptoms at birth or neonatal period
      i. Maculopapular rash
      ii. Generalized lymphadenopathy
      iii. Hepatosplenomegaly
      iv. Jaundice
      v. Thrombocytopenia
      vi. Consequences of intrauterine meningoencephalitis
         a) CSF abnormalities
         b) Hydrocephalus
         c) Microcephaly
         d) Chorioretinitis
         e) Seizures
      vii. Signs of the "classic triad" (hydrocephalus, intracranial calcifications, and chorioretinitis) without systemic signs of disease
   c. Sequelae during childhood or early adult life in 50–90% of cases
      i. Learning disability
      ii. Visual impairment
      iii. Chorioretinitis: the most frequent congenital manifestation and is progressive in >80% of patients by 20 years of age
      iv. Mental retardation
      v. Hearing loss
   d. Ocular lesions: the most frequent manifestations of congenital toxoplasmosis (Metz 2001)
      i. Strabismus (33%)
      ii. Nystagmus (27%)
      iii. Microphthalmia (13%)
      iv. Phthisis (4%)
      v. Microcornea (19%)
      vi. Cataract (10%)
      vii. Active vitritis (11%)
      viii. Active retinitis (11%)
      ix. Chorioretinal scars (79%)
      x. Optic atrophy (20%)

e. Severely affected congenital infection
   i. Die in utero
   ii. Die within a few days of life

Diagnostic Investigations

1. Serological testing (Beasley and Egerman 1998; Lynfield and Eaton 1995)
   a. IgM anti-*Toxoplasma* antibodies
      i. Produced 1–2 weeks after an infection
      ii. Levels detectable for years after the acute infection
   b. IgG anti-*Toxoplasma* antibodies
      i. Levels peak approximately 2 months after the initial infection
      ii. Remain positive for life
   c. IgA anti-*Toxoplasma* antibodies
      i. Parallels IgM production
      ii. Peak levels occur approximately 2 months after the initial infection and then rapidly decline
   d. IgE anti-*Toxoplasma* antibodies
      i. Detected early after an acute infection
      ii. Usually present for 4–8 months
      iii. May provide useful information regarding the timing of an acute infection
2. Detection of antibodies to toxoplasmosis in the neonatal period
   a. Specific *T. gondii* IgM antibody
      i. A positive IgM antibody in the newborn: diagnostic of congenital toxoplasmosis
      ii. A negative IgM antibody in the newborn does not exclude the diagnosis and may be due to the following reasons:
         a) Lack of production of IgM
         b) Waning of the IgM response by the time of birth
         c) Insensitivity of the assay
      iii. A positive IgM antibody in the mother
         a) Associated with recent maternal infection
         b) Would support the diagnosis of congenital toxoplasmosis
   b. Specific *T. gondii* IgA antibody: more sensitive test than IgM antibodies
   c. Neonatal screening with IgM or IgA antibodies fails to detect majority of children with congenital toxoplasmosis when the maternal infection occurred before the 20 week of pregnancy
3. Definitive postnatal diagnosis of congenital toxoplasmosis
   a. Detection of parasites in material collected from the newborn (blood, cerebrospinal fluid, or other clinical material) by inoculation into mice or tissue culture
   b. Detection of persisting specific IgG antibodies at the age of 1 year
   c. Reappearance of specific IgG antibodies in the child after cessation of postnatal antibiotic therapy
   d. Diffuse cerebral calcifications and hydrocephalus detected by radiography, ultrasonography, CT scan, or MRI of the brain
4. Other diagnostic evaluation of the infants
   a. Physical examination
   b. Dilated retinal examination
   c. Examination of the cerebrospinal fluid
      i. Protein
      ii. Glucose
      iii. Cell count
      iv. Antibody determination
   d. Audiologic screen
   e. Examination of the placenta
      i. Evidence of infection, although the gross appearance may not parallel the severity of fetal disease
      ii. Inoculation of the placental tissue into mice or tissue culture to attempt isolation of the parasite
      iii. The feasibility of placental analysis, in terms of sample recovery and rapid *T. gondii* detection by PCR, makes it a useful diagnostic tool for early monitoring and treatment of neonates at risk for congenital infection (Robert-Gangnex et al. 2010)

Genetic Counseling

1. Recurrence risk: women with previous infection not at risk for delivering a fetus with congenital toxoplasmosis unless immunosuppressed
2. Prenatal diagnosis
   a. Seroconversion during pregnancy
      i. Absence of specific *Toxoplasma gondii* IgG antibodies in the first serum sample obtained during gestation
      ii. Detection of specific IgG and IgM antibodies in the follow-up sample at a later prenatal visit or at birth

b. Suggestive but not diagnostic signs by prenatal ultrasonography (Beasley and Egerman 1998)
   i. Ventriculomegaly: the most common sonographic finding in utero
   ii. Intracranial calcifications
   iii. Hydrops
   iv. Microcephaly
   v. Choroid plexus cysts
   vi. Growth retardation
   vii. Hepatomegaly
   viii. Splenomegaly
   ix. Ascites
   x. A thickened placenta
c. Prenatal diagnosis of acute infection in the fetus
   i. Amniocentesis or cordocentesis
      a) Detection of parasites in amniotic fluid or in fetal blood by inoculation into tissue culture or mice
      b) Detection of anti-*Toxoplasma gondii* IgM, IgA, and IgE antibodies in the fetal blood. The diagnosis of fetal *T. gondii* infection before 22 weeks using cordocentesis is not possible because fetal IgM or IgA may not be produced before 22 weeks' gestation
      c) Detection of *T. gondii* DNA (B1 gene) by gene amplification in amniotic fluid: more accurate and faster diagnosis of congenital toxoplasmosis
   ii. Chorionic villus sampling not helpful because it will show placental but not fetal infection

3. Management
   a. Prevention of *Toxoplasma* infection
      i. Cook meat to a safe temperature to kill *Toxoplasma*
      ii. Peel or thoroughly wash fruits and vegetables before eating
      iii. Clean cooking surfaces and utensils after they have contacted raw meat, poultry, seafood, or unwashed fruits or vegetables
      iv. Avoid changing cat litter during pregnancy or use gloves and wash hands thoroughly
      v. Do not feed raw or undercooked meat to cats and keep cats inside to prevent acquisition of *Toxoplasma* by eating infected prey
      vi. Avoid risk factors for *T. gondii* infection including careful adherence to simple hygienic measures during pregnancy (decrease *Toxoplasma* infection by 60%)
   b. Treat *Toxoplasma* infection with spiramycin, pyrimethamine, sulfonamides, and folinic acid
      i. Reduce sequelae of congenital infection by treating the mother as soon as possible after the serologic screening program identifies the infection
      ii. Treat infected neonates: sooner the treatment, the better the outcome
   c. Newborn screening for *Toxoplasma*-specific IgM allows the identification and treatment of subclinical cases so that the sequelae of infection with toxoplasmosis may be prevented or attenuated

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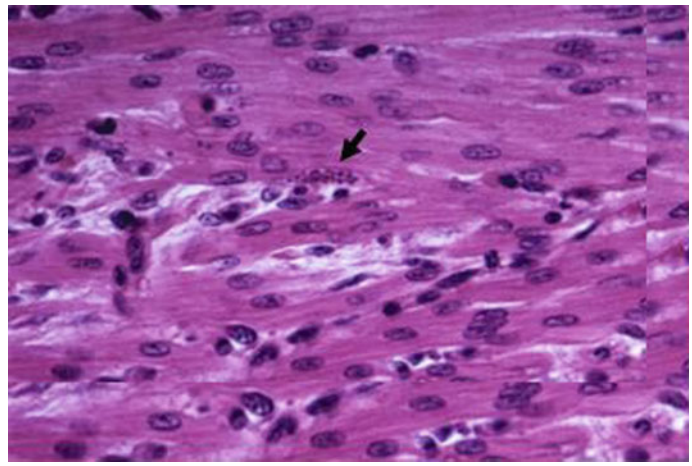

Fig. 1 A newborn died of congenital generalized *Toxoplasma* infection. The heart showed myocarditis with presence of *Toxoplasma* cyst (*arrow*) (H and E, ×400)

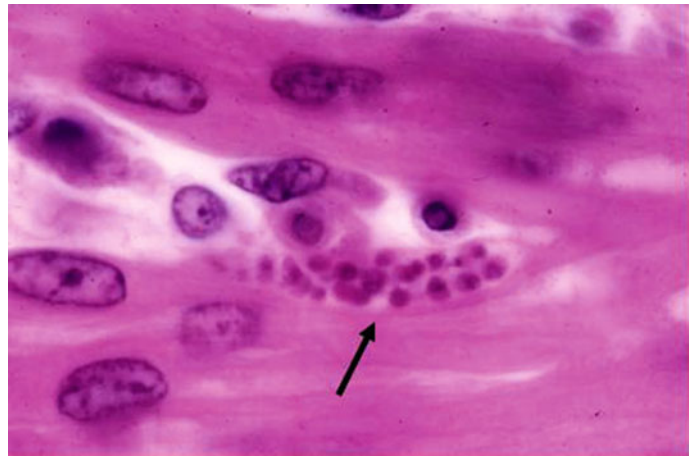

Fig. 2 *Toxoplasma* cyst seen in high magnification (*arrow*) (H and E, ×1,000)

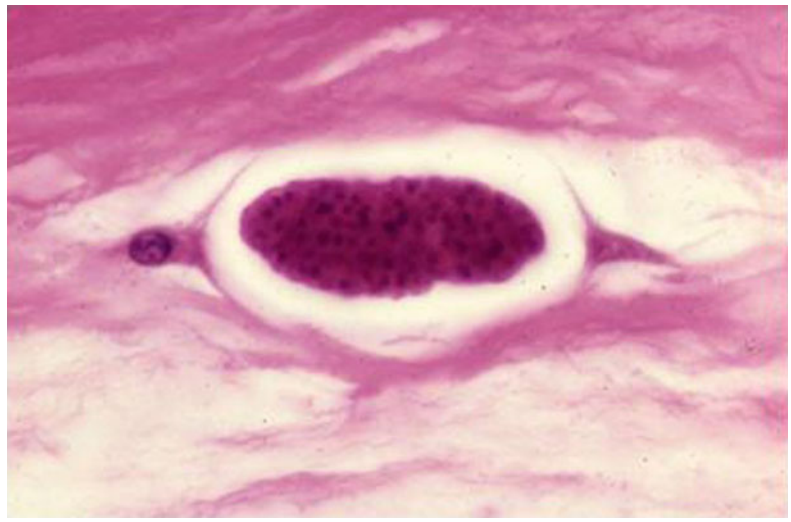

Fig. 3 Mild acute chorionitis associated with *Toxoplasma* infection. A *Toxoplasma* cyst was found in chorionic plate of the placental disc (H and E, ×1,000)

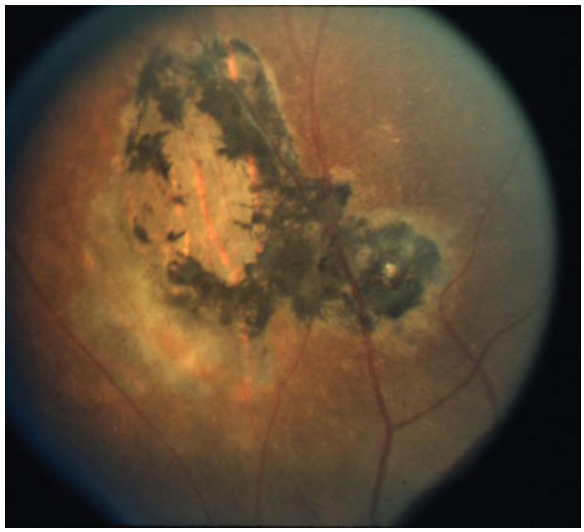

Fig. 4 A small area of resolving acute toxoplasmic retinochoroiditis adjacent to a larger area of healed congenital toxoplasmosis scar

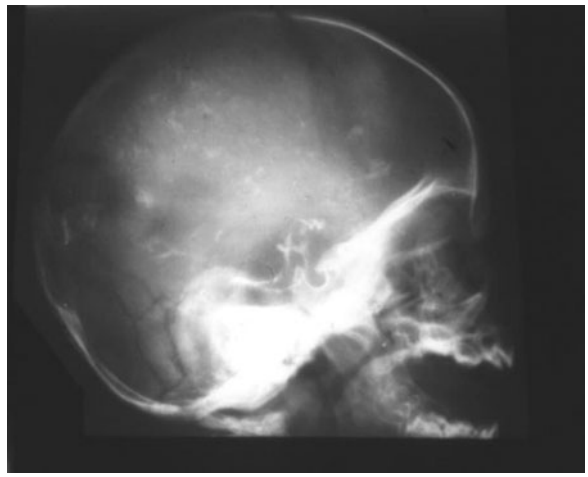

Fig. 6 Diffusely scattered punctate cerebral calcifications secondary to congenitally acquired toxoplasmosis

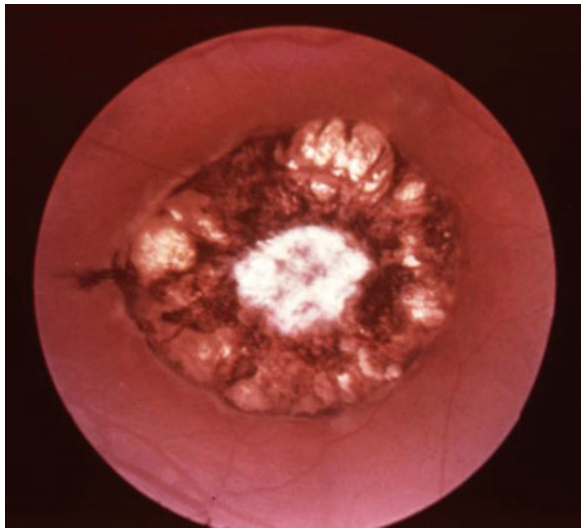

Fig. 5 Satellite lesions of acute exacerbation of toxoplasmic retinochoroiditis adjacent to a larger scar of healed congenital ocular toxoplasmosis

Fig. 7 (**a**, **b**) An adult with congenital toxoplasmosis who had mental retardation, seizures, and chorioretinitis. CT of the brain showed scattered multiple foci of intracerebral calcifications

Conjoined Twins

Conjoined twins are incompletely separated monozygotic twins. They have long fascinated both medical profession and lay public. Such events are rare and occur in 1/50,000 to 1/100,000 births and 1 in 400 sets of monozygotic twins. Over 60% succumb in utero or are stillborn (Spitz 2005). It is a complication of monochorionic twinning at 13–15 days after conception.

Synonyms and Related Disorders

Cephalopagus; Craniopagus; Dicephalus; Diprosopus; Epigastrius; Fetus-in-fetu; Ischiopagus; Omphalopagus; Pygoparus; Rachipagus; Thoracopagus

Genetics/Basic Defects

1. Conjoined twins
   a. Rare variants of monozygotic, monochorionic twins
   b. Two theories of conjoined twin formation
      i. Resulting from the secondary union of two originally separate monovular embryonic disks
      ii. Resulting from an incomplete separation of the inner cell mass at around 13–15 days of gestation of the monovular twins
   c. Twins can be conjoined at any site from the cranium downward to the sacrococcygeal region
   d. Approximately 60% are stillborn
   e. Female predominance: approximately 3:1 female-to-male ratio
2. Embryologic classification of conjoined twins (Spencer 2000a; McHugh et al. 2006; Winkler et al. 2008): Greek word "pagus" is added to denote fixing to union site
   a. Ventral union (87%)
      i. Rostral (48%)
         a) Cephalopagus (11%): fusion from top of head to umbilicus; each twin has two arms and legs; separate lower abdomen and pelvis
         b) Thoracopagus (20–40%): position face to face, with fused thoraces and with a shared heart or single interatrial vessel
         c) Omphalopagus (18–33%): similar fusion to thoracopagus without shared heart or interatrial vessel
      ii. Caudal (11%) (ischiopagus): a large, conjoined pelvis, more commonly joined end to end; can be face to face with a conjoined abdomen; always shared external genitalia and anus
   b. Dorsal union (13%)
      i. Craniopagus (5%): joined by any portion of the skull except the face and foramen magnum, shared cranium, meninges, and occasionally, the brain
      ii. Rachipagus(2%): dorsal fusion above the sacrum
      iii. Pygopagus (6%): fused sacrococcygeal and perineal regions, typically with shared anus but separate rectums; spinal cord may be shared

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   c. Lateral union (28%): Parapagus (side-to-side connection with shared pelvis and variable cephalad sharing), defined as follows:
      i. Dithoracic parapagus (separate thoraces and heads)
      ii. Dicephalic parapagus (separate head with fused thoraces)
      iii. Diprosopus parapagus (two faces on the same side of single head)
3. Anatomic classifications of conjoined twins, based on how the body axes of the twins are mutually oriented in the embryonic disk
   a. Notochordal axes facing each other
      i. Ventro-ventral
         a) Thoracopagus
         b) Xiphopagus
         c) Omphalopagus
      ii. Cranial ventro-ventral (cephalothoracopagus)
      iii. Caudal ventro-ventral (ischiopagus)
      iv. Cranial end to end (craniopagus)
      v. Caudal end to end (pygopagus)
   b. Notochordal axes facing side by side
      i. Dicephalus
      ii. Diprosopus
4. Anatomic classifications of conjoined twins, based on how the subsequent events of migration, growth, and body folding result in different types of conjoined twins
   a. Dipygus
   b. Fetus-in-fetu
      i. A fetiform mass located within a basically normal fetus (Spencer 2001)
      ii. Inclusion of a monozygotic diamniotic twin within the bearer is the best explanation
5. Duplicitas symmetros (symmetrical conjoined twins resulting from incomplete fission of the uniovum) (Gilbert-Barness et al. 2003)
   a. Terata katadidyma (twins joined at the lower part of the body and double above)
      i. Dicephalus (twins with two separate heads and necks side by side with one body; lateral conjugation)
      ii. Diprosopus (twins with two faces side by side, one head, and one body)
      iii. Ischiopagus (twins joined by the inferior margins of the coccyx and sacrum with two completely separate spinal columns; caudal conjugation)
      iv. Pygopagus (twins joined by posterior surfaces of the coccyx and sacrum, back to back; posterior conjugation)
      v. Craniothoracopagus
      vi. Ileothoracopagus
   b. Terata anadidyma (twins joined at the upper part of the body and double below)
      i. Craniopagus (twins joined at the top of cranial vaults; cephalic conjugation)
      ii. Dipygus (twins with one head, one thorax, one abdomen, and double pelvis with or without two sets of external genitalia and up to four legs; lateral conjugation)
      iii. Syncephalus (twins joined by the face; the faces turn laterally)
   c. Terata anakatadidyma (twins joined by the midportion of the body)
      i. Omphalopaus (twins joined from the umbilicus to xiphoid cartilage; anterior conjugation)
      ii. Xiphopagus (twins joined at xiphoid process)
      iii. Rachipagus (twins joint by the vertebral column; back to back)
      iv. Thoracopagus (twins joined at the chest wall; anterior conjugation)
6. Duplicatas asymmetros (asymmetrical conjoined twins resulting from unequal and incomplete fission of the uniovum and unequal placental circulation to twins)
   a. Cephalic conjugation
      i. Craniopagus parasiticus
      ii. Janus parasiticus
      iii. Epignathus heteropagus
   b. Anterior conjugation
      i. Thoracopagus parasiticus
      ii. Epigastrius
   c. Posterior conjugation
      i. Ischiopagus parasiticus
      ii. Pyopagus parasiticus
      iii. Sacral parasiticus

Clinical Features

1. Thoracopagus twins
   a. Represents 40% of conjoined twins
   b. Conjoined at the thoracic region
   c. Face to face

   d. Associated congenital heart defects
      i. Present in 75% of cases
      ii. Presence of varying degree of pericardial sac fusion
      iii. A conjoined heart with two ventricles and a varying number of atria (most frequent abnormality)
      iv. Ventricular septal defect in virtually all patients
2. Omphalopagus twins (fused umbilical region)/ Xiphopagus twins (fused xiphoid process of sternum)
   a. Constitutes one third of all types of conjoined twins
   b. The most readily separable conjoined twins since their union may involve only skin and portions of the liver, occasionally including portions of the sternum
   c. Most omphalopagus twins joined by a skin bridge that contains liver and bowel
   d. Conjoined liver in 81%
   e. Conjoined sternal cartilage in 26%
   f. Conjoined diaphragm in 17%
   g. Conjoined genitourinary tract in 3%
   h. Malformations of the abdominal wall (usually omphalocele) in at least one of the twins in 33%
   i. Congenital heart defects in at least one of the twins in 25%
      i. Ventricular septal defects
      ii. Tetralogy of Fallot
   j. Concordant congenital heart defects in only one out of nine sets of twins
3. Pygopagus twins
   a. Constitutes 19% of conjoined twins
   b. Conjoined at sacrum (buttocks and lower spine)
   c. Most commonly back to back (face away from each other)
   d. May share part of the sacral spinal canal
   e. May share common rectum and anus
   f. Often with fused genitalia
4. Ischiopagus twins
   a. Constitutes 6% of conjoined twins
   b. Conjoined back to back at the coccyx
   c. Often with a common large pelvic ring formed by the union of the two pelvic girdles
   d. May have four legs (ischiopagus tetrapus)
   e. May have three legs (ischiopagus tripus)
   f. Frequently share the lower gastrointestinal tract
      i. Intestines joined at the terminal ileum
      ii. Emptying into a single colon
   g. May have a single bladder and urethra
   h. Displaced anus
   i. Common vaginal anomalies
   j. Common rectovaginal communications
5. Craniopagus twins (fused at the cranial vault) (2%)
   a. Classification according to the area of junction
      i. Frontal craniopagus
      ii. Parietal craniopagus (most common)
      iii. Temporal craniopagus
      iv. Occipital craniopagus
   b. Classification based on surgical and prognostic purposes
      i. Partial type (brains separated by bone or dura with each brain having separate leptomeninges)
      ii. Complete type (presence of cerebral connection)
6. Rachiopagus twins (fused upper spinal column; back to back)
7. Pygodidymus twins (fused cephalothoracic region; duplicate pelves and lower extremities)
8. Pygopagus twins/pygomelus twins (joined back to back at the sacrum; additional limb or limbs at or near buttock)
9. Iniopagus twins/craniopagus occipitalis twins (fused head, at parasitic occipital region)
10. Epicomus twins/craniopagus parasiticus twins (smaller, parasitic twin joined to larger autosite at occiput)
11. Monocephalus twins (single head with two bodies)
12. Diprosopus twins (single body with two faces)
13. Dicephalus twins (symmetric body with two heads)
14. Dipygus parasiticus twins (head and thorax completely merged; pelvis and lower extremities duplicated)
15. Cephalopagus conjoined twins
   a. The rarest type of conjoined twins
   b. Fused from the top of the head to the umbilicus
   c. Presence of two faces on the opposite sides of the head with one face usually being rudimentary
   d. Separation of the lower abdomen
   e. With four arms and four legs
   f. Prognosis dismal dependent on the following factors
      i. Presence of associated anomalies
      ii. Degree of fusion of the intracranial, intra-thoracic, and/or intra-abdominal structures
      iii. Extent of venous connections

16. Epigastric heteropagus twins
    a. A rare type of conjoined twinning
    b. Resulting from an ischemic atrophy of one fetus at an early stage of gestation
    c. Pelvis and lower limbs of the ischemic fetus (incomplete parasitic twin; heteropagus) attached to the epigastrium of the well-developed fetus (the autosite)
17. Fetus-in-fetu
    a. The parasites embodied in the autosite, usually within cranial, thoracic, and abdominal cavities during the developmental process of the asymmetrical conjoined twins
    b. Most likely arise from inclusion of a monochorionic, diamniotic, monozygotic twin within the bearer due to anastomoses of vitelline circulation (Nastanski and Downey 2001)
18. Prognosis
    a. A high mortality rate
        i. Nearly 40% are stillborn.
        ii. One third die within 24 h of birth.
        iii. No prospect of survival when complex cardiac union is present.
    b. Causes of death
        i. Severely abnormal conjoined heart
        ii. Pulmonary hypoplasia due to distortion of fused thoracic cages
19. Examples of historically famous conjoined twins (Sills et al. 2001; Gilbert-Barness et al. 2003; Spitz 2005)
    a. So-called Biddenden Maids (1100–1134) in England
        i. Probably pyopagus twins
        ii. Their famous image imprinted on the "cakes"
        iii. Walks with their arms around each other
        iv. They lived together for 34 years and died within 6 h
    b. Chang and Eng Bunker (1811–1874) from Bangkok and settled in the USA ("Siamese twins")
        i. Born on a river boat in Siam
        ii. Joined at the xiphisternum by a short bank that stretched so they were eventually able to stand side by side
        iii. Taken by Hunter, a traveling Scottish merchant, to the USA where they were exhibited by the showman
        iv. Later married to twin sisters
        v. Fathered 22 children
        vi. Lived together for 63 years and one died shortly from other twin
    c. Blažek sisters (1878–1922) from Bohemia
        i. Two heads
        ii. Four arms
        iii. Four legs
        iv. Partially fused torso
        v. Combined reproductive organs
        vi. Delivered an infant through a single vagina but the gestation had occurred in the uterus of one of the twins

Diagnostic Investigations

1. Prenatal echocardiography
    a. Presence and extent of cardiac conjunction
    b. Associated cardiac defects
2. Prenatal radiography
3. Prenatal ultrasonography (including transvaginal two-dimensional sonography), especially three-dimensional sonographic examinations (The surface-rendered image of the conjoined twin and its demonstration on an axially rotating cine loop facilitates explanation of the precise nature of the abnormalities, especially in the case of cephalothoracopagus conjoining)
4. CAT scan and MRI of the abdomen and the chest
    a. Anatomy of the heart
    b. Anatomy of the livers
    c. Anatomy of the genitourinary systems
5. Gastrointestinal contrast studies to demonstrate the presence and level of conjunction of the intestinal tract
6. Ventrally fused conjoined twins
    a. Prenatal radiography/ultrasonography
        i. Fetal body parts on the same level
        ii. Constant relative fetal position
        iii. Fetal extremities in unusual proximity
        iv. Face-to-face fetal position
        v. Bibreech, less commonly bicephalic presentation
        vi. Hyperextension of one or both cervical spines
    b. Prenatal ultrasonography
        i. Nonseparable continuous external skin contour
        ii. Single heart sound by Doppler

iii. Solitary large liver and heart
iv. Multiple shared omenta
v. Solitary umbilical cord with >3 vessels

7. Cephalothoracopagus
   a. Prenatal radiographic criteria
      i. Both fetal heads at the same level
      ii. Backward fusion of the cervical spines
      iii. A narrow space between lower cervical and upper thoracic spines
      iv. No change in fetal relative positions after maternal movement
   b. Prenatal sonographic criteria
      i. Fusion of the skulls, face, thorax, and upper abdomen
      ii. Fetal body parts at the same level
      iii. Constant relative fetal motion
      iv. Fetal extremities in unusual positions
      v. Breech position
      vi. Hyperextension of both cervical spines
      vii. Nonseparable external skin contour
      viii. A solitary umbilical cord with multiple vessels
      ix. Polyhydramnios
      x. Two actively beating hearts
      xi. Two sets of pelves, limbs, and spine

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not higher according to family study
   b. Patient's offspring: report of delivery of a healthy male infant to the pygopagus Blažek sisters
2. Prenatal diagnosis
   a. Radiography
   b. 2D/3D ultrasonography: prenatal diagnosis made as early as 10–12 weeks' gestation
   c. Transcervical embryoscopy for first trimester embryonic evaluation of conjoined twins after a missed abortion
3. Management
   a. Early prenatal diagnosis: highly desirable, given the extremely poor prognosis of some types of conjoined twins
   b. Psychological and prognosis counseling
   c. Accurate preoperative investigation
   d. A team approach
   e. Previous experience
   f. Meticulous operative and postoperative management
   g. Substantial mortality rate related to the underlying conditions
   h. High likelihood of success if major associated anomalies are absent
   i. Options of obstetrical management
      i. Continue the vaginal delivery and deliver the twins intact
      ii. Deliver the twins vaginally after intrauterine separation or a destructive procedure
      iii. Cesarean section and deliver the twins intact
      iv. Cesarean section and deliver the twins after intrauterine separation or destruction
   j. Anesthetic management for separating operations
      i. Extensive cross circulation
         a) Through a liver bridge
         b) Common cerebral venous sinus
      ii. Mechanical problems
         a) One anesthetist required for each infant
         b) A third anesthetist to look after intravenous infusions and monitors
         c) A fourth anesthetist to look after massive blood loss, circulatory collapse, or other catastrophic occurrence
      iii. Anticipate complex congenital heart defects that was not diagnosed preoperatively
   k. Four separate time frames of management (Spitz 2005)
      i. Prenatal
         a) Define the anatomy of the union once the diagnosis of conjoined twins is suspected
         b) Termination can be considered in the event of complex cardiac fusion in thoracopagus twins or extensive cerebral fusion in craniopagus twins: required detailed echocardiography and accurate ultrasonography complemented as necessary with MRI scanning
         c) Obtain informed decision as to either terminate or proceed with the pregnancy
         d) Delivery by cesarean section at 36–38 weeks of gestation
      ii. Nonoperative treatment
         a) In the presence of complex cardiac fusion
         b) Where a severe unacceptable deformity would follow separation

iii. Emergency separation
   a) When one twin is dead or dying, threatening the survival of the remaining twin
   b) Presence of a life-threatening correctable congenital abnormality (e.g., intestinal atresia, malrotation with or without volvulus, ruptured omphalocele, or anorectal agenesis)
   c) Emergency separation carries a significantly higher mortality rate compared with elective procedures

iv. Elective separation
   a) Normally takes place between 2 and 4 months
   b) Allows time to stabilize, thrive, carry out detailed investigation to define the nature and the extent of union, and detailed planning of the operative procedure with all members of the operating team
   c) Survival rate: approaches 80%

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Fig. 1 The conjoined twins are joined at the level of abdomen from umbilicus to the xiphoid cartilage (xiphoomphalopagus). This type of conjoined twins is the one most amenable to successful surgical correction because the incidence of complex anatomical anomalies is low. Left twin was successfully separated from the right twin who succumbed shortly after surgery to multiple congenital anomalies including exstrophy of the cloaca, left Bochdalek hernia, hypoplastic kidney, hypoplastic lungs, imperforate anus, and a large sacral meningomyelocele

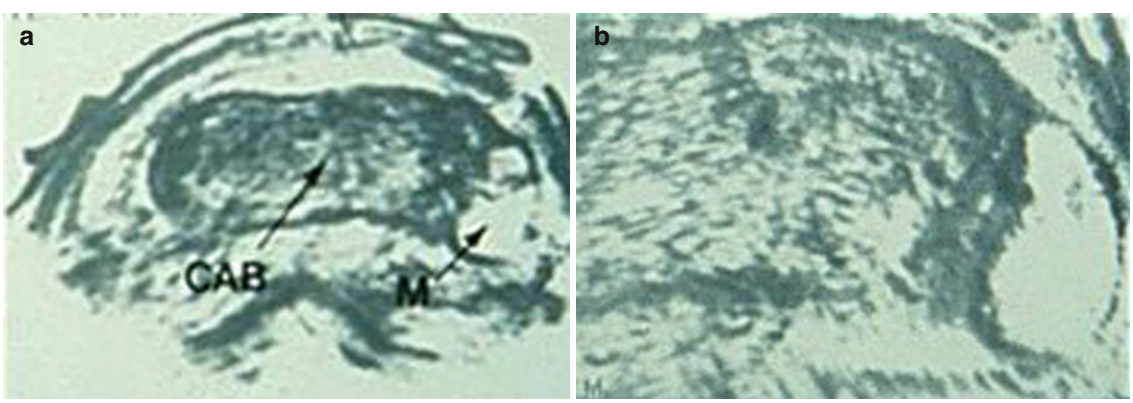

Fig. 2 Prenatal ultrasound (**a**) detected the above conjoined twins with a shared liver (CAB) and separate hearts, stomach, pelvis, and extremities. One fetus was noted to have a meningomyelocele (M). The magnified view (**b**) shows part of the shared liver and meningomyelocele

Fig. 3 These twins are thoraco-omphalopagus, connected at the thorax and upper abdomen. The heart showed complex anomalies with a common atrium and a single ventricle. Therefore, separation of the twins was not attempted

Fig. 4 The radiograph of the twins in Fig. 3 showing the connection at the thorax and the upper abdomen

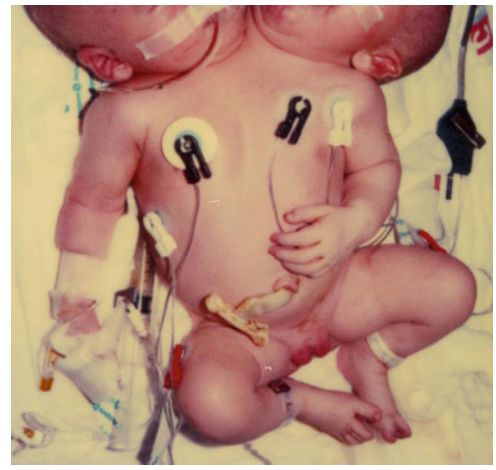

Fig. 5 Dicephalic conjoined twins. Two separate heads, two separate necks, and only one body are evident. The twins shared a common pericardium with complex cardiac anomalies, a common aorta at the level of iliac arteries, a common small intestine and other GI tract distally, a common bladder and urethra drained from a single kidney from each twin, and single normal female genitalia with normally placed fallopian tubes and ovaries. Surgical separation of the twins was deemed impossible and was not attempted

Fig. 6 Prenatal ultrasound study showed lateral view of the dicephalic twins with two heads side by side, one trunk with two overlapping vertebral columns, and two *upper* extremities

Fig. 7 Prenatal ultrasound study showed two separate vertebral columns

Fig. 9 The postnatal radiograph of the above conjoined twins showing separate heads, separate vertebrae, and separate *upper* GI tract. There is one pericardium sac and a fused liver

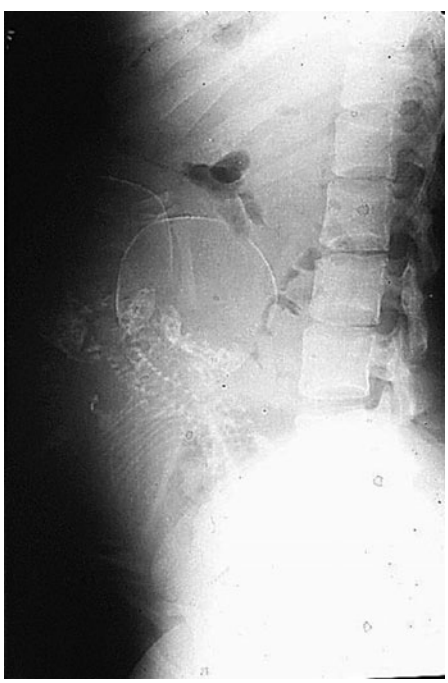

Fig. 8 Prenatal radiographic study showed dicephalic twins with two separate heads and two separate vertebral columns

Fig. 10 A stillbirth with dicephalic conjoined twins

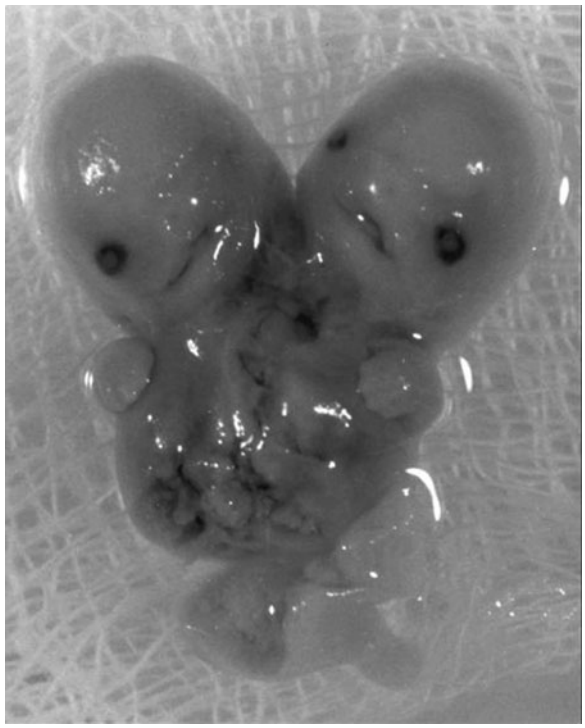

Fig. 11 A set of dicephalic conjoined twin embryos at 6–7 weeks of gestation

Corpus Callosum Agenesis/Dysgenesis

The corpus callosum is an interhemispheric structure that permits the integration of motor, sensory, and cognitive performance between the two cerebral hemispheres. Agenesis/dysgenesis of the corpus callosum is among the most common brain developmental malformation with a wide spectrum of associated clinical and pathologic abnormalities. The prevalence and clinical significance are uncertain. It is estimated to be 0.3–0.7% in the general population and 2–3% in the developmentally disabled (Jeret et al. 1985).

Synonyms and Related Disorders

Agenesis of corpus callosum; Dysgenesis of corpus callosum

Genetics/Basic Defects

1. Markedly heterogeneous etiology of agenesis/dysgenesis of the corpus callosum (Dobyns 1996)
   a. Sporadic in most cases
   b. Environmental factors
      i. Alcoholism
      ii. Maternal rubella
      iii. Maternal diabetes
   c. A multifactorial trait
   d. As a part of autosomal dominant syndrome
      i. Agenesis/dysgenesis of the corpus callosum
      ii. Apert syndrome
      iii. Basal cell nevus syndrome
      iv. Miller–Dieker syndrome
      v. Rubinstein–Taybi syndrome
      vi. Tuberous sclerosis
   e. As a part of autosomal recessive syndrome
      i. Agenesis/dysgenesis of the corpus callosum
      ii. Agenesis/dysgenesis of the corpus callosum with thrombocytopenia
      iii. Acrocallosal syndrome
      iv. Andermann syndrome
         a) Agenesis/dysgenesis of the corpus callosum with peripheral neuropathy
         b) Mapping of the gene to a 5-cM region in chromosome 15q13-15
      v. Cerebro-oculo-facio-skeletal (COFS) syndrome
      vi. Cogan syndrome (ocular motor apraxia)
      vii. Craniotelencephalic dysplasia
      viii. Dincsoy syndrome
         a) Multiple midline malformations
         b) Limb abnormalities
         c) Hypopituitarism
      ix. Fukuyama congenital muscular dystrophy
      x. Hydrolethalis syndrome
      xi. Joubert syndrome (cerebellar vermis agenesis)
      xii. Leprechaunism
      xiii. Lowry–Wood syndrome
         a) Epiphyseal dysplasia
         b) Microcephaly
         c) Nystagmus
      xiv. Meckel–Gruber syndrome
      xv. Microcephalic osteodysplastic primordial dwarfism type I/III
      xvi. Neu–Laxova syndrome
      xvii. Opitz G syndrome
      xviii. Peters plus syndrome
         a) Peters anomaly
         b) Short-limb dwarfism

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xix. Shapiro syndrome (recurrent hypothermia)
xx. Smith–Lemli–Opitz syndrome
xxi. Toriello–Carey syndrome
  a) Agenesis/dysgenesis of the corpus callosum
  b) Facial anomalies
  c) Robin sequence
xxii. Vici syndrome
  a) Agenesis/dysgenesis of the corpus callosum
  b) Immunodeficiency
  c) Cleft lip/palate
  d) Cataract
  e) Hypopigmentation
xxiii. Walker–Warburg syndrome
  a) Hydrocephalus
  b) Agyria
  c) Retinal dysplasia
xxiv. Warburg micro syndrome
  a) Microcephaly
  b) Microphthalmia
  c) Cerebral malformations
  d) Other anomalies

f. As a part of X-linked syndrome
  i. Agenesis/dysgenesis of the corpus callosum
  ii. Agenesis/dysgenesis of the corpus callosum with Hirschsprung disease
  iii. Agenesis/dysgenesis of the corpus callosum with hypohidrotic ectodermal dysplasia
  iv. Aicardi syndrome (retinovertebral anomalies in females)
  v. ATR-X syndrome (X-linked alpha thalassemia mental retardation syndrome)
  vi. Craniofrontonasal syndrome
  vii. Curatolo syndrome
    a) Agenesis/dysgenesis of the corpus callosum
    b) Chorioretinal abnormality
  viii. FG syndrome
    a) Mental retardation
    b) Large head
    c) Imperforate anus
    d) Congenital hypotonia
    e) Partial agenesis/dysgenesis of the corpus callosum
  ix. HSAS syndrome (*h*ydrocephalus due to congenital *s*tenosis of *a*queduct of *S*ylvius)
  x. Lenz dysplasia
    a) Microphthalmia/anophthalmia
    b) Associated anomalies
  xi. Lujan–Fryns syndrome
    a) X-linked mental retardation
    b) Marfanoid habitus
  xii. MASA syndrome
    a) *M*ental retardation
    b) *A*phasia
    c) *S*huffling gait
    d) *A*dducted thumbs
  xiii. MLS syndrome
    a) *M*icrophthalmia
    b) *L*inear *s*kin defects
  xiv. Opitz G syndrome
  xv. OFD I
  xvi. Proud syndrome
    a) X-linked syndrome
    b) Seizures
    c) Acquired micrencephaly
    d) Agenesis/dysgenesis of the corpus callosum
  xvii. XLIS syndrome (X-linked lissencephaly)

g. As a part of unknown-genesis syndrome
  i. Calloso-genital dysplasia
  ii. Delleman (oculocerebrocutaneous) syndrome
  iii. Frontonasal dysplasia
  iv. Opitz C trigonocephaly syndrome
  v. Sebaceous nevus syndrome

h. As a part of metabolic disorders
  i. Adenylosuccinase deficiency
  ii. Adipsic hypernatremia
  iii. β-hydroxyisobutyryl coenzyme A deacyclase deficiency
  iv. Glutaric aciduria type II
  v. Histidinemia
  vi. Hurler syndrome
  vii. Leigh syndrome
  viii. Menkes syndrome
  ix. Neonatal adrenoleukodystrophy
  x. Nonketotic hyperglycinemia
  xi. Pyruvate dehydrogenase deficiency
  xii. Zellweger syndrome

i. Associated chromosome abnormalities
  i. Trisomy 18
  ii. Trisomy 8
  iii. Trisomy 21
  iv. Trisomy 22
  v. Other trisomies

vi. Deletions
vii. Translocations
viii. Duplications
j. Agenesis of the corpus callosum with interhemispheric cyst: a heterogeneous group of disorders that have in common callosal agenesis and extraparenchymal cysts, both of which are among the commonest CNS malformations (Barkovich et al. 2001)
k. Incidental finding in normal individuals (isolated dysgenesis of the corpus callosum)

2. Embryogenesis of the corpus callosum
   a. Development of the corpus callosum
      i. A late event in cerebral ontogenesis
      ii. Taking place between 12 and 18 weeks of gestation
   b. An important brain commissure connecting the cerebral hemispheres (Achiron and Achiron 2001)
   c. Essential for efficient cognitive function (Achiron and Achiron 2001)
   d. Failure of development of the commissural fibers connecting the cerebral hemispheres produces dysgenesis or agenesis of the corpus callosum
   e. Diagnosis of agenesis: a challenge even for expert sonologists, particularly prior to 20 weeks of gestation
3. Types of agenesis
   a. Complete agenesis: commonly regarded as a malformation deriving from faulty embryogenesis
   b. Type I agenesis
      i. Not associated with other disorders
      ii. Usually absent or associated with mild neurologic manifestations
   c. Type II agenesis
      i. Associated with other migrational, genetic, and chromosomal disorders
      ii. Usually associated with severe neurologic manifestations
   d. Partial agenesis
      i. Referred to as dysgenesis
      ii. Either a true malformation or a disruptive event occurring at any time during pregnancy
      iii. Missing caudad portion (splenium and body) to varying degrees
4. Agenesis/dysgenesis of the corpus callosum (da-Silva 1988)
   a. Without other associated brain anomalies
   b. Frequently associated with other brain anomalies
      i. Defects of septum pellucidum and fornix
      ii. Hydrocephalus
      iii. Dandy–Walker malformation
      iv. Interhemispheric cyst
      v. Holoprosencephaly
      vi. Porencephaly
      vii. Polymicrogyria
      viii. Macrogyria
      ix. Cortical heterotopia and atrophy
      x. Lipoma
      xi. Encephalocele
      xii. Hypoplasia of cerebellum
   c. Frequently associated other anatomical anomalies
      i. Congenital heart defects
      ii. Costovertebral defects
      iii. Gastrointestinal anomalies
      iv. Genitourinary anomalies

Clinical Features

1. Craniofacial abnormalities
   a. Microcephaly
   b. Macrocephaly
2. Developmental anomalies
   a. Nonspecific mental retardation
   b. Developmental delay
   c. Learning disabilities
   d. Behavioral disorder
   e. Mental retardation
   f. Failure to thrive
3. Infantile spasms/seizures
4. Signs and symptoms related to type I and type II agenesis
   a. Type I
      i. Variable intelligence: normal to mild or moderate mental retardation
      ii. Seizure disorder
      iii. Impaired visual, motor, and/or bimanual coordination
      iv. Mild impairment of crossed tactile localization and skills requiring matching of visual patterns
   b. Type II
      i. Mental retardation
      ii. Seizures
      iii. Hydrocephaly

iv. Microcephaly
v. Hemiparesis
vi. Diplegia
vii. Spasticity
viii. Failure to thrive

Diagnostic Investigations

1. Psychometric tests (Finlay et al. 2000)
   a. Difficulties in motor coordination
   b. Difficulties in interhemispheric transfer of tactile information
   c. Difficulties in some areas of memory
   d. A marked difference in verbal IQ and performance IQ in children
2. EEG for seizure activities
3. CT and/or ultrasound of the brain (Gupta and Lilford 1995)
   a. Absence of the corpus callosum
   b. Absence of septum pellucidum
   c. Increased separation of the lateral ventricles
   d. Marked separation of the slit-like anterior horns of the lateral ventricles and dilatation of the occipital horns creating the typical "rabbit's ear" or "tear drop" appearance
   e. Upward displacement of the third ventricle
   f. Evidence of other migration disorders
4. Coronal radiographs showing a pathognomonic bat-wing ventricular pattern
5. Karyotyping for underlying chromosomal disorder
6. Metabolic studies for underlying inborn error of metabolism

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: depending on the etiology and the mode of inheritance
      i. Isolated agenesis/dysgenesis of the corpus callosum: recurrence risk not increased
      ii. Environmental factor: recurrence risk not increased by avoiding the environmental factor
      iii. Autosomal recessive inheritance: 25% of siblings affected, 50% siblings carriers, and 25% of siblings normal
      iv. Autosomal dominant inheritance: recurrence risk not increased unless a parent is affected in which case the recurrence risk is 50%
      v. X-linked recessive inheritance
         a) Carrier mother (50% of brothers affected; 50% of sisters carriers)
         b) Affected father (all brothers normal, all sisters carriers)
      v. X-linked dominant inheritance
         a) Affected mother (50% of brothers and sisters affected)
         b) Affected father (all brothers normal; all sisters affected)
      vi. Chromosomal disorder: recurrence risk increased, especially if a parent carries a balanced translocation
   b. Patient's offspring
      i. Environmental factor: recurrence risk not increased by avoiding the environmental factor
      ii. Autosomal recessive inheritance: recurrence risk not increased unless the spouse is also a carrier in which case the recurrence risk is 50%
      iii. Autosomal dominant inheritance: 50%
      iv. X-linked recessive inheritance
         a) Carrier female (50% of sons affected, 50% of daughters carriers)
         b) Affected male (all sons normal, all daughters carriers)
      v. X-linked dominant inheritance
         a) Affected female (50% of sons and daughters affected)
         b) Affected male (all sons normal, all daughters affected)
      vi. Chromosomal disorder: recurrence risk increased, especially if a parent carries a balanced translocation
2. Prenatal diagnosis
   a. Ultrasonography
      i. Prenatal detection of the agenesis of the corpus callosum usually not possible before 22 weeks of gestation (Bennett et al. 1996)
      ii. Direct demonstration of the absence or partial absence of the corpus callosum

iii. Failure to visualize the cavum septum pellucidum
iv. Third ventricle lying between widely separated lateral ventricles due to absent corpus callosum
v. Lateral ventricles more parallel to the midline than usual
vi. A cyst arising from the superior aspect of the third ventricle communicating with the lateral ventricles
vii. Vertical orientation of the gyri with agenesis instead of normal horizontal alignment
viii. Colpocephaly (locally dilated occipital horns of the lateral ventricle) forming an appearance on axial views similar to bulls' horns
ix. Absence of pericallosal artery
x. Up to 50% of cases with other associated anatomic defects
xi. Variable developmental outcome on prenatal detection of an isolated agenesis of the corpus callosum

b. MRI
   i. Allows more detailed visualization of the fetal brain than ultrasonography
   ii. Constitutes a useful additional procedure after ultrasonographic diagnosis or suspicion of corpus callosum agenesis
c. Amniocentesis recommended for karyotyping as there is 10–20% risk of aneuploidy associated with the agenesis of the corpus callosum
d. Prenatal counseling for ultrasonically diagnosed fetal agenesis of the corpus callosum remains very difficult, as giving precise information on outcome is impossible. (Moutard et al. 2003) The following observation, however, may be of help in prenatal counseling: (Gupta 1995)
   i. Isolated agenesis/dysgenesis of the corpus callosum (in the absence of other sonographically detectable anomalies) carrying apparent excellent prognosis
      a) 85% chance of a normal developmental outcome
      b) 15% risk of handicap
   ii. Agenesis/dysgenesis of the corpus callosum with other associated anomalies: poor outcome

3. Management
   a. Identification of actual deficits resulting from the absence of such a major structure (corpus callosum): clearly an issue
   b. Multidisciplinary team approach to intervention programs
   c. Anticonvulsants for seizures
   d. Management based on the underlying etiology

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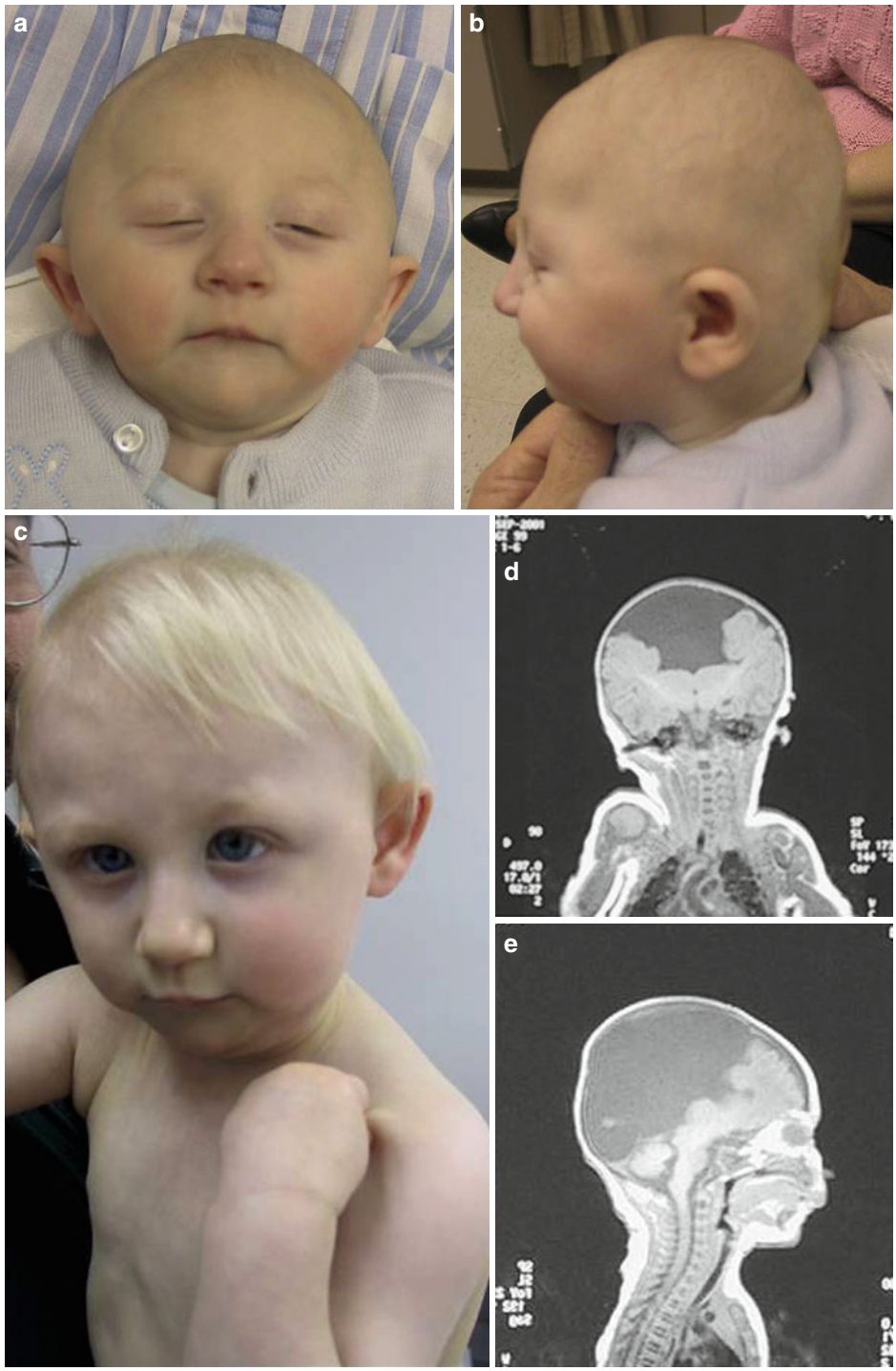

Fig. 1 (**a**–**e**) An infant (ages 3 months and 16 months) with agenesis of the corpus callosum and interhemispheric cyst, illustrated by MRI

Craniometaphyseal Dysplasia

In 1954, Jackson et al. coined the term "craniometaphyseal dysplasia" for a hereditary bone disease with metaphyseal widening of the tubular bones and bony overgrowth of the facial and skull bones (leonteasis ossea).

Genetics/Basic Defects

1. Genetic heterogeneity (Beighton 1995)
   a. Autosomal dominant form [also called CMD, Jackson type (CMDJ)]:
      i. CMDJ locus mapped to 5p15.2-p14.1 within a region harboring the human homolog (*ANKH*) of the mouse progressive ankylosis (*ank*) gene
      ii. Mutations in ANKH have been associated in craniometaphyseal dysplasia in some families (Nürnberg et al. 2001; Reichenberger et al. 2001)
      iii. ANKH mutations that cause CMD most likely entail a loss of function (Kornak et al. 2010) or a loss of ANKH protein expression and activity in the plasma membrane as a result of aberrant intracellular protein trafficking (Zajac et al. 2010)
   b. Autosomal dominant form cosegregating with chondrocalcinosis
      i. Mutations in ANKH have been associated with familial chondrocalcinosis (OCAL2) in some families (Pendleton et al. 2002; Williams et al. 2003)
      ii. A family was reported with an *ANKH* mutations in which these conditions cosegregated in some affected family members (Baynam et al. 2009)
   c. Autosomal recessive form
      i. Rare
      ii. Ill-defined
      iii. Probably heterogeneous
      iv. Often difficult to diagnose with precision
      v. Autosomal recessive CMD locus mapped to 6q21-22
2. Basic defects
   a. Autosomal dominant form: caused by mutations in the human homolog of the mouse progressive ankylosis gene (*ANKH*) (Reichenberger et al. 2001)
   b. Autosomal recessive form (Beighton 1995)
      i. May involve dysfunctional osteoclasts because reported metabolic responses of affected children to therapy with calcitonin and clacitrol
      ii. Osteoclast-like cells derived from the bone marrow shown to lack expression of the osteoclast vacuolar proton pump

Clinical Features

1. Autosomal dominant form
   a. General features
      i. Good general health
      ii. Normal intelligence
      iii. Normal stature
   b. Bony overgrowth of the facial bone resulting in the typical facies:
      i. Frontal bossing
      ii. Hypertelorism
      iii. Paranasal bossing (30% of cases in childhood)
         a) May be present during infancy
         b) Tends to regress with age

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c) Virtually absent by adolescence and early adulthood
d) May be associated with some degree of nasal obstruction and frequent mouth breathing

iv. Mild to moderate mandibular prognathism
v. An open mouth secondary to bony encroachment of the nasal passages
vi. Malalignment of the teeth
vii. Grotesque hyperostosis of the facial bones
viii. Decreased facial movement

c. Bony overgrowth of the cranial foramina resulting in the following features:
i. Cranial nerve paralysis
ii. Nystagmus
iii. Optic atrophy
iv. Facial palsy (30% of cases)
a) Common but variable
b) May be unilateral or bilateral
c) May occur at any age
d) The involvement often fluctuant in early childhood
e) May be permanent in adulthood
v. Deafness (50% of cases)
a) Due to compromised auditory nerve and inner ear by bone overgrowth
b) May be unilateral or bilateral
c) Often "mixed" in type due to chronic otitis media and upper respiratory tract infection secondary to minor anatomical abnormalities of the airway and sinuses
d) Usually partial and rarely profound
vi. Less commonly reported conditions (Kietzer and Paparella 1969)
a) Compression of the cerebellar tonsils and medulla secondary to a narrowed foramen magnum
b) Obstruction of Eustachian tube
c) Obstruction of nasolacrimal duct
d) Obstruction of nasal passages
e) Raised intracranial pressure: rare instances of a potentially lethal rise in intracranial pressure due to hyperostosis of the calvarium

d. Abnormal modeling of the metaphyses of the long bones
i. Metaphyseal widening of the long and short tubular bones
ii. Thin cortical layer
iii. Coarse trabeculations

e. Clinical and radiographic features improved in later childhood in the dominant form

2. Autosomal recessive form
a. Similar to, but more severe than, those seen in the dominant form
b. An increasing severity with age
c. Progressive overgrowth and craniofacial deformity
i. Very severe facial distortion
ii. A thick bony wedge over the bridge of the nose
iii. Dystopia canthorum
iv. Ocular hypertelorism
v. Enlarged malar prominences and mandible (marked prognathism)
vi. Wide alveolar ridge
vii. Narrowed nasal passages leading to mouth breathing
viii. Dental abnormalities
ix. Blindness
x. Facial palsy
xi. Deafness

d. Abnormal modeling of the metaphyses of the long bones
i. Gradual, club-shaped widening of the metaphyses
ii. Thin cortex and undermineralized medullary bone

3. Differential diagnosis (Cole and Cohen 1988)
a. Pyle disease (metaphyseal dysplasia)
i. Frequently confused with craniometaphyseal dysplasia. In Pyle disease, metaphyseal flaring occurs but there is minimal involvement of the skull
ii. Autosomal recessive inheritance

b. Craniodiaphyseal dysplasia (Cole and Cohen 1988)
i. Most severe thickening, distortion, and enlargement of the craniofacial region
ii. Characterized by diaphyseal endostosis
iii. Does not exhibit metaphyseal flaring
iv. Inheritance likely autosomal recessive

c. Frontometaphyseal dysplasia (Cooper 1974)
i. A pronounced bony supraorbital ridge
ii. Hirsutism
iii. Long-bone alterations
iv. Conductive deafness

d. Camurati–Engelmann disease (progressive diaphyseal dysplasia) (Cooper 1974)
   i. Presence of excess subperiosteal bone in the diaphyses of the long bone
   ii. Normal metaphyses
   iii. Rare craniofacial involvement
e. Van Buchem disease (hyperostosis corticalis generalisata) (Cooper 1974)
   i. Dense and thickened craniofacial skeleton
   ii. Generalized cortical thickening of the long bones mainly due to endosteal bone apposition

Diagnostic Investigations

1. Normal serum calcium, phosphorous, and alkaline phosphatase
2. Radiographic features (Beighton 1995)
   a. Autosomal dominant form: age-related radiographic features
      i. Characteristic hyperostosis and sclerosis of the skull
      ii. Paranasal bony bossing, most evident in early childhood
      iii. May be present with prognathism and asymmetry
      iv. Characteristic non-sclerotic widening of the metaphyses of the tubular bones: a major radiographic feature
         a) Most obvious at the lower end of the femur
         b) An "Erlenmeyer flask" configuration in childhood
         c) A "club" shape in adulthood
   b. Autosomal recessive form: severe radiographic manifestations (Penchaszadeh et al. 1980)
      i. Increasing severity with age
      ii. Sclerosis and hyperostosis of the calvarium, the base of the skull, and the facial bones and mandible
      iii. Increased bone deposition on the walls of the paranasal sinuses
      iv. Underpneumatization of mastoid cells
      v. Gradual, club-shaped widening of the metaphyses
      vi. Thin cortex and undermineralized medullary bone
3. Gross pathological features (Kietzer and Paparella 1969)
   a. Thickened "ivory-hard" facial and cranial bones
   b. Narrow cranial foramina
   c. Narrowing of the nasal chambers and posterior choanae
4. Histological features (Kietzer and Paparella 1969)
   a. Compact laminar cortical bone with dilated Haversian canals containing osteoblasts
   b. No osteoclasts identified in the periosteal or endosteal layers
   c. An increased amount of ground substance and excessive formation of subperiosteal and subendosteal bone
5. Molecular genetic analysis for human ankylosis gene (*ANKH*): Sequence analysis detects mutations in about 90% of individuals meeting the diagnostic criteria for CMD (Reichenberger and Chen 2010)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal dominant form: 50% risk if one parent is affected, otherwise risk not increased
      ii. Autosomal recessive form: 25%
   b. Patient's offspring
      i. Autosomal dominant form: 50%
      ii. Autosomal recessive form: not increased unless the spouse is also a carrier in which case there is 50% recurrence risk
2. Prenatal diagnosis for pregnancies at risk may be available through laboratories offering custom prenatal testing if the disease-causing mutations in the family is known (Reichenberger and Chen 2010)
3. Management
   a. Medical treatment attempted with the following two hormones
      i. Calcitonin: has an inhibitory effect on bone formation
      ii. Calcitriol (Key et al. 1988)
         a) Stimulates resorption of bone by promoting osteoclast formation
         b) Partial resolution of facial nerve paralysis, increased size of the cranial nerve foramina, and demineralization of the

cranial base during treatment of one patient with high doses of calcitriol

b. Hearing aids for hearing loss
c. Psychological support for facial disfigurement
d. Surgical treatment with mixed results (Day et al. 1997)
   i. Resection of dysplastic bone arduous because it is highly mineralized with a consistency like thick ivory
   ii. Craniofacial reduction performed with some difficulty
   iii. Optic canal decompression for progressive visual loss
   iv. Facial nerve decompression
   v. Middle ear exploration and implantation of total ossicular replacement prosthesis for conductive hearing loss
   vi. Foramen magnum decompression for cervicomedullary encroachment

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Fig. 1 (**a**–**d**) A girl with craniometaphyseal dysplasia showing characteristic craniofacial features consisting of hypertelorism, broadening nasal base with paranasal bossing, short nose, and prominent facial bones

Cri-Du-Chat Syndrome

Cri-du-chat syndrome is a chromosome 5p deletion syndrome first described by Lejeune et al. in 1963. The name of the syndrome refers to the most characteristic clinical feature, a high-pitched crying similar to the mewing of a cat, which usually disappears in the first years of life. The incidence is estimated to be approximately 1 in 15,000 (Higurashi et al. 1990) to 1 in 50,000 births (Niebuhr 1978). The prevalence among mentally retarded individuals is approximately 1.5 in 1,000.

Synonyms and Related Disorders

Cat cry syndrome; Chromosome 5p deletion syndrome

Genetics/Basic Defects

1. Cause
   a. Caused by deletion of short arm of chromosome 5: The size of the deletion ranges from the entire short arm to the region 5p15 (Overhauser et al. 1994) and a deletion size ranging from 5 to 40 Mb (Simmons et al. 1995)
      i. De novo deletion (80%): paternally derived deletions in 80% of cases
      ii. Familial rearrangement (12%)
      iii. Mosaicism (3%)
      iv. Rings (2.4%)
      v. De novo translocation (3%)
   b. A high-resolution physical and transcription map generated a 3.5-Mb region of 5p15.2 that is associated with the Cri-du-chat syndrome region (Church et al. 1997)
2. Genotype–phenotype correlation (Gersh et al. 1997)
   a. Deletion of 5p15.3 results in a cat-like cry and speech delay (Gersh et al. 1995; Church et al. 1995)
   b. Deletion of 5p15.2 results in the distinct facial features associated with the syndrome as well as the severe mental and developmental delay
3. Hemizygosity of δ-catenin (*CTNND2*, mapped to 5p15.2), reported to be associated with severe mental retardation in cri-du-chat syndrome (Medina et al. 2000)
4. Deletion of the *telomerase reverse transcriptase* (h*TERT*) gene (mapped at 5p15.33) and haploinsufficiency of telomere maintenance is probably a genetic element contributing to the phenotypic changes in cri-du-chat syndrome (Zhang et al. 2003)

Clinical Features

1. Characteristic mewing cry (Niebuhr 1978)
   a. A high-pitched monochromatic cry with subtle dysmorphism and neonatal complications: commonly observed in infants with this syndrome
   b. Observed in many infants with cri-du-chat syndrome
   c. Not associated with other aneuploidies
   d. Usually considered diagnostic
   e. Loss of the characteristic cry by age 2 years in one third of children
2. Clinical findings during infancy
   a. Low birth weight
   b. Hypotonia

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c. Microcephaly
d. Poor sucking/swallowing difficulties
e. Need for incubator care
f. Respiratory distress
g. Jaundice
h. Pneumonia
i. Dehydration
j. Failure to thrive/growth retardation
k. Early ear infections
l. Severe cognitive, speech, and motor delays
m. Facial features
    i. Round face with full cheek
    ii. Hypertelorism
    iii. Epicanthal folds
    iv. Down-slanting palpebral fissures
    v. Strabismus
    vi. Flat nasal bridge
    vii. Down-turned mouth
    viii. Micrognathia
    ix. Low-set ears
n. Cardiac defects
    i. VSD
    ii. ASD
    iii. PDA
    iv. Tetralogy of Fallot
o. Short fingers
p. Single palmar creases
q. Less frequent features
    i. Cleft lip and palate
    ii. Preauricular tags and fistulas
    iii. Thymic dysplasia
    iv. Gut malrotation
    v. Megacolon
    vi. Inguinal hernia
    vii. Dislocated hips
    viii. Cryptorchidism
    ix. Hypospadias
    x. Rare renal malformations
        a) Horseshoe kidneys
        b) Renal ectopia or agenesis
        c) Hydronephrosis
    x. Clinodactyly of the fifth fingers
    xi. Talipes equinovarus
    xii. Pes planus
    xiii. Syndactyly of the second and third fingers and toes
    xiv. Oligosyndactyly
    xv. Hyperextensible joints

3. Clinical findings in childhood
    a. Severe mental retardation
    b. Developmental delay
    c. Microcephaly
    d. Hypertonicity
    e. Premature graying of the hair
    f. Small, narrow, and often asymmetric face
    g. Dropped-jaw
    h. Open-mouth expression secondary to facial laxity
    i. Short philtrum
    j. Malocclusion of the teeth
    k. Scoliosis
    l. Short third-fifth metacarpals
    m. Chronic medical problems
        i. Upper respiratory tract infections
        ii. Otitis media
        iii. Severe constipation
        iv. Hyperactivity
4. Clinical findings in late childhood and adolescence
    a. Coarsening of facial features
    b. Prominent supraorbital ridges
    c. Deep-set eyes
    d. Hypoplastic nasal bridge
    e. Affected females reaching puberty and developing secondary sex characteristics and menstruate at the usual time (Martinez et al. 1993)
    f. Small testis and normal spermatogenesis in males
5. Dermatoglyphics
    a. Transverse flexion creases
    b. Distal axial triradius
    c. Increased whorls and arches on digits
6. Behavioral profile
    a. Hyperactivity
    b. Aggression
    c. Tantrums
    d. Stereotypic and self-injurious behavior
    e. Repetitive movements
    f. Hypersensitivity to sound
    g. Clumsiness
    h. Obsessive attachments to objects
    i. Able to communicate needs and interact socially with others
    j. Autistic-like features and social withdrawal: more characteristic of individuals who have a 5p deletion as the result of an unbalanced segregation of a parental translocation

7. Prognosis
   a. Ability of many children to develop some language and motor skills
   b. Ability of these children to attain developmental and social skills observed in 5- to 6-year-old children, although their linguistic abilities are seldom as advanced
   c. Older, home-reared children
      i. Usually ambulatory
      ii. Able to communicate verbally or through gestural sign language
      iii. Independent in self-care skills

Diagnostic Investigations

1. Conventional cytogenetic studies once the suspected diagnosis is established. The size of the 5p deletion may vary from the entire short arm to only 5p15. A small deletion of 5p may be missed by a conventional cytogenetic technique
2. High-resolution cytogenetic studies are required for a smaller 5p deletion
3. Molecular cytogenetic studies using fluorescent in situ hybridization (FISH)
   a. Allow the diagnosis to be made in the patients with very small deletions
   b. Use genetic markers that have been precisely localized to the area of interest
   c. The absence of a fluorescent signal from either the maternal or paternal chromosome 5p regions: indicative of monosomy for that chromosomal region
4. Comparative genomic hybridization (CGH) especially the CGH method based on DNA microarray and quantitative PCR (Mainardi et al. 2001; Rodriguez-Caballero et al. 2010)
5. Skeletal radiographs
   a. Microcephaly
   b. Retromicrognathia
   c. Cranial base malformations
      i. Reduced cranial base angle
      ii. Malformed sella turcica and clivus
   d. Disproportionately short third, fourth, and fifth metacarpals and disproportionately long second, third, fourth, and fifth proximal phalanges (frequent) (Fenger and Niebuhr 1978)
6. Echocardiography to rule out structural cardiac malformations
7. MRI of the brain (Kjaer and Niebuhr 1999)
   a. Atrophic brainstem, middle cerebellar peduncles, and cerebellar white matter
   b. Possible hypoplasia of cerebellar vermis with enlargement of the cisterna magna and fourth ventricle
8. Swallowing study for feeding difficulty
9. Comprehensive evaluation for receptive and expressive language. Most children have better receptive language than expressive language
10. Developmental testing and referral to early intervention and appropriate school placement

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Recurrence risk for a de novo case is 1% or less (possibility of gonadal mosaicism in one of the parents cannot be ruled out)
      ii. Rare recurrences in chromosomally normal parents: most likely the result of gonadal mosaicism for the 5p deletion in one of the parents
      iii. The risk is substantially high if a parent is a balanced carrier of a structural rearrangement. Risk should be assessed based on the type of structural rearrangement and its pattern of segregation
   b. Patient's offspring: Female patients are fertile and can deliver viable affected offspring, with an estimated recurrence risk of 50%
2. Prenatal diagnosis by amniocentesis, CVS, and PUBS for chromosome analysis to detect 5p deletion
3. Management
   a. Supportive care: No treatment exists for the underlying disorder
   b. Appropriate treatment for chronic medical problems
      i. Upper respiratory tract infections
      ii. Otitis media
      iii. Severe constipation
   c. Using the relatively good receptive skills to encourage language and communicative development rather than relying on traditional verbal methods (Cornish and Munir 1988)

d. Early intervention programs
   i. Physical therapy
   ii. Occupational therapy
   iii. Speech therapy
e. Introduction to sign language, an effective means of developing communication skills (>50% of children are able to use sign language to communicate) (Cornish and Munir 1988)
f. Behavior modification programs to successfully manage hyperactivity, short attention span, low threshold for frustration, and self-stimulatory behaviors (e.g., head-banging, hand-waving)
g. Surgical interventions
   i. Correction of congenital heart defects if indicated
   ii. Medical problems involving minor malformations such as strabismus and clubfoot
   iii. Gastrostomy in infancy to protect airway of patients with major feeding difficulties
   iv. Orchiopexy for undescended testes
   v. Issues important to anesthetic plan
      a) Anatomical abnormalities of the airway
      b) Congenital heart disease
      c) Hypotonia
      d) Mental retardation
      e) Temperature maintenance

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Fig. 1 (**a**, **b**) Two infants with cri-du-chat syndrome. Note a round face with full cheeks, hypertelorism, epicanthal folds, and apparently low-set ears

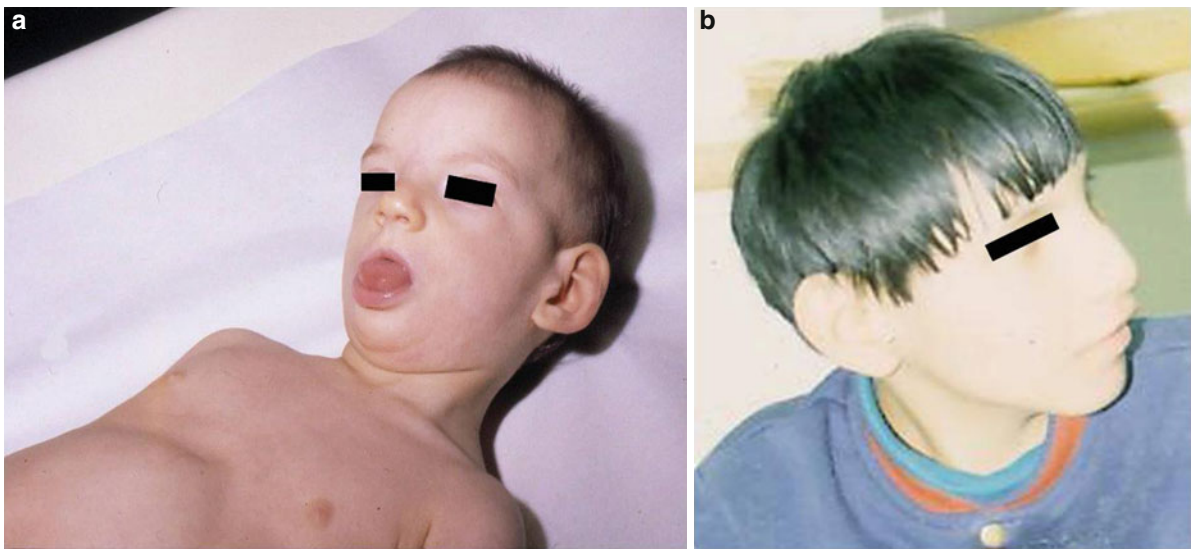

Fig. 2 (**a**, **b**) Cri-du-chat syndrome in an older child and a teenager showing a long and narrow face

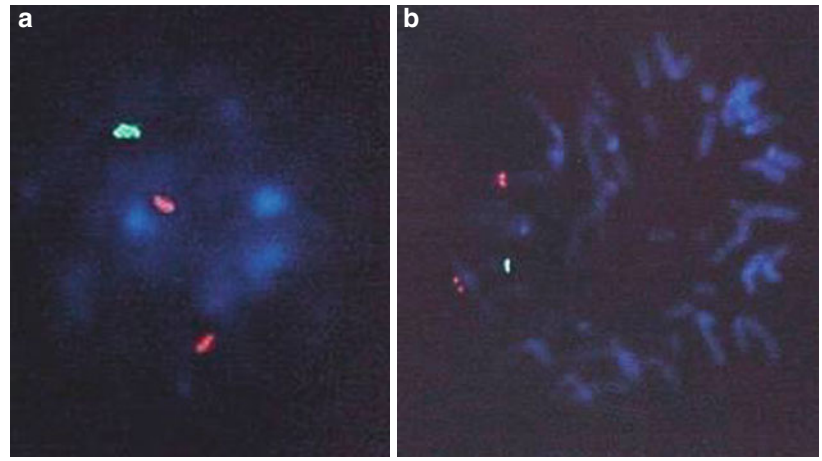

Fig. 3 (**a**, **b**) FISH of an interphase cell and a metaphase spread with two *orange* signals (LSI SpectrumOrange, D5S721) and one *green* signal (LSI SpectrumGreen, D5S23 chromosome 5p15.2-specific probe) indicating deletion of 5p15.2

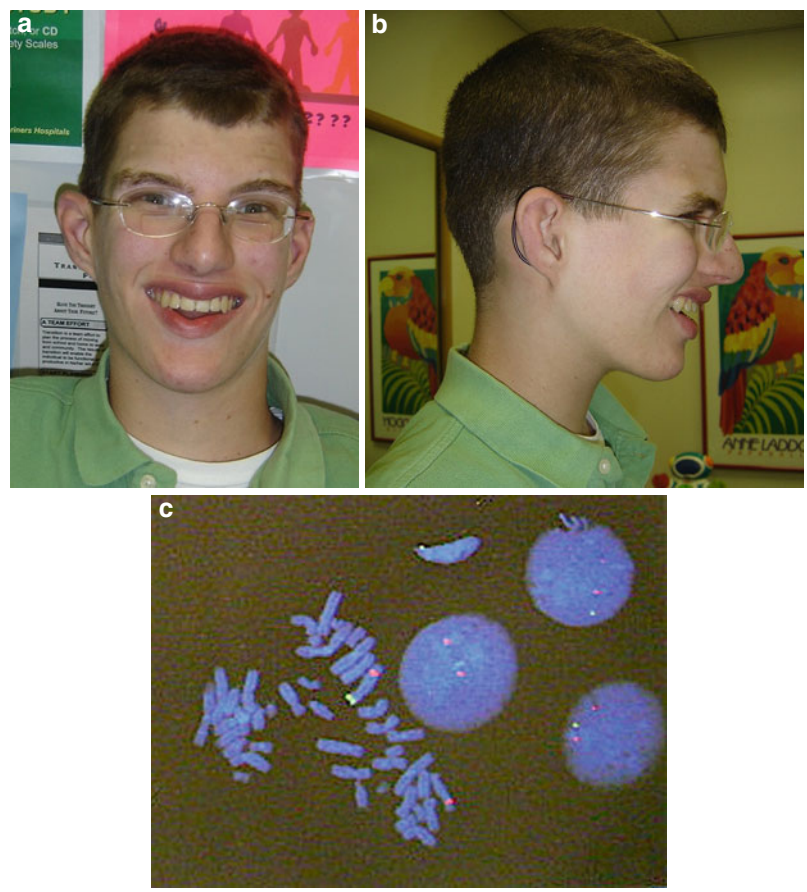

Fig. 4 (**a–c**) The 16-year-old boy was evaluated for developmental delay. He was noted to have unusual cry during early infancy, poor muscle control, and unable to hold his head up until 6 months of age. FISH using a locus specific for 5p11.2 cri-du-chat syndrome region showed 5p11.2 deletion (illustrated by a metaphase chromosome spread and interphase cells)

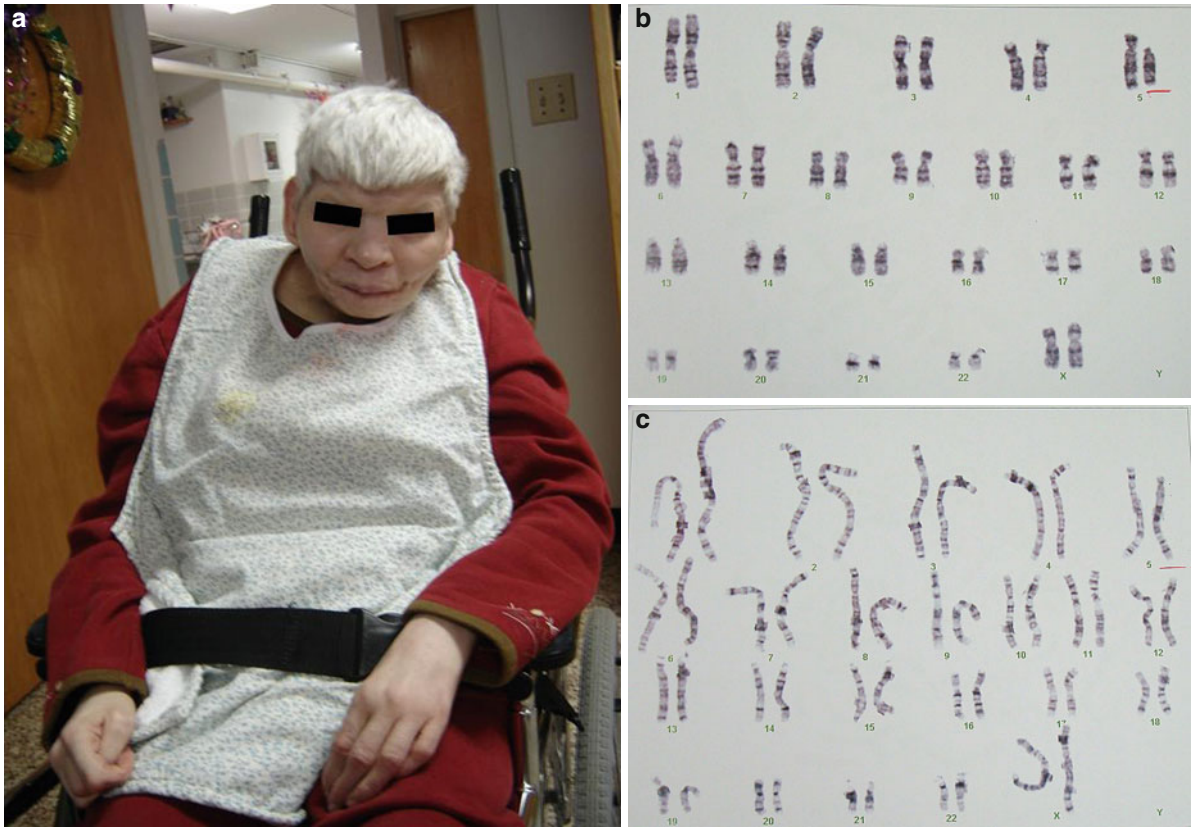

Fig. 5 (**a–c**) A blond-haired 60-year-old female with cri-du-chat syndrome, showing microcephaly with severe mental retardation. The karyotypes showed deletion of most of the short arm of a chromosome 4

Crouzon Syndrome

In 1912, Crouzon described the hereditary syndrome of craniofacial dysostosis in a mother and son. He described the triad of calvarial deformities, facial anomalies, and exophthalmos. Crouzon syndrome is characterized by premature closure of calvarial and cranial base sutures as well as those of the orbit and maxillary complex (craniosynostosis). Other clinical features include hypertelorism, exophthalmos, strabismus, beaked nose, short upper lip, hypoplastic maxilla, and relative mandibular prognathism. Prevalence is 1 per 60,000 (approximately 16.5 per 1,000,000) live births (Cohen and Kreiborg 1992). Crouzon syndrome makes up approximately 4.8% of all cases of craniosynostosis.

Synonyms and Related Disorders

Craniofacial dysostosis type I; Crouzon craniofacial dysostosis

Genetics/Basic Defects

1. Inheritance
   a. An autosomal dominant disorder with
      i. Complete penetrance
      ii. Variable expressivity
   b. Sporadic in 50% of patients resulting from new mutations
2. Cause
   a. Mutations in the fibroblast growth factor receptor-2 (*FGFR2*) gene which is mapped to 10q25-q26
   b. Mutations reported in the third immunoglobulins-like domain (Meyers et al. 1996)
   c. Different mutations detected in both exon IIIa and exon IIIc. Most of these mutations are missense, although several different mutations leading to alternative splicing have been recognized (Meyers et al. 1996)
   d. Crouzon syndrome exhibits locus heterogeneity with causal mutations in *FGFR2* and *FGFR3* in different affected individuals
   e. Crouzon syndrome with acanthosis nigricans (Crouzonodermoskeletal syndrome)
      i. Described as a separate entity from Crouzon syndrome (Cohen 1999)
      ii. Caused by the GAG to GCG transversion mutation in the *FGFR3* gene, leading to Ala391Glu substitution (Wilkes et al. 1996)
3. Pathophysiology
   a. Premature synostosis of the coronal, sagittal, and occasional lambdoidal sutures
      i. Begins in the first year of life
      ii. Completed by the second or third year
   b. Degree of deformity and disability determined by the order and rate of suture fusion
   c. After fusion of a suture
      i. Growth perpendicular to that suture becoming restricted
      ii. Fused bones acting as a single bony structure.
   d. Compensatory growth occurring at the remaining open sutures to allow continued brain growth
   e. Multiple sutural synostoses often extend to premature fusion of the skull base sutures causing the following effects
      i. Midfacial hypoplasia
      ii. Shallow orbit

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iii. A foreshortened nasal dorsum
iv. Maxillary hypoplasia
v. Occasional upper airway obstruction.

Clinical Features

1. History
   a. Presence of mildly affected individuals in the family
   b. Craniofacial abnormalities often present at birth and may progress with time
   c. Decreased mental function in approximately 12% of the patients
   d. Headaches (29%) and failing vision due to elevated intracranial pressure
   e. Visual disturbance results from corneal injury due to exposed conjunctivitis and keratitis
   f. Conductive deafness common due to ear canal stenosis or atresia
   g. Causes of upper airway obstruction
      i. Septal deviation
      ii. Mid-nasal abnormalities
      iii. Choanal abnormalities
      iv. Nasopharyngeal narrowing
   h. Meniere disease
   i. Seizures (12%)
2. Skull and face
   a. Craniosynostosis
      i. Onset: commonly seen during the first year
      ii. Usually completing by the second or third year
      iii. Coronal suture most commonly involved
      iv. Acrocephaly
      v. Brachycephaly
      vi. Turricephaly
      vii. Oxycephaly
      viii. Flat occiput
      ix. High prominent forehead with or without frontal bossing
      x. Ridging of the skull usually palpable
   b. Cloverleaf skull
      i. Rare
      ii. Occurring in most severely affected individuals
      iii. Flattened sphenoid bone
      iv. Shallow orbits
      v. Hydrocephalus (progressive in 30%)
      vi. Midface (maxillary) hypoplasia
3. Eyes
   a. Exophthalmos (proptosis) (100%) secondary to shallow orbits resulting in frequent exposure conjunctivitis or keratitis
   b. Ocular hypertelorism (100%)
   c. Divergent strabismus
   d. Rare occurrence
      i. Nystagmus
      ii. Iris coloboma
      iii. Aniridia
      iv. Anisocoria
      v. Microcornea
      vi. Megalocornea
      vii. Cataract
      viii. Ectopia lentis
      ix. Blue sclera
      x. Glaucoma
      xi. Luxation of the eye globes
      xii. Blindness from optic atrophy
4. Nose
   a. Beaked appearance (parrot-like nose)
   b. Compressed nasal passage
   c. Choanal atresia or stenosis
   d. Deviated nasal septum
5. Mouth
   a. Mandibular prognathism
   b. Overcrowding of upper teeth
   c. Malocclusions
   d. V-shaped maxillary dental arch
   e. Narrow, high, or cleft palate and bifid uvula
   f. Oligodontia
   g. Macrodontia
   h. Peg-shaped
   i. Widely spaced teeth
6. Ears
   a. Narrow or absent ear canals
   b. Deformed middle ears
   c. Mild-to-moderate hearing losses
7. Other skeletal
   a. Cervical fusion (18%), C2–C3 and C5–C6
   b. Block fusions involving multiple vertebrae
   c. Subluxation of the radial heads
   d. Ankylosis of the elbows
8. Acanthosis nigricans (5%)
   a. Velvety, light-brown to black darkened, thickened skin with accentuated markings that occur in areas including the neck, axillae, groin, and breasts
   b. Usual age of onset: first decade (80%)

c. Only one case reported at birth (Koizumi et al. 1992)
d. Typical presentation (Arnaud-Lopez et al. 2007; Sharda et al. 2010)
   i. Crouzonoid facies
   ii. Acanthosis nigricans with atypical distribution
   iii. Choanal atresia
   iv. Hydrocephalus
   v. Oral abnormalities
   vi. Melanocytic nevi
   vii. Less frequent findings: vertebral abnormalities and deafness
9. CNS
   a. Chronic tonsillar herniation (approximately 73%). Of these, 47% have progressive hydrocephalus (Cinalli et al. 1995)
   b. Syringomyelia
   c. Mental retardation (3%)

Diagnostic Investigations

1. Skull radiographs
   a. Synostosis: The coronal, sagittal, lambdoidal, and metopic sutures may be involved.
   b. Craniofacial deformities
   c. Digital markings of skull
   d. Basilar kyphosis
   e. Widening of hypophyseal fossa
   f. Small paranasal sinuses
   g. Maxillary hypoplasia with shallow orbits
2. Cervical radiographs (Anderson 1997b)
   a. Butterfly vertebrae
   b. Fusions of the vertebral bodies and the posterior elements
      i. Cervical fusions in approximately 18% of patients
      ii. C2–C3 and C5–C6 affected equally
      iii. Block fusions may involve multiple vertebrae.
3. Limb radiographs
   a. Metacarpophalangeal analysis
   b. Subluxation of the radial head
4. Computed tomography (CT) scan: Comparative 3-D reconstruction analysis of the calvaria and cranial bases to precisely define the pathologic anatomy and to permit specific operative planning
5. Magnetic resonance imaging (MRI): Used to demonstrate occasional corpus callosum agenesis and optic atrophy
6. Molecular analysis
   a. *FGFR2* mutations in more than 50% of patients (*FGFR2* mutations also observed in Apert syndrome, Pfeiffer syndrome, and Jackson-Weiss syndrome)
   b. *FGFR3* ala391-to-glu mutation in all patients with associated acanthosis nigricans: Finding of acanthosis nigricans in a young child with Crouzon syndrome should prompt testing for the Ala391Gln substitution in *FGFR3* before testing for *FGFR2* mutations (Sharda et al. 2010)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased unless a parent is affected or with germinal mosaicism (Navarrete et al. 1991)
   b. Patient's offspring: 50%
2. Prenatal diagnosis
   a. Prenatal ultrasonography
      i. Exophthalmos
      ii. Ocular hypertelorism
   b. Identification of the disease-causing *FGFR2* mutation using
      i. CVS in the first trimester
      ii. Amniocentesis in the second trimester
      iii. Preimplantation genetic diagnosis (Harper et al. 2002)
3. Management
   a. Medical care
      i. No specific medical therapy available
      ii. Nasal continuous positive airway pressure device to relieve airway obstruction
      iii. Management of speech
   b. Surgical care
      i. Stage reconstruction to coincide with facial growth patterns, visceral function, and psychosocial development.
      ii. Early craniectomy with frontal bone advancement most often indicated to prevent or treat increased intracranial pressure because newborns with Crouzon syndrome develop multiple suture synostosis and fused synchondrosis.

iii. Fronto-orbital and midfacial advancements to help in the cosmetic reconstruction of facial dysmorphisms.
iv. A new technique, craniofacial disjunction, followed by gradual bone distraction (Ilizarov procedure) has been reported to produce complete correction of exophthalmos and improvement in the functional and esthetic aspects of the middle third of the face without the need for bone graft in patients aged 6–11 years.
v. Shunting procedures for hydrocephalus.
vi. Tracheostomy for airway compromise.
vii. Myringotomy to drain middle ear secretions secondary to distorted nasopharynx.
viii. Orthodontic management.

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Fig. 1 (**a–d**) Two children with Crouzon syndrome showing proptosis secondary to shallow obits and hypertelorism

Fig. 2 A neonate with Crouzon syndrome showing typical craniofacial features with tracheostomy in place for the respiratory problem

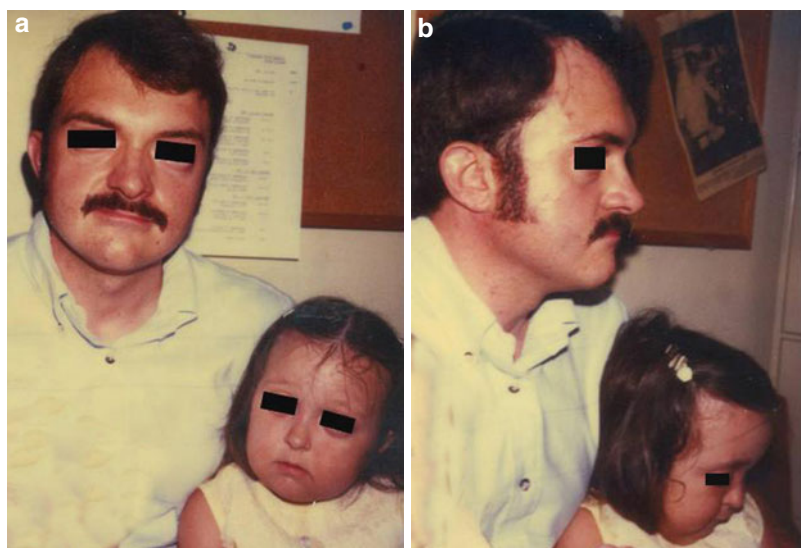

Fig. 3 (**a**, **b**) A father and a daughter with Crouzon syndrome showing characteristic craniofacial features

Cutis Marmorata Telangiectatica Congenita

In 1922, van Lohuizen1 first described cutis marmorata telangiectatica congenita (CMTC) as a pattern of reticulate erythema and telangiectasia, skin atrophy and/or ulceration.

Genetics/Basic Defects

1. Pathogenesis
   a. Unknown
   b. Most cases are sporadic
2. Hypothesis
   a. Environmental factors
   b. Multifactorial cause
   c. A nerve conduction defect (Bormann et al. 2001)
   d. A lethal gene surviving by mosaicism suggested by segmental distribution often with a sharp midline separation (Rogers and Poyzer 1982)
   e. Autosomal dominant inheritance with low or variable penetrance
      i. An affected parent showing more limited involvement than his offspring (Kurczynski 1982)
      ii. Two siblings with one having CMTC alone and the other showing associated anomalies (hypertension and acrocyanosis) (Andreev and Pramatarov 1979)

Clinical Features

1. Onset (Garzon and Schweiger 2004)
   a. Congenital: common
   b. Later onset (Way et al. 1974)
2. Reticulated vascular pattern
   a. Finely reticular or coarse pattern: will not resolve completely with warming of the skin
   b. Broad streaks of discolored skin in a "train-track-like" pattern
   c. Relatively fixed and discernable at rest
   d. Pallor of the skin between the vascular network pattern: often reported (Ben-Amitai et al. 2000)
   e. Often accompanied by:
      i. Phlebectasia (prominent veins)
      ii. Telangiectasias
      iii. Cutaneous and subcutaneous tissue atrophy: may manifest as hypoplasia of the affected limb (an inconsistent feature) (South and Jacobs 1978)
      iv. Ulceration of the affected skin, particularly involving the skin overlying the elbows and knees (Picascia and Esterly 1989)
      v. Hyperkeratosis
   f. The presence of atrophy and ulceration helps to differentiate CMTC from physiologic cutis marmorata
   g. Localized lesions
      i. Most commonly affecting the trunk and extremities
      ii. Sharp segmental pattern: easy to differentiate from physiologic cutis marmorata
   h. Generalized lesions
      i. Often unilateral
      ii. May involve face but mucosal involvement uncommon (Ben-Amitai et al. 2000)
      iii. Do not occur on the entire body surface (Devillers et al. 1999)

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3. Associated anomalies (27–80%) (Picascia and Esterly 1989; Devillers et al. 1999)
   a. Relatively high associated defects
      i. May represent true associations or coincidental
      ii. May represent a bias toward reporting cases with more severe anomalies
      iii. Inconsistency among authors regarding diagnostic criteria
   b. Asymmetry
      i. Limb asymmetry (hyperplasia or hypoplasia of a limb)
         a) The most common associated anomaly
         b) Cutaneous atrophy may be noted concomitantly with asymmetry
      ii. Facial asymmetry may occur
   c. Skeletal defects
      i. Syndactyly
      ii. Tendinitis stenosans
      iii. Hip dysplasia
      iv. Clubfoot
      v. Scoliosis
      vi. Macrocephaly
      vii. Skull asymmetry
      viii. Scaphoid scapula
      ix. Micrognathia
      x. Generalized osteoporosis
      xi. Consider Adams–Oliver syndrome and macrocephaly-CMTC if limb defects are present
   d. Other vascular anomalies
      i. May occur distant to the area of CMTC or within the same affected area (Picascia and Esterly 1989)
      ii. Capillary malformations (port-wine stains): the most commonly associated vascular birthmark occurring in 20% of patient (Ben-Amitai et al. 2000)
      iii. Sturge–Weber syndrome (Petrozzi et al. 1970)
      iv. Hemangiomas of infancy
      v. Multiple angiokeratomas
   e. Ocular anomalies
      i. Glaucoma
      ii. Infrequent anomalies
         a) Persistent arterial hyaloidia (an embryonic vessel that typically regresses)
         b) Granular retinal pigmentation
         c) Small optic disks
         d) Optic nerve atrophy
   f. Neurologic anomalies
      i. Macrocephaly: diagnostic feature of macrocephaly-CMTC syndrome
      ii. Hydrocephaly
      iii. Psychomotor retardation
      iv. Seizures
      v. Cerebral atrophy
      vi. Agenesis of the corpus callosum
      vii. Dilated ventricles
   g. Other cutaneous anomalies (may be coincidental) (Ben-Amitai et al. 2000)
      i. Congenital melanocytic nevi
      ii. Café au lait macules
      iii. Mongolian spots
   h. Other systemic anomalies (uncommon)
      i. Hypothyroidism
      ii. Cardiac defects
      iii. Genitourinary tract anomalies (Del Guidice and Nydorl 1986; Ben-Amitai et al. 2001; Sills et al. 2002; Fujita et al. 2003)
         a) Hypospadias
         b) Renal cysts
         c) Duplication of the renal collecting system
         d) Rectovaginal and ureterovaginal fistulae
         e) Absent clitoris
         f) Imperforate anus
         g) Unilateral ovarian agenesis
         h) Septate uterus
         i) Premature gonadal failure associated with de novo balance translocation affecting chromosomes 8 and 9
4. Suggested diagnostic criteria for cutis marmorata telangiectatica congenita (Kienast and Hoeger 2009)
   a. Major criteria
      i. Congenital reticulate (marmorated) erythema (27%)
      ii. Absence of venectasia (27%)
      iii. Unresponsiveness to local warming (27%)
   b. Minor criteria
      i. Fading of erythema within 2 years (18%)
      ii. Telangiectasia (5%)
      iii. Port-wine stain outside the area affected by CMTC (2%)
      iv. Ulceration (2%)
      v. Atrophy (2%)

5. Differential diagnosis
   a. Cutis marmorata (physiologic)
   b. Cutis marmorata (associated with genetic syndrome)
      i. Cornelia de Lange syndrome
      ii. Down syndrome
      iii. Homocystinuria
      iv. Divry and Van Bogaert syndrome
         a) A rare disorder
         b) Corticomeningeal angiomatosis
         c) Visual field defects
         d) Seizures
         e) "Marble" skin
   c. Reticulated capillary malformations
      i. A diffuse, generalized form of a "livedoid" capillary malformation involving the entire skin
      ii. Not associated with atrophy, ulceration or limb hypoplasia
      iii. Associated with a significant risk of associated visceral vascular anomalies (eye, brain, kidneys, and heart) and requires evaluation and follow-up (Enjolras and Garzon 2001)
   d. Bockenheimer syndrome (diffuse phlebectasia):
      i. A very rare disorder
      ii. Onset in infancy
      iii. Characterized by progressive venous varicosity
   e. Neonatal lupus erythematosus
   f. CMTC "syndrome"
      i. CMTC-macrocephaly syndrome
      ii. Adams–Oliver syndrome
      iii. CMTC phakomatosis pigmentovascularis

Diagnostic Investigations

1. Physical evaluation (Garzon and Schweiger 2004)
   a. Reticulated vascular pattern
   b. Limb length and girth
   c. Limb defects
   d. Scalp defects
   e. Head circumference
   f. Other associated anomalies
   g. Facial lesions
2. Ophthalmologic evaluation

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Sporadic cases: a low recurrence risk
      ii. A 50% risk if one of the parents is affected
   b. Patient's offspring: a 50% risk in autosomal dominant transmission, otherwise a low recurrence risk
2. Prenatal diagnosis: not reported
3. Management
   a. Careful physical examination to assess for other congenital anomalies
   b. Measurement of limb length and girth at the time of evaluation
   c. Baseline and follow-up ophthalmologic examinations should be performed when the vascular lesions affect the periocular skin
   d. Local supportive care including application of hydrocolloid dressings for ulcerations

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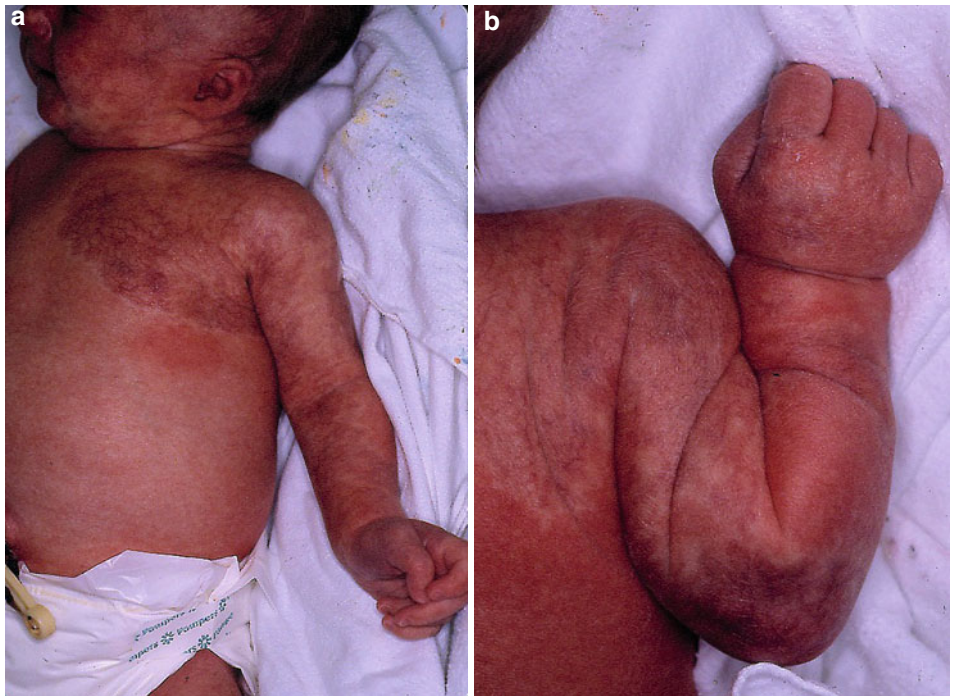

Fig. 1 (**a**, **b**) A 2-month-old infant with cutis marmorata telangiectatica congenita showing a reticular vascular pattern which was present from birth

Fig. 2 (**a**, **b**) The same infant at 14 months of age

Fig. 3 (**a**, **b**) The same patient at 26 months of age showing development of a large diffuse vascular lesion extending from the whole left anterior chest to the left neck

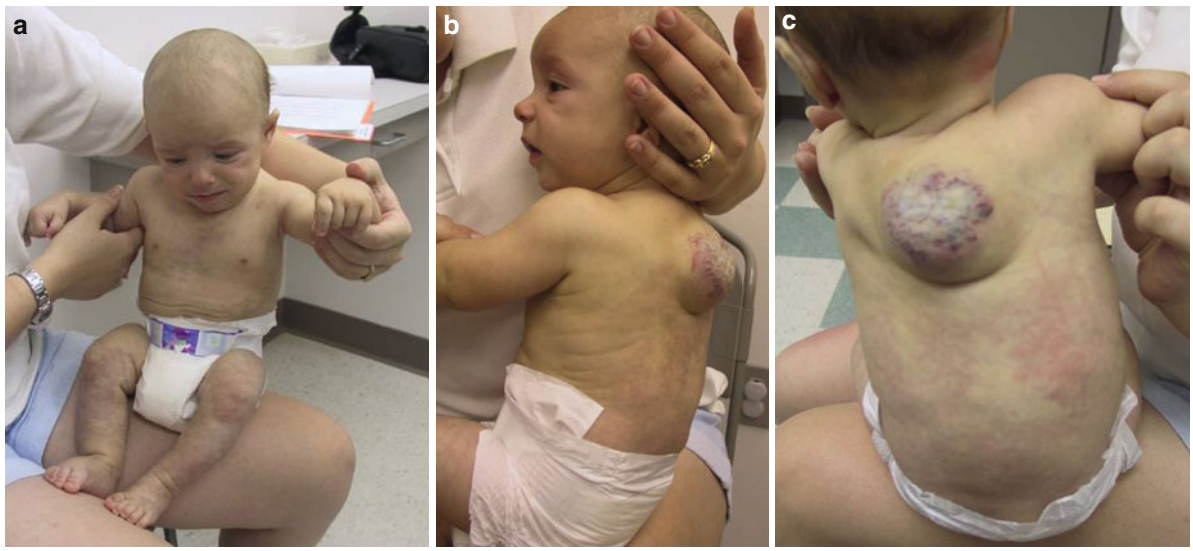

Fig. 4 (**a–c**) A 3-month-old infant boy with cutis marmorata telangiectatica congenita. Cutaneous vascular lesions consist of a 4 × 4 × 2 cm soft vascular lesion of the upper posterior back and diffuse bluish vascular lesions on front chest, shoulders, arms, trunk, buttock, and legs. The right leg is larger than the left

Fig. 5 Another infant with a reticular vascular pattern on the *right* leg

Fig. 6 (**a–f**) A child with cutis marmorata telangiectatica congenita at different ages (newborn, 4 months, and 4 years of age)

Cystic Fibrosis

Cystic fibrosis (CF) is the most common Caucasian lethal genetic disorder (with gene frequency of 1 in 25) in the United States, where 4–5% of population have at least one CF allele. CF affects approximately 1 in 2,500 live births among Caucasians, 1 in 17,000 among African-Americans, and 1 in 90,000 among Asians. (Ruzal-Shapiro 1998)

Synonyms and Related Disorders

CFTR-related disorders; Congenital absence of vas deferens; Mucoviscidosis

Genetics/Basic Defects

1. Inheritance
   a. Autosomal recessive
   b. *CF* gene mapped to chromosome 7q31.2
2. Molecular defect (Moskowitz et al. 2008)
   a. Caused by a single gene defect on chromosome 7 that encodes a cAMP-regulated chloride channel known as the cystic fibrosis transmembrane conductance regulator (CFTR)
      i. CFTR usually resides in the apical membrane of epithelial cells lining the airway, biliary tree, intestines, vas deferens, sweat ducts, and pancreatic ducts.
      ii. Insufficient fluid secretion secondary to inability of CFTR to transport chloride ion at the above sites causes higher viscidity of the protein portions of the secretions and obstructing the ducts, leading to plugging and dysfunction at the organ level.
      iii. CFTR also regulates the activity of other proteins that conduct ions and affects intracellular regulatory processes at the cellular level.
   b. Presence of close to 1,500 different disease-causing mutations of the *CFTR* gene (Ruzal-Shapiro 1998; O'Sullivan and Freedman 2009)
      i. Deletion mutations including delta F508 which, observed in over 70% of patients with CF, have a deletion of three contiguous base pairs resulting in the loss of a single amino acid, phenylalanine at codon 508)
      ii. Missense mutation (single base pair exchange within a normal length CFTR protein)
      iii. Nonsense mutations (exchange of a single base pair resulting in premature termination of the protein)
      iv. Frameshift mutations (the deletions or insertion of a single base pair)
   c. Classification of CFTR mutations (Culling and Ogle 2010)
      i. Class I mutations
         a) Introduce a stop codon prematurely
         b) Produce either an unstable mRNA with no detectable protein being made or an unstable protein that is rapidly degraded or has no functional capability
         c) No CFTR protein in the cell membrane
         d) E.g., G542X, 394delTT, 1717-1 G → A
      ii. Class II mutations
         a) Block the processing of the protein due to aberrant folding and subsequent

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degradation when recognized as abnormal by cellular "quality control" mechanisms
   b) No CFTR protein at the apical cell membrane
   c) E.g., N1303K, ΔF508, 3905insT
iii. Class III mutations:
   a) Produce a CFTR protein that does not function as a chloride channel due to a block in regulation, despite being fully processed and correctly located
   b) Within this class there are mutations that have very little function (G551D), those where ATP is less potent at stimulating activity (S1255P) and those with reduced absolute activity (G551S, G1244E and G1349D).
iv. Class IV mutations
   a) Produce a fully processed and correctly located CFTR protein
   b) However, the conductance and/or gating properties of the channel have been altered by mutations in the membrane spanning domains
   c) Extent to which conduction is affected varies between mutations
   d) E.g., R117H, R347P
v. Class V mutations
   a) Result in a reduction in the synthesis of CFTR protein
   b) Include promoter mutations, the promotion of alternative splicing and inefficient protein maturation
   c) E.g., A455E, 2789 + 5G → A, IVS8-5T
vi. Class VI mutations
   a) Presence of functional but unstable CFTR protein at the apical membrane
   b) Decreased stability on CFTR protein
   c) E.g., Q1412X, 4326delTC, 4279insA

d. Genotype-phenotype correlations (Ruzal-Shapiro 1998)
   i. Phenotypic presentation of the disease: probably related to the underlying genetic abnormality
   ii. Patients with homozygous delta F508 typically have respiratory distress and malabsorption.
   iii. Patients with less severe variations of the disease or typical CF with borderline normal sweat tests may have other haplotypes

Clinical Features

1. Signs and symptoms of cystic fibrosis (O'Sullivan and Freedman 2009)
   a. General (any age)
      i. Family history of cystic fibrosis
      ii. Salty-tasting skin
      iii. Clubbing fingers and toes
      iv. Cough with sputum production
      v. Mucoid *Pseudomonas aeruginosa* isolated from airway secretions
      vi. Hypochloremic metabolic alkalosis
   b. Neonatal
      i. Meconium ileus
      ii. Protracted jaundice
      iii. Abdominal or scrotal calcifications
      iv. Intestinal atresia
   c. Infancy
      i. Persistent infiltrates on chest radiographs
      ii. Failure to thrive
      iii. Anasarca or hypoproteinemia
      iv. Chronic diarrhea
      v. Abdominal distention
      vi. Cholestasis
      vii. *Staphylococcus aureus* pneumonia
      viii. Idiopathic intracranial hypertension (vitamin A deficiency)
      ix. Hemolytic anemia (vitamin E deficiency causes anemia by increasing fragility and reducing lifespan of red blood cells)
   d. Childhood
      i. Chronic pansinusitis or nasal polyposis
      ii. Steatorrhea
      iii. Rectal prolapse
      iv. Distal intestinal obstruction syndrome or intussusceptions
      v. Idiopathic recurrent or chronic pancreatitis
      vi. Liver disease
   e. Adolescence and adulthood
      i. Allergic bronchopulmonary aspergillosis
      ii. Chronic pansinusitis or nasal polyposis
      iii. Bronchiectasis
      iv. Hemoptysis
      v. Idiopathic recurrent pancreatitis
      vi. Portal hypertension
      vii. Delayed puberty
      viii. Azoospermia secondary to congenital bilateral absence of the vas deferens

2. Classic clinical triad
   a. Exocrine pancreatic insufficiency
   b. Chronic obstructive pulmonary disease
   c. Elevation of sodium and chloride concentration in sweat
3. Chronic sino-pulmonary disease
   a. Varying widely in age of onset and rate of progression
   b. Clinical course
      i. Newborn with CF with histologically normal respiratory systems
      ii. First few months of age
         a) Epithelial chloride channel defect, leading to abnormal respiratory secretions, bronchopulmonary infections, and airway obstruction
         b) Clinical manifestations including cough, wheezing, retractions, and tachypnea
   c. Persistent endobronchial infection and inflammation with typical CF pathogens (Ruzal-Shapiro, 1998)
      i. *Staphylococcus aureus*
         a) Responsible for the majority of lung disease when CF was first described
         b) Commonly isolated in the first year of life from the sputum of patients with CF
         c) Typically controlled by antibiotic therapy
         d) Currently only 10% of adult patients with CF are chronically colonized by the pathogen.
      ii. Mucoid and non-mucoid *Pseudomonas aeruginosa*
         a) The most prevalent of the pathogens in CF, causing chronic infection in up to 90% of adults and 80% of children
         b) Initial colonization with non-mucoid forms
         c) Subsequent conversion to mucoid variants
      iii. *Hemophilus influenzae*
         a) Commonly seen in babies
         b) Rarely encountered in the adults
      iv. Other pulmonary pathogens
         a) *Burkholderia cepacia*
         b) Aspergillus
         c) Mycobacteria
         d) Respiratory viruses
   d. Upper airway disease
      i. Opacified or maldeveloped sinuses
      ii. Nasal polyps (up to 26% of patients)
      iii. Sinusitis
         a) Facial pain
         b) Swelling
         c) Tenderness
         d) Air-fluid levels on radiograph
   e. Pulmonary exacerbations
      i. Persistent cough and sputum production
      ii. Increased dyspnea
      iii. Reduction in pulmonary function
      iv. Increased hemoptysis: a life-threatening complication but fatal hemoptysis is rare
      v. Digital clubbing
      vi. Changes in chest radiographic findings
      vii. Bronchiolitis
      viii. Increased rales or rhonchi
      ix. Decreased air exchange
      x. Increased use of accessory muscles of respiration
      xi. Spontaneous pneumothorax (5–8%), a life-threatening complication
      xii. Obstructive airway disease, leading to respiratory insufficiency associated with bronchiectasis
4. Gastrointestinal abnormalities
   a. Intestine
      i. Meconium ileus at birth
         a) An obstruction of the distal ileum or proximal colon with thickened, viscous meconium in 15–20% of CF patients developed *in utero* in the second trimester
         b) Virtually diagnostic of CF
      ii. Meconium peritonitis (rupture of the intestine secondary to complete obstruction)
      iii. Meconium plug syndrome in the newborn infants, a more benign condition characterized by blockage of the colon
      iv. Distal intestinal obstruction syndrome later in childhood, adolescence, or adulthood (10%), presenting as crampy abdominal pain, usually with decreased stooling
      v. Rectal prolapse occurring in less than 1% of patients but may be the presenting symptom, particularly in infants
      vi. Occasional intussusception
      vii. Gastroesophageal reflux

b. Pancreas
   i. Pancreatic exocrine insufficiency
      a) Failure of the pancreas to produce sufficient digestive enzymes to allow breakdown and absorption of fats and protein
      b) Obstruction of the pancreatic duct *in utero* with resultant progressive loss of exocrine pancreatic acini and their function
      c) A hallmark of the disease, occurring in 90% of patients by 1 year of age
      d) Leads to frequent, bulky, foul-smelling, oily stools
      e) Steatorrhea (presence of excessive undigested fat in the stool)
      f) Failure to thrive is commonly in the patients with CF
   ii. Recurrent pancreatitis in few patients
   iii. CF-related diabetes mellitus (Nathan et al. 2010)
      a) Affect approximately one third of all CF patients
      b) Rare before 10 years of age
      c) Resulting from a loss of functional pancreatic β cells and a state of relative insulin deficiency
      d) Oral glucose tolerance test as a screening tool
      e) HbA1c, an accepted diagnostic test for diabetes in the general population (International Expert Report 2009), cannot be used as screening tool because levels are often falsely low (Holl et al. 2000).

c. Liver
   i. Prolonged obstructive jaundice in a few affected infants, presumably secondary to obstruction of extrahepatic bile ducts by thick bile along with intrahepatic bile stasis
   ii. Chronic hepatic disease manifested by clinical or histologic evidence of focal biliary cirrhosis or multi-lobular cirrhosis

5. Genitourinary manifestations (Ruzal-Shapiro 1998)
   a. Congenital bilateral absence of the vas deferens in most males
      i. Leading to azoospermia
      ii. A significant cause of infertility
   b. Infertility common in women
      i. Due to increased amounts of thick mucus in the cervical canal
      ii. An increased incidence of amenorrhea
      iii. Occasional patients carrying pregnancies to term without significant respiratory deterioration
6. Skeletal manifestations (Ruzal-Shapiro 1998)
   a. Hypertrophic pulmonary osteoarthropathy
      i. Rarely seen in children with CF
      ii. Increasing frequency with increasing age and severity of disease
   b. Triad of skeletal manifestations
      i. Clubbing of fingers and toes
      ii. Arthritis
      iii. Periosteal new bone formation
7. Nutritional abnormalities
   a. Failure to thrive, a common manifestation during infancy and beyond
   b. Poor appetite
   c. Weight loss
   d. Fatigue
   e. Prone to heat prostration
   f. Hypoproteinemia with or without edema, anemia, and deficient fat-soluble vitamins A, D, E, and K
   g. Peripheral neuropathy secondary to deficient vitamin E
   h. Delayed puberty largely due to nutritional factors
   i. Potentially lethal protein-energy malnutrition in some infants
   j. Development of some degree of malabsorption by 4 years of age in roughly 85% of patients
8. Salt losing syndromes
   a. Acute salt depletion
   b. Chronic hypochloremic or hyponatremic alkalosis
   c. Excessive salt loss in the sweat potentially fatal for patients exposed to moderate heat or during prolonged hot weather
9. Prognosis
   a. Respiratory failure: the leading cause of death in CF and occurs eventually in nearly all patients
   b. Current median survival: approximately 35 years in the United States
   c. Current data suggesting a lifespan exceeding 50 years for those diagnosed and treated early

Diagnostic Investigations

1. Newborn screening
   a. Measuring blood immunoreactive trypsinogen in dried blood spots
      i. Elevated levels in most CF infants (85–90% sensitive)
      ii. Associated with a relatively large number of false positive results
      iii. Diagnosis must be confirmed by sweat tests or genotyping (CF multimutational analysis)
   b. Use DNA-based testing on dried blood spots by CFTR multimutational analysis
2. Sweat test
   a. The traditional method of CF diagnosis
   b. Remains the most readily available and clinically useful way of making the diagnosis of CF, provided it is done according to strict guidelines with pilocarpine iontophoresis and a quantitative determination of chloride concentration (LeGrys et al. 2007)
   c. Reliably identifies the vast majority of patients with CF who have multiorgan involvement including the lungs and pancreas
   d. Using pilocarpine iontophoresis technique to produce sweat for chloride analysis
   e. Sweat chloride concentrations
      i. >60 mEq/L, observed in:
         a) CF patients with clinical manifestation of chronic pulmonary disease and/or pancreatic insufficiency
         b) CF patients with positive family history
         c) Untreated Addison disease
         d) Ectodermal dysplasia
         e) Certain types of glycogen storage diseases
         f) Untreated hypothyroidism
         g) A few normal adults
      ii. <60 mEq/L, observed in:
         a) Very few patients with CF (fewer than 1% of CF patients when they are well)
         b) CF patients with malnutrition and edema
3. Indications for sweat testing
   a. Meconium ileus or peritonitis (neonate)
   b. Jaundice (infancy)
   c. Hypochloremic alkalosis (infancy)
   d. Heat prostration (infancy or adulthood in males)
   e. Failure to thrive (infancy to childhood)
   f. Rectal prolapse (childhood)
   g. Nasal polyposis (childhood to adulthood)
   h. Panopacification of sinuses or pansinusitis (childhood)
   i. Pancreatitis (late childhood to early adulthood)
   j. Unexplained cirrhosis (childhood to adolescence)
   k. Gallstones (late childhood to early adulthood)
   l. Congenital bilateral absence of the vas deferens or azoospermia (any age but more obvious in adults)
   m. Recurrent or persistent pneumonia (any age)
   n. Staphylococcal pneumonia (any age but especially infants)
   o. Mucoid *Pseudomonas* in lung (any age)
   p. Bronchiectasis (any age)
   q. Positive family history in siblings or first cousins (any age)
4. Causes of false-positive or false-negative sweat test results (O'Sullivan and Freedman 2009)
   a. False-positive result
      i. Atopic dermatitis (eczema)
      ii. Malnutrition
      iii. Congenital adrenal hyperplasia
      iv. Mauriac syndrome
      v. Fucosidosis
      vi. Ectodermal dysplasia
      vii. Klinefelter syndrome
      viii. Nephrogenic diabetes insipidus
      ix. Adrenal insufficiency
      x. Hypothyroidism
      xi. Autonomic dysfunction
      xii. Environmental deprivation
      xiii. Munchausen syndrome by proxy
   b. False-negative result
      i. Dilution of sample
      ii. Malnutrition
      iii. Peripheral edema
      iv. Low sweat rate (quantity not sufficient)
      v. Hypoproteinemia
      vi. Dehydration
      vii. CFTR mutations with preserved sweat duct function (e.g., 3,849 + 10 kb C → T; Arg117His–7T)

5. Other clinical laboratory tests
   a. Prolonged prothrombin time secondary to deficient vitamin K
   b. Shortened red blood cell survival time secondary to deficient vitamin E
   c. Hypochloremic alkalosis secondary to high salt loss
   d. Isolation of organisms from the respiratory tract
      i. *Pseudomonas aeruginosa*
      ii. *Burkholderia cepacia*
      iii. *Staphylococcus aureus*
   e. Oxygen saturation
6. Radiographic findings
   a. Chest X-ray
      i. Earliest finding: hyperinflation often with right upper lobe mucus retention
      ii. Progression to widespread bronchial dilatation, cysts, linear shadows, and infiltrates
   b. Sinuses X-ray: nearly universal presence of pansinusitis
   c. Abdominal X-ray
      i. Uncomplicated meconium ileus: multiple loops of dilated small bowel
      ii. Meconium peritonitis
         a) Calcifications within the abdominal cavity or even within the scrotum
         b) Resulting from an in utero perforation or complicated meconium ileus associated with volvulus
   d. Skeletal X-ray
      i. Arthritis
      ii. Periostitis in the diaphysis of the tubular bones
7. CT scan, especially high-resolution CT scan (Ruzal-Shapiro 1998)
   a. Readily identify air-trapping in the expiratory phase
   b. Mosaic perfusion, a secondary sign of small airway abnormality
   c. Centilobular nodule characterized by a cluster of ill-defined nodules corresponding to branching terminal airways filled with secretions
   d. Classic findings of CF of progressive bronchiectasis involving the large airways
      i. Thick parallel bronchial walls seen as linear shadows or tram-line tracts
      ii. Ring shadows representing dilated thick-walled bronchi
      iii. Multiple nodular densities representing mucus plugging
8. Pulmonary function test
9. Molecular testing
   a. More than 1,000 different mutations described to date
   b. ΔF508 mutation (deletion of a phenylalanine residue at position 508 in the 1,480 amino acid protein)
      i. Present in about 70% of CF alleles in the U.S.
      ii. Homozygous ΔF508 mutation in about 50% of American CF patients
   c. Higher frequencies of certain mutations in different ethnic groups
      i. A455E mutation in Dutch CF patients
      ii. W1282X mutation in Ashkenazi Jewish CF patients
   d. Presence of two alleles with CF causing mutations confirms the diagnosis
   e. Conventional commercial genotyping testing for about 80 specific mutations in CFTR (including ΔF508 mutation) identifies about 95% of all CF alleles.
10. Carrier testing available for family members of known patients or for couples without a family history
11. In general, a diagnosis of cystic fibrosis can be made in a patient with clinical features of the disease if the concentration of chloride in sweat is greater than 60 mmol/L or if it is in the intermediate range (30–59 mmol/L for infants less than 6 months of age, 40–59 mmol/L for older individuals), and two disease-causing CFTR mutations are identified (Farrell et al. 2008).

Genetic Counseling

1. Recurrence risk
   a. Both parents carrying at least one abnormal copy of the *CF* gene
   b. Patient's siblings
      i. 25% with CF disease
      ii. 50% with CF carrier
   c. Patient's offspring: low recurrence risk unless the spouse is affected or a carrier of CF mutation

2. Prenatal diagnosis (Rosenstein 1998)
   a. Ultrasonography
      i. Hyperechogenic fetal bowel suggestive of intestinal obstruction: perform carrier testing for CF gene mutations in the parents
         a) Diagnosis of CF highly likely in the fetus if both parents are carriers of a CF mutation
         b) Confirmed CF diagnosis by direct mutation analysis of amniotic fluid cells
      ii. Meconium peritonitis secondary to small bowel perforation *in utero*
         a) Associated with CF in only 7% of cases
         b) Presence of abdominal calcification usually associated with causes of meconium peritonitis other than CF
         c) Absence of abdominal calcifications favors the diagnosis of CF, to be confirmed by parental CF carrier testing and mutation analysis of fetal cells in at-risk couples
   b. Molecular genetic analysis
      i. Prenatal diagnosis accomplished in most families with an affected member by mutation analysis from fetal cells obtained from CVS (10 weeks) or amniocentesis (15–18 weeks)
      ii. Preimplantation genetic diagnosis to screen embryos before implantation, an alternative for at-risk couples
         a) A cleavage stage biopsy of embryo on day 2 or 3 after in vitro fertilization
         b) Removal of one or two cells for genetic analysis by nested polymerase chain reaction and heteroduplex formation
         c) Transfer of normal or carrier embryos to establish pregnancy
         d) Followed by CVS or amniocentesis to confirm the original diagnosis
   c. Postnatal sweat testing mandatory in all cases in which the diagnosis of CF has been made or excluded on the basis of prenatal DNA analysis
3. Management
   a. Antibiotic treatment of acute respiratory infections and exacerbations of chronic endobronchial infections
      i. Purpose
         a) To improve pulmonary function
         b) To improve exercise tolerance
         c) To improve quality of life
      ii. Short term oral ciprofloxacin for mild exacerbations by pseudomonas agent with caution in the younger pediatric age patients
      iii. Intravenous antibiotics, a mainstay of treatment of acute exacerbations of pulmonary disease
         a) Aminoglycoside (usually tobramycin) and β-lactam antibiotics
         b) Implanted central lines or peripheral vein catheters to maintain IV access
      iv. Aerosol (inhaled) antibiotics such as tobramycin
      v. Other aerosol antibiotics such as colistin
   b. Airway clearance and exercise (Marshall and Samuelson 1998)
      i. Percussion and postural drainage in an attempt to keep the airways free of infected and obstructive secretions
      ii. Positive expiratory pressure (PEP) devices to promote mucous clearance by preventing airway closure and increase collateral ventilation
      iii. ThAIRapy Vest, a chest wall compression and oscillation system comprising a fitted vest coupled to a pneumatic compressor
      iv. Flutter valve vibrating devices
      v. Directed exhalation techniques
   c. Sodium cromolyn (Intal™) or nedocromil (Tilade™) beneficial in some patients
   d. Use of inhaled (aerosolized) bronchodilators such as β-adrenergics
   e. Use of inhaled alpha dornase (DNase) (Pulmozyme™) to reduce sputum viscosity by cleaving extracellular neutrophil-derived DNA and brings about sustained improvement in pulmonary function in many patients with CF
   f. Avoid cough depressants
   g. Oxygen therapy if indicated
   h. Anti-inflammatory therapies
      i. Glucocorticoids: useful in selected patients
      ii. Ibuprofen
   i. Nutritional support to prevent malnutrition
      i. Provide pancreatic enzyme supplements and vitamins to correct malabsorption
      ii. Provide normal or high-fat diets with essential fatty acids necessary for growth and development
      iii. Provide fat-soluble vitamin supplements

j. Management of gastrointestinal obstructive complications
   i. Gastrografin enema for treatment of fecal impaction with distal intestinal obstruction syndrome
   ii. Surgery for intussusception if indicated
   iii. Surgery necessary to correct obstruction due to meconium ileus in most newborns
k. Management of biliary tract disease
   i. Treatment of severe focal or multi-lobular biliary cirrhosis, portal hypertension, and hypersplenism
      a) Sclerosing of esophageal varices
      b) Hepatic shunt procedures
      c) Liver transplantation
   ii. Cholecystectomy for gallstones
   iii. Urodeoxycholic acid for selected cases of liver dysfunction
l. Management of CF-related diabetes mellitus
   i. Dietary management
   ii. Insulin often required
   iii. Complementary diabetes pharmaceutical agents: no current place in management of CF related diabetes (Nathan et al. 2010)
m. Management of pneumothorax
   i. Chest tube drainage
   ii. Followed by simple surgical oversewing of blebs if the initial air leak does not resolve
   iii. Followed by definitive pleural ablation if necessary
n. Management of hemoptysis
   i. Reassurance in most cases
   ii. Additional vitamin K
   iii. Discontinue drugs that may interfere clotting
   iv. Bronchial artery embolization by interventional radiologic techniques in unusual cases
o. Management of respiratory failure
   i. Oxygen administration
   ii. Tracheal intubation and mechanical ventilation in terminally ill patients on the lung transplant waiting list
   iii. Lung transplantation: now an accepted therapy in patients with end-stage lung disease (Rosenblatt 2009)
      a) Acceptable survival rate
      b) Good quality of life
      c) Overall survival, however, still lags behind other solid-organ transplants
      d) Despite the higher incidence of diabetes mellitus, poor nutrition, and colonization with both multi-resistant and pan-resistant Gram-negative organisms, the patients with CF clearly benefit from lung transplantation
   iv. Heart-lung and lung transplantation successfully applied to patients with end-stage CF patients (Zuckerman and Kotloff 1998)
p. Cystic fibrosis in pregnancy (Whitty 2010)
   i. Women with cystic fibrosis (CF): now living to childbearing age and many have successful pregnancies
   ii. Improvement of fertility and pregnancy outcome:
      a) Preconception care with optimization of pulmonary function
      b) Eradication of pulmonary infection
      c) Improved nutritional status
      d) Improved diabetes
   iii. Women with CF with poor pulmonary function and nutrition, and less than ideal body weight: more likely to suffer adverse outcomes
   iv. Women with CF and pulmonary hypertension: risk mortality
   v. Women with lung transplants can have successful pregnancy, but the risk of organ rejection and death are high
q. Fertility in men with cystic fibrosis (Smith 2010)
   i. Men with CF, now surviving longer, may wish to be fertile and want to have children regardless of the disease severity (Sawyer et al. 2005).
   ii. Obstructive azoospermia in men with CF are due to (Kaplan et al. 1968; Holsclaw et al. 1971):
      a) Congenital bilateral absence of the vas deferencs, or
      b) Atrophy or complete absence of the epididymis or seminal vesicles
   iii. Sperm capable of fertilizing mature oocytes by intracytoplasmic sperm injection in vitro can be extracted from the majority of men with cystic fibrosis

iv. Sperm may be retrieved either by aspiration from the caput of the epididymis or directly from the testis or other alternative procedures

r. Gene therapy in CF patients by *in vivo* gene transfers (targeted lung delivery of aerosolized gene vectors)

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Fig. 1 This 5-month-old infant has history of failure to thrive, foul-smelling stools and excessive spitting. The patient is positive for two copies of the ΔF508 mutation

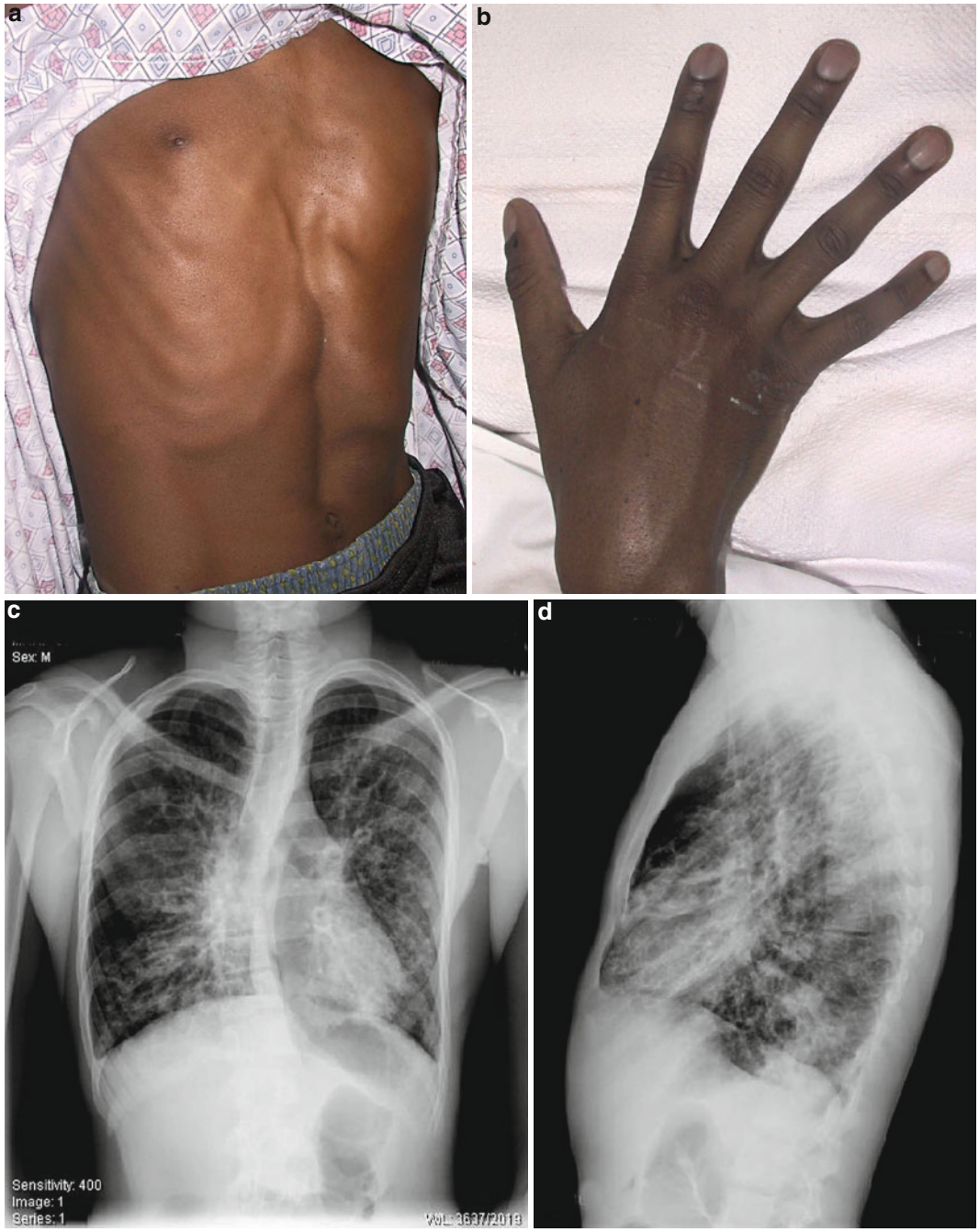

Fig. 2 (**a–d**) A 16-year-old boy with cystic fibrosis showing an emaciate chest, club fingers, and a honeycomb-like chest with air trapping illustrated by chest radiographs

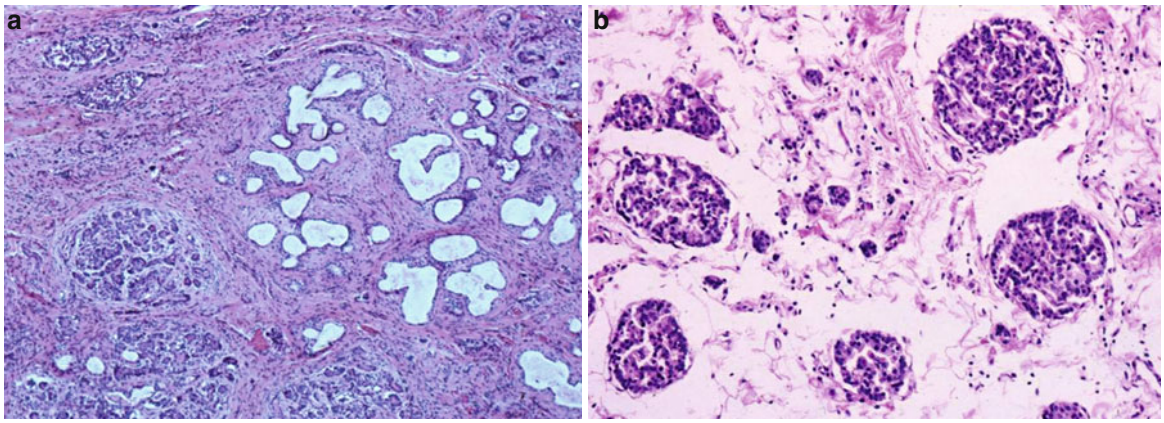

Fig. 3 (**a**, **b**) Photomicrograph of the pancreas of a 16-year-old male who died of bronchiectasis and bronchopneumonia. In the left photomicrograph, the exocrine glands (acini) are mostly absent. Irregularly dilated exocrine ductules are lined by flattened atrophic epithelium. Many unaffected islets of Langerhans are present at left lower corner. In the right photomicrograph with higher magnified, there are many islets of Langerhans but normal exocrine glands and ductules are absent

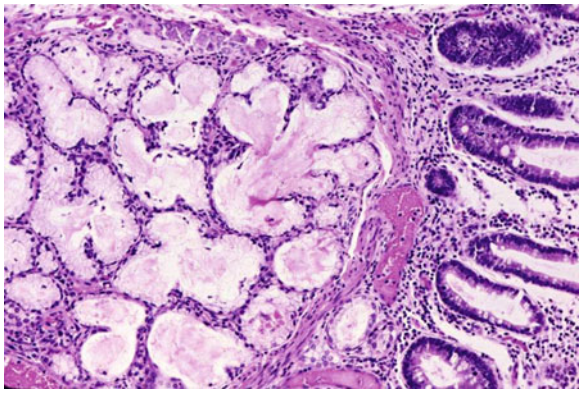

Fig. 4 Photomicrograph of the duodenum of the same patient. The Brunner's glands in the submucosa are distended by inspissated secretion. Three mucosal crypts are also slightly dilated

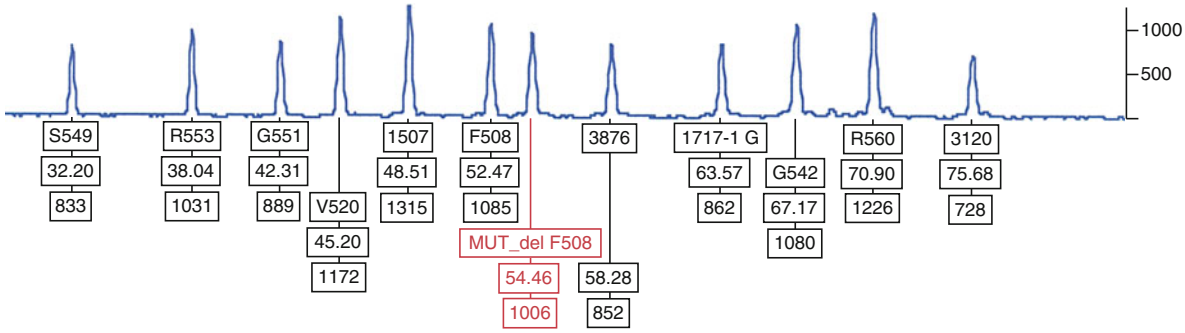

Fig. 5 Fragment size separation of CFTR mutations using capillary gel electrophoresis (ABI 310 genetic analyzer, Applied Biosystems). A mutation in ΔF508 is noted in *red*

Dandy–Walker Malformation

In 1954, Benda introduced the term Dandy–Walker syndrome to indicate the association of (1) ventriculomegaly of variable degree, (2) a large cisterna magna, and (3) a defect in the cerebellar vermis through which the cyst communicates with the fourth ventricle. Currently, the following findings are included in the Dandy–Walker syndrome or malformation: (4) cystic dilatation of the fourth ventricle, (5) dysgenesis of the cerebellar vermis, and (6) a high position of the tentorium. The Dandy–Walker malformation has prevalence of about 1 in 30,000 live births and found in 4–12% of infantile hydrocephalus.

Genetics/Basic Defects

1. Heterogeneous etiology
   a. Isolated
   b. A part of a Mendelian disorder
   c. A part of a chromosome disorder
      i. Trisomy 18
      ii. Triploidy
      iii. Trisomy 13
   d. Environmental factors
2. Uncertain significance of Dandy–Walker variant and mega-cisterna magna

Clinical Features

1. Maternal polyhydramnios/oligohydramnios
2. Fetal anomalies
   a. Echogenic bowel
   b. Effusions/hydrops
   c. Single umbilical artery
   d. Growth restriction
   e. Abundant nuchal folds
   f. Cystic hygroma
3. Neuropathologic triad
   a. Cystic dilatation of the fourth ventricle
   b. Hypoplasia of the cerebellar vermis
   c. Hydrocephalus
4. Associated intracranial anomalies (70% of cases)
   a. An enlarged posterior fossa
   b. Ventriculomegaly
   c. Atresia of the foramina of Magendie and Luschka
   d. Midline anomalies
      i. Agenesis of the corpus callosum
      ii. Holoprosencephaly
      iii. Occipital meningocele and encephalocele
   e. Porencephalic cyst
   f. Migrational disorder
   g. Gyral abnormalities
   h. Microcephaly
5. Non-CNS associated malformations
   a. Facial clefting
   b. Cardiovascular defects
   c. Diaphragmatic hernia
   d. Omphalocele
   e. Polycystic kidneys
   f. Spinal defects
   g. Limb defects
      i. Polydactyly
      ii. Syndactyly
6. Common presenting signs and symptoms
   a. Macrocrania
   b. Bulging fontanel
   c. Upward gaze palsy
   d. Hypertelorism
   e. Strabismus

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f. Hypotonia
g. Headache and vomiting
h. Seizures
i. Hemiparesis
j. Facial palsy
k. Palpebral ptosis
l. Pyramidal signs
m. Cerebellar dysfunction
n. Motor dysfunction
o. Mental retardation: subnormal intelligence reported in 40–70% of cases

7. Prognosis
   a. Grim but not uniformly fatal
   b. Worst prognosis when there are associated anomalies and chromosome abnormalities
   c. Better chance of normal outcome for isolated Dandy–Walker variant

Diagnostic Investigations

1. Sonography
   a. Sonographic diagnosis of classic Dandy–Walker malformation: straightforward from mid-gestation
   b. Detection of Dandy–Walker malformation as early as 14 weeks using vaginal sonography
   c. In the transcerebellar view
      i. An enlarged cisterna magna connected to the area of the fourth ventricle through a defect in the cerebellar vermis
      ii. Presence of borderline-to-overt ventriculomegaly
      iii. Frequent association of other neural and extra-neural malformation
2. CT and MRI of the brain
   a. Large median posterior fossa cyst widely communicating with the fourth ventricle
   b. Cystic enlargement of the fourth ventricle
   c. Cerebellar vermis dysgenesis
   d. An upwardly displaced tentorium
   e. Hydrocephalus
   f. Atresia of the foramina of Magendie and Luschka
   g. Frequently associated CNS anomalies
      i. Agenesis of corpus callosum
      ii. Occipital encephalocele
      iii. Porencephalic cyst
      iv. Holoprosencephaly
      v. Others

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: a low recurrence risk in the order of 1–5% unless the Dandy–Walker malformation is a part of a mendelian disorder or associated with chromosome anomaly.
   b. Patient's offspring: not surviving to reproductive age because of severe neurologic deficits associated with major malformations.
2. Prenatal diagnosis
   a. Ultrasonography for detecting unique previously described CNS malformations
   b. MRI of the fetal CNS
   c. Prenatal amniocentesis for fetal karyotyping
3. Management
   a. Ventriculoperitoneal shunt
   b. Cyst-peritoneal shunt
   c. Ventriculocystoperitoneal shunt
   d. Posterior fossa craniectomy with cyst fenestration

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Fig. 1 (**a–c**) An 8-month-old patient with Dandy–Walker malformation associated with multiple congenital anomalies including facial dysmorphism, skin tags (pseudotails) on the cheek, and limb anomalies

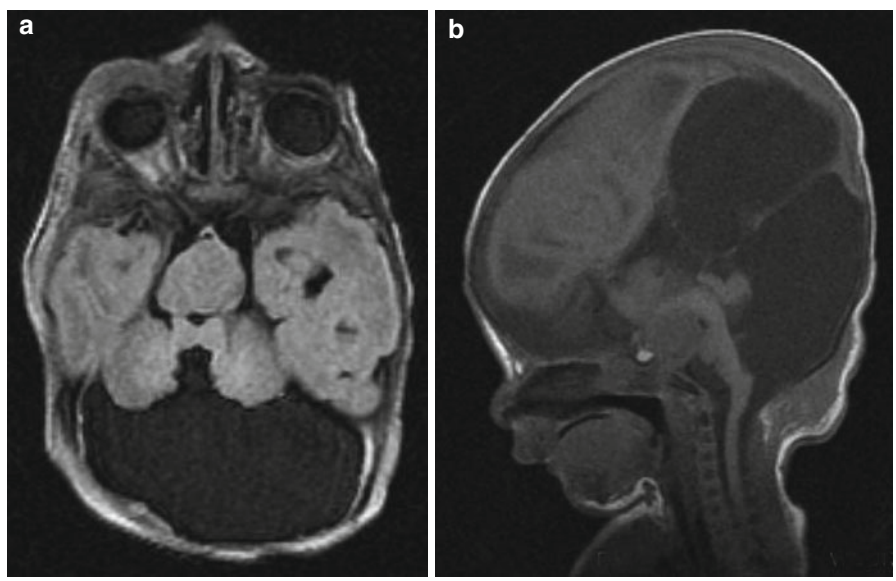

Fig. 2 (**a, b**) MRI of the brain of the patient in Fig. 1 shows Dandy–Walker malformation with a large posterior fossa cyst which communicates with dilated fourth ventricle. In addition, this patient also has agenesis of corpus callosum, hydrocephalus, and vermis dysgenesis

De Lange Syndrome

In 1933, Cornelia de Lange reported two non-familial infant girls with severe mental retardation and multiple abnormalities of the skull, face, and extremities. Earlier in 1916, Brachmann had described a child with similar features. The syndrome is also called Brachmann-de Lange syndrome or Cornelia de Lange syndrome. The prevalence is estimated to be 1 in 10,000 births (Opitz 1985).

Synonyms and Related Disorders

Brachmann-de Lange syndrome; NIPBL-related Cornelia de lange syndrome; SMC1A-related Cornelia de Lange syndrome; Typus degenerativus amstelodamensis

Genetics/Basic Defects

1. A heterogeneous clinical entity
   a. Sporadic in vast majority of cases (99%) (Russell et al. 2001)
   b. Striking concordance in MZ twins
   c. Rare familial occurrences
      i. Autosomal dominant inheritance
      ii. Autosomal recessive inheritance: unlikely
2. Inconsistent chromosome abnormalities occasionally associated with de Lange phenotype. In addition, the following significant cytogenetic findings were reported:
   a. Deletions of chromosome 5p13 where Cornelia de Lange syndrome gene (*NIPBL*) have been reported in two cases (Taylor and Josifek 1981; Hulinsky et al. 2005)
   b. An increased rate of precocious sister chromatic separation has been reported in affected individuals (Kaur et al. 2005)
3. Combined mutations in *NIPBL*, *SMC1A*, and *SMC3*: identified in nearly 60% of patients with a confident clinical diagnosis of de Lange syndrome (Dorsett and Krantz 2009)
   a. *Nipped-B-like* (*NIPBL*) gene on chromosome 5p13 (Krantz et al. 2004)
      i. At least 50% of cases are caused by loss-of-function mutations of *NIPBL* gene
      ii. Required for binding of the cohesion complex that mediates sister chromatid cohesion to chromosome (Dorsett 2007)
   b. *SMC1A* gene
      i. X-linked (on Xp11)
      ii. Encodes the SMC1 subunit of mitotic cohesion
      iii. Missense or small in-frame deletion was noted in approximately 5% of individuals with clinical diagnosis of de Lange syndrome
   c. *SMC3* gene
      i. On chromosome 10q25
      ii. Mutation is heteroallelic with a wild-type allele
4. De Lange syndrome, thus, considered to be a cohesinopathy, along with Roberts syndrome/SC phocomelia (Tekin and Bodurtha 2009)
5. Genotype-phenotype correlations
   a. More severe *NIPBL* mutations (such as deletions or truncations): usually cause more severe clinical manifestations than missense mutations
   b. Missense mutations in *NIPBL*: associated with mild phenotypic features

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c. Mutations in SMC1A and SMC3: associated with a milder phenotype with absence of limb defects and other structural anomalies
d. In the mildest forms, affected individuals generally have mild to moderate mental retardation and, at least at a young age, typical facial characteristics

Clinical Features

1. Marked clinical variability
2. General history
   a. Prenatal and/or postnatal growth deficiency
   b. Prematurity
   c. Diminished sucking and swallowing ability
   d. Low pitched cry (74%) in the newborn period and in the early infancy but may disappear in the late infancy
   e. Global developmental delay
   f. Initial hypertonicity
   g. Recurrent respiratory tract infections
   h. Gastroesophageal reflux
   i. Failure to thrive
3. Growth
   a. Prenatal onset growth retardation
   b. Short stature
4. Skin
   a. Hypertrichosis (hirsutism) (78%): often with hairy whorls over the shoulders, lower back, and extremities
   b. Cutis marmorata (60%)
   c. Periorbital "cyanosis"
5. Characteristic craniofacial appearance
   a. Microcephaly (98%)
   b. Brachycephaly
   c. Hairy (low hairline) forehead
   d. Mask like (grim, devoid of expression) facies
   e. Hypertelorism
   f. Antimongoloid slant of palpebral fissures
   g. Synophrys (prominent bushy, confluent eyebrows joining at the nose) (99%)
   h. Long and curly eyelashes (99%)
   i. Depressed nasal bridge (83%)
   j. Small nose
   k. Anteverted nares (88%)
   l. Micrognathia (84%)
   m. Long bulging, prominent philtrum (94%)
   n. Thin upper lip (94%)
   o. Central depression below lower lip
   p. Down-turned corners of the mouth (94%)
   q. Late eruption of teeth
   r. Widely spaced teeth (86%)
   s. High-arched palate (86%)
   t. Low set, malformed, and hairy ears (70%)
   u. Low posterior hairline (92%)
   v. Short neck (66%)
6. Eye abnormalities (57%)
   a. Strabismus
   b. Nystagmus (37%)
   c. Myopia (60%)
   d. Ptosis (45%)
   e. Microcornea
   f. Astigmatism
   g. Optic atrophy
   h. Coloboma of the optic nerve
   i. Eccentric pupils
   j. Microphthalmia
   k. Blue sclerae
7. Limb abnormalities
   a. Upper extremities
      i. Micromelia (shortened limbs) (93%)
      ii. Ectrodactyly/oligodactyly/phocomelia (27%)
      iii. Clinodactyly of the fifth fingers (74%)
      iv. Small hands
      v. Proximally placed thumbs
      vi. Camptodactyly
      vii. Webbings of fingers
      viii. Brachydactyly
      ix. Flexion contractures of the elbows common (64%)
      x. Restriction of supination and pronations
      xi. Subluxation or dislocation of the radial head
   b. Lower extremities
      i. Small feet
      ii. Cutaneous syndactyly of the second and third toes (86%)
      iii. Tight Achilles tendon (equines deformity)
      iv. Pes planus
      v. Valgus heel
      vi. Flexion contractures of the knees
8. CNS anomalies
   a. Variable mental retardation to near-normal intellect

b. Seizures (23%)
c. Abnormal speech development
d. Hearing deficits (60–100%)
e. Hypoplasia of the vermis
f. Hypertonia/hypotonia

9. Behavior disorder
   a. Sleep disturbance (55%)
   b. Aggression (49%)
   c. Self-destructive tendencies (44%)
   d. Hyperactivity (40%)
   e. Low-pitched growling sound rather than cry
   f. Infrequent facial expressions of emotion
   g. Severe language delay
   h. Autistic-like behavior
   i. Repetitive stereotypic movement
   j. Eliciting pleasurable responses by vestibular stimulation or vigorous movement
10. Other anomalies
   a. Small hypoplastic nipples (55%)
   b. Small hypoplastic umbilicus (53%)
   c. Cardiovascular anomalies (15–20%)
      i. Ventricular septal defect
      ii. Atrial septal defect
      iii. Patent ductus arteriosus
      iv. Aortic valve anomaly
      v. Hypoplasia of the aorta
      vi. Persistent left superior vena cava
      vii. Pulmonary stenosis
      viii. Endocardial cushion defect
      ix. Tetralogy of Fallot
   d. Gastrointestinal anomalies
      i. Inguinal hernia
      ii. Hiatus hernia
      iii. Congenital diaphragmatic hernia
      iv. Gut duplication
      v. Malrotation of colon
      vi. Pyloric stenosis
   e. Genitourinary anomalies
      i. Hypoplastic, dysplastic, or cystic kidneys
      ii. Hypoplastic external genitalia, cryptorchidism or hypospadias in males
      iii. Small labia majora, bicornuate or septate uterus in females
   f. Abnormal dermatoglyphics
      i. Transverse palmar creases (51%)
      ii. Increased atd angle
      iii. Hypoplastic finger ridge patterns

Diagnostic Investigations

1. Radiography
   a. Skull
      i. Microcephaly: frequent
      ii. Brachycephaly: frequent
      iii. Trigonocephaly with orbital hypotelorism
      iv. Parietal foramina
      v. Micrognathia
      vi. High-arched palate
      vii. Cleft palate
   b. Spine
      i. Kyphoscoliosis
      ii. Platyspondyly
      iii. Scheuermann disease
      iv. Spina bifida
      v. Square vertebrae
      vi. Coxa valga
   c. Chest
      i. Aspiration pneumonia: frequent
      ii. Thin ribs
      iii. Short clavicles
      iv. Short hypoplastic sternum with reduced number of ossification centers
      v. Abnormal sternal angle
      vi. Cervical ribs
      vii. Hypoplasia of the first rib
      viii. Chronic pneumonia
      ix. Bronchiolitis
   d. Congenital heart diseases
   e. Gastrointestinal tract
      i. Swallowing dysfunction: frequent
      ii. Bowel rotation anomalies with bands: frequent
      iii. Hiatal hernia
      iv. Hypertrophic pyloric stenosis
      v. Duodenal stenosis
      vi. Colon duplication
      vii. Inguinal hernia
      viii. Umbilical hernia
   f. Genitourinary tract
      i. Incomplete rotation of the kidneys
      ii. Renal duplication
      iii. Polycystic kidneys
      iv. Chronic pyelonephritis
      v. Abnormal renal function with poor visualization on excretory urography

vi. Vesicoureteral reflux
vii. Divided uterine canal with septate vagina

g. Limbs
i. Micromelia: frequent
ii. Short humerus and/or forearm bones: frequent
iii. Elongated humeral neck (similar to femoral neck): frequent
iv. Subluxation or dislocation of malformed radius and/or ulna at elbow with fixation in flexion
v. Absent or hypoplastic ulna: frequent
vi. Retarded bone maturation with abnormal sequence of appearance of ossification centers: frequent
vii. Absent carpals, metacarpals, and fingers (ectrodactyly/oligodactyly): frequent
viii. Short, broad metacarpals, particularly one and five: frequent
ix. Hypoplastic phalanges particularly middle fifth (curved) and middle second fingers: frequent
x. Cutaneous syndactyly of second and third toes or other toes and fingers: frequent
xi. Cutis valgus
xii. Absent or hypoplastic radius
xiii. Lunate and triquetral fusion
xiv. Aplastic or hypoplastic ulnar styloid
xv. Double distal phalanges of thumbs and/or great toes
xvi. Congenital dislocated hips
xvii. Aseptic necrosis of femoral head
xviii. Broad ischial bones
xix. Large obturator foramina
xx. Short broad femoral necks
xxi. Absent tibia with deformed fibula
xxii. Fusion of phalanges of fifth toe
xxiii. Rocker-bottom foot
xxiv. Metatarsus adductus
xxv. Planovalgoid foot
xxvi. Talipes equinovarus
xxvii. Shortening of femur and/or leg bones
xxviii. Wide gap between first and second toes
xxix. Osteoporosis

2. Endocrinologic studies in patients with severe growth retardation
3. Echocardiography for evaluation of congenital heart defects
4. Abdominal ultrasonography for GU anomalies
5. EEG for seizures
6. High resolution chromosome analysis for associated chromosome anomaly
7. Mutation scanning and sequence analysis (Deardorff et al. 2006)
   a. Mutation scanning of *NIPBL* gene detected mutations in approximately 50% of 179 individuals from three studies (Borck et al. 2004; Gillis et al. 2004; Tonkin et al. 2004)
      i. Frameshift mutations
      ii. Nonsense mutations
      iii. Splice-site mutation
      iv. Missense mutations
   b. Study by Musio et al. (2006)
      i. A *NIPBL* mutation was identified in 44% (24/54) of probands
      ii. A *SMC1A* mutation was detected in 4% (2/54) of probands

Genetic Counseling

1. Recurrence risk (Deardorff et al. 2006)
   a. Patient's sib
      i. Autosomal dominant inheritance
         a) An empiric risk of about 1–4%
         b) Possibility of recurrence in siblings exists since gonadal mosaicism cases have been demonstrated (Niu et al. 2006)
      ii. X-linked recessive inheritance
         a) The risk to sibs depends on the carrier status of the mother
         b) If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will usually not be affected
         c) If the disease-causing mutation cannot be detected in the DNA of the mother of the only affected male in the family, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism
   b. Patient's offspring
      i. Autosomal dominant inheritance
         a) A 50% risk

b) While most familial recurrences are the result of germline mosaicism in a phenotypically normal parent, rare cases of a mildly affected individual having affected children have been reported

ii. X-linked recessive inheritance: Males with X-linked de Lange syndrome will pass the disease-causing mutation to all of their daughters and none of their sons

2. Prenatal diagnosis
   a. Ultrasonography (2-D and 3-D) (Sepulveda et al. 2009)
      i. Intrauterine growth retardation
      ii. Characteristic facies
         a) Long eyelashes
         b) A small bulging nose
         c) Hypoplastic nasal bone
         d) Depressed nasal bridge
         e) Anteverted nostrils
         f) A long philtrum
         g) Protruding and overhanging upper lip
         h) Micrognathia
      iii. Limb defects
         a) Micromelia
         b) Monodactyly
         c) Ulnar agenesis
      iv. Diaphragmatic hernia
   b. Molecular genetic diagnosis: Prenatal diagnosis is possible by demonstrating *NIPBL* mutation by DNA analysis of fetal cells obtained from amniocentesis or CVS
3. Management
   a. Adequate caloric intake
   b. Treat gastroesophageal reflux with thickened feeds in a upright position and pharmacotherapy
   c. Fitting of hearing aids and early consistent training for hearing impaired children
   d. Early intervention and special education programs for psychomotor delay
   e. Behavioral modification
   f. Correction of refractory errors with glasses
   g. Anticonvulsants for seizures
   h. Surgical repairs
      i. Fundoplication and gastrostomy feedings necessary in patients with severe esophagitis and progressive failure to thrive despite conservative intervention
      ii. Diaphragmatic hernia
      iii. Cardiac defect
      iv. Severe skeletal deformities
      v. Renal malformations
      vi. Ptosis obstructing the visual axis
      vii. Orchiplexy

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Fig. 1 (**a**–**h**) Three neonates with de Lange syndrome showing characteristic facies, oligodactyly, hirsutism, and ambiguous genitalia in one

Fig. 2 (**a**, **b**) Another neonate with de Lange syndrome showing similar phenotype (characteristic facies, oligodactyly, and severe hirsutism)

Fig. 3 (**a**–**d**) A 12-year-old boy with de Lange syndrome showing characteristic facies and reduction malformation with ectrodactyly/oligodactyly of the right arm and partial syndactyly of second to third fingers with transverse palmar crease of the left hand

Fig. 4 (**a**–**d**) Four patients with classic de Lange syndrome of different ages showing typical facial appearance (synophrys, coarse eyebrows, long curly eyelashes, depressed nasal bridge with anteverted nares, long thin upper lip, down-turned angles of the mouth, and widely spaced teeth) and ectrodactyly/oligodactyly in the first two cases

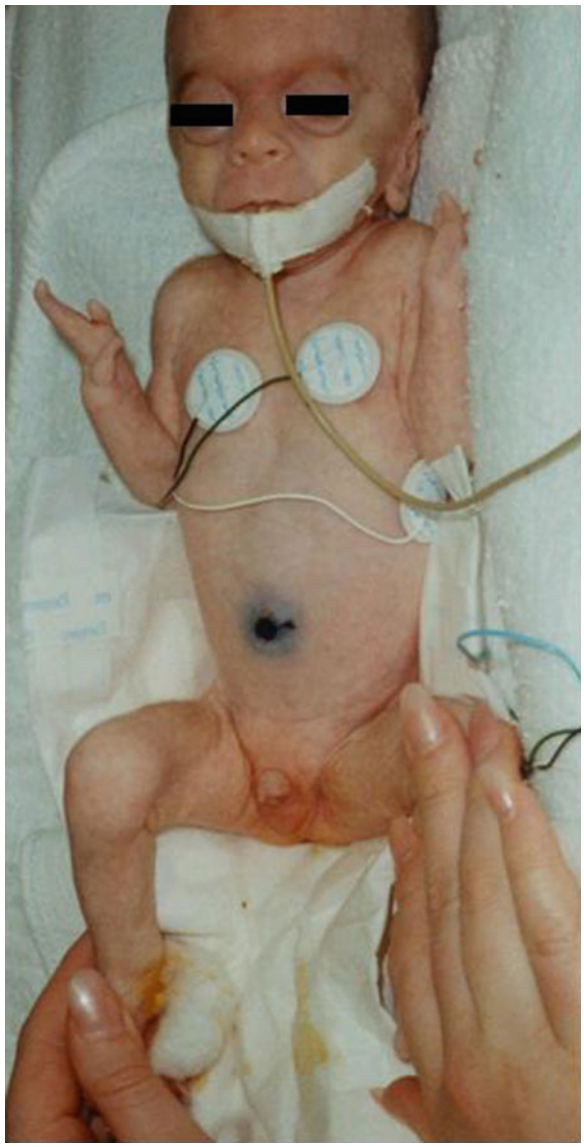

Fig. 5 A 46, XX male with de Lange phenotype

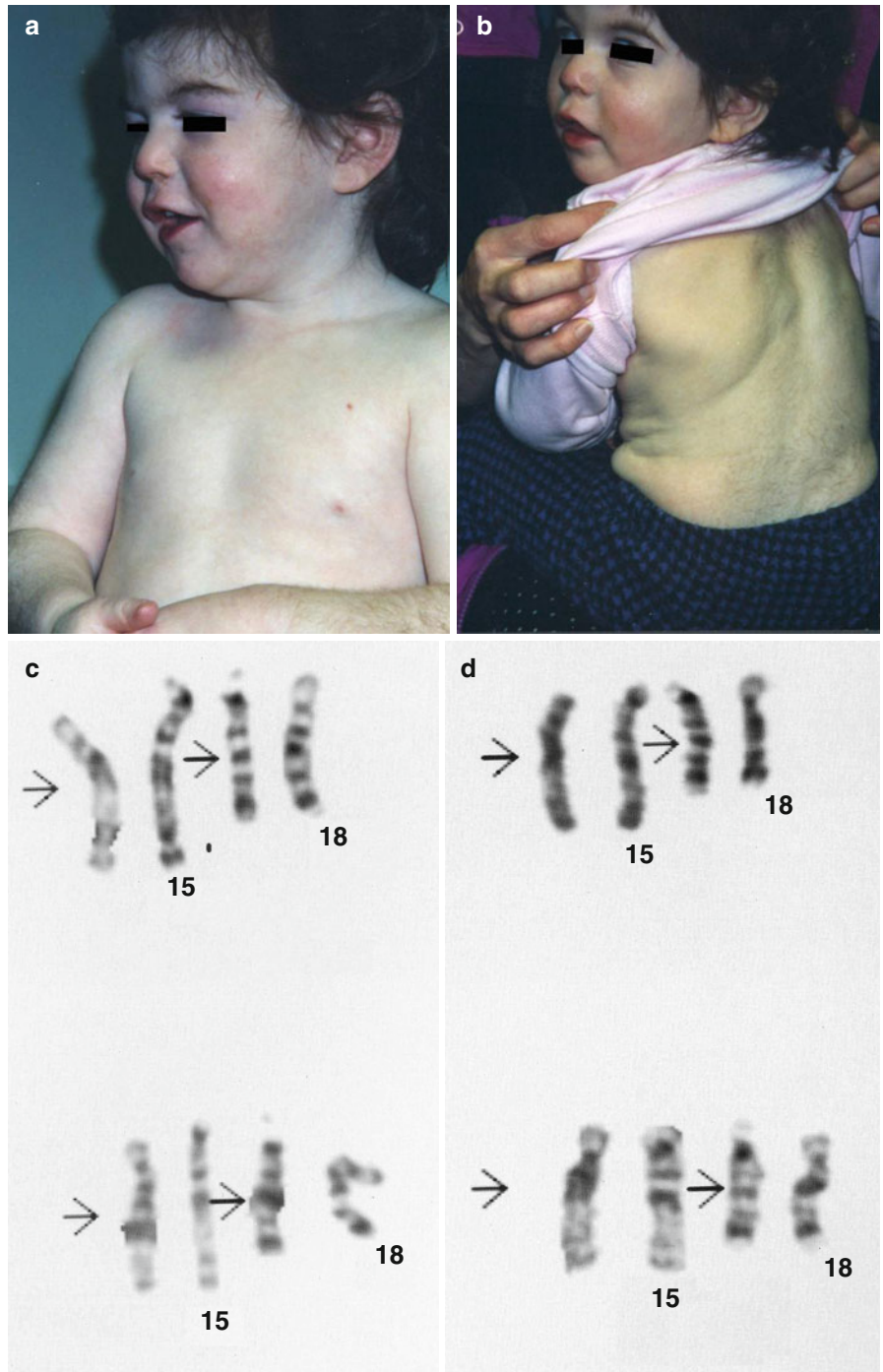

Fig. 6 (**a**–**d**) A child with t(15q;18q) showing de Lange phenotype

Fig. 7 (**a**, **b**) Two adults with de Lange syndrome showing hirsutism and mental retardation

Del(18p) Syndrome

de Grouchy in 1963 reported the syndrome, the first example of a partial monosomy compatible with life. The incidence is approximately 1 in 50,000 live-born infants (Turleau 2008).

Synonyms and Related Disorders

18p- syndrome; Monosomy 18p syndrome

Genetics/Basic Defects

1. Monosomy 18p syndrome (Turleau 2008)
   a. Refers to a chromosomal disorder, resulting from the deletion of all or part of the short arm of chromosome 18
   b. One of the most frequent autosomal terminal deletion syndromes
2. Types of 18p deletion
   a. Monosomies of the entire short arm as well as partial monosomies 18p have been reported (Schaub et al. 2002).
   b. De novo deletions in most cases (about two third).
   c. Consequences of an unbalanced whole arm translocation: usually occurring between the long arm of an acrocentric chromosome and the long arm of the chromosome 18 and resulting in a karyotype with 45 chromosomes (Wang et al. 1997).
   d. Consequences of malsegregation of a balanced parental translocation with a variable breakpoint on 18p and are accompanied by a partial trisomy for another chromosome.
   e. Cryptic subtelomeric deletions or translocations: evidenced using subtelomeric screening (Horsley et al. 1998; Babovic-Vuksanovic et al. 2004).
   f. Mosaicism or association with another aneuploidy.
   g. Ring 18 chromosome (Stankiewicz et al. 2001) or after recombination in a pericentric inversion leading to a 18p monosomy associated with a 18q trisomy (Leonard et al. 2000).
   h. Familial transmission of 18p- from one of the parents to the child reported in at least eight cases, all of them maternally inherited (Uchida et al. 1965; Velagaleti et al. 1996; Tonk and Krishna 1997; Rigola et al. 2001; Tsukahara et al. 2001; Maranda et al. 2006; Portnoi et al. 2007; Misceo et al. 2009).
      i. 18p- may be in a homogeneous or a mosaic state in the parent.
      ii. Intrafamilial clinical variability
3. The most distal segment of 18p contains the critical region of HPE4 (Overhauser et al. 1995).
   a. Mutations in the *TGIF* gene located on 18p11.3 have been shown to cause holoprosencephaly (Gripp et al. 2000).
   b. Hemizygosity of HPE4 does not automatically confer the phenotype of HPE, since only 10–15% of patients have features consistent with HPE, confirming that multiple genetic and environmental factors intervene in HPE spectrum phenotypes.

Clinical Features

1. Very frequent clinical features (Turleau 2008)
   a. Mental retardation with variable severity

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b. Speech delay
c. Short stature
d. Hypotonia

2. Frequent clinical features
   a. Variable features of the holoprosencephaly (HPE) spectrum
   b. Ptosis
   c. Flat nasal bridge
   d. Wide mouth with short upper lip
   e. Small mandible
   f. Excessive caries
   g. Large, protruding ears
   h. Short, webbed neck
   i. Broad trunk
   j. Pectus excavatum
   k. Kyphoscoliosis
3. Rare clinical features
   a. Behavioral disorders
   b. Autoimmune diseases
   c. Alopecia
   d. Dystonia

Diagnostic Investigations

1. Cytogenetic analysis including subtelomeric FISH
   a. Patient: to detect absence of all or part of the short arm of one chromosome 18
   b. Parent: to determine if either parent is a balanced translocation carrier or has the unbalanced 18p deletion
2. Array-based comparative genomic hybridization (CGH)

Genetic Counseling

1. Recurrence risk (Turleau 2008)
   a. Patient's sib
      i. A de novo case
         a) Not significantly increased above that of the general population
         b) Caution: cryptic mosaicism may be present in one of the parents.
      ii. Presence of a structural rearrangement in one of the parents (most frequently balanced translocation, followed by pericentric inversion)
         a) Recurrence risk depends on the type of rearrangement, in which chromosomes are involved, and on the size of the rearranged segments.
         b) A high recurrence risk of either a monosomy or a trisomy for 18p for some rearrangement
      iii. One of the parents with a 18p deletion
         a) A 50% risk if the parent has non-mosaic 18p deletion
         b) Lower than 50% risk if the parent has mosaic 18p deletion
   b. Patient's offspring
      i. A 50% risk if the patient has non-mosaic 18p deletion
      ii. Lower than 50% risk if the patient has mosaic 18p deletion
2. Prenatal diagnosis
   a. Cytogenetic analysis including FISH: can detect deletion 18p when a parent is heterozygous for a balanced rearrangement involving 18p or carrier of a 18p deletion, following detection of a holoprosencephaly-type defect at sonography, or after the birth of a first affected child
   b. Deletion 18p is rarely observed in first-trimester abortions suggesting that this imbalance is not selected against
3. Management
   a. No specific treatment available
   b. Early rehabilitative and educations interventions, mainly speech therapy
   c. Physical therapy for hypotonia

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Fig. 1 (**a**, **b**) A girl with monosomy 8p syndrome showing flat nasal bridge and ptosis with history of developmental delay

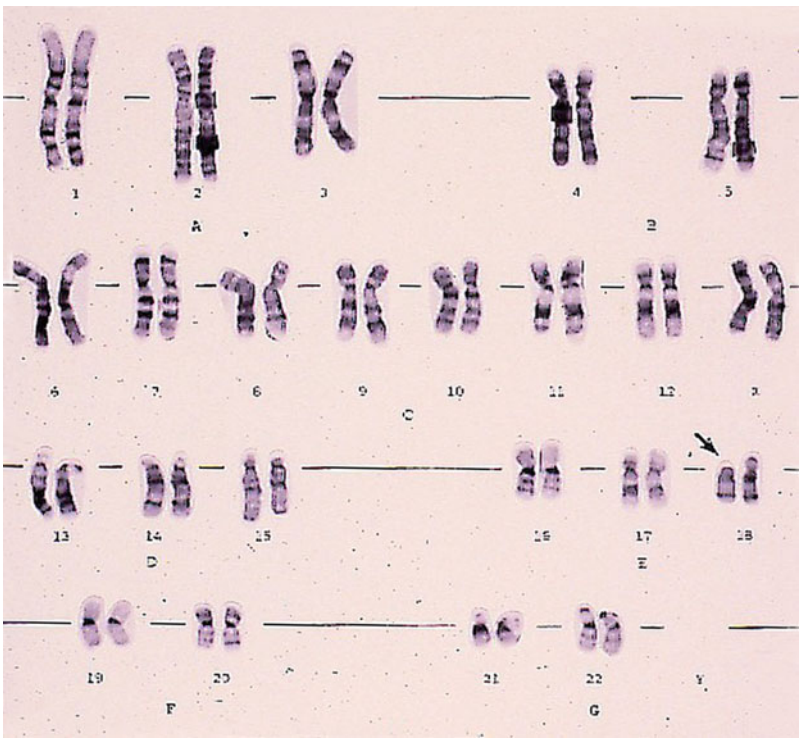

Fig. 2 Karyotype of the previous patient is illustrated here

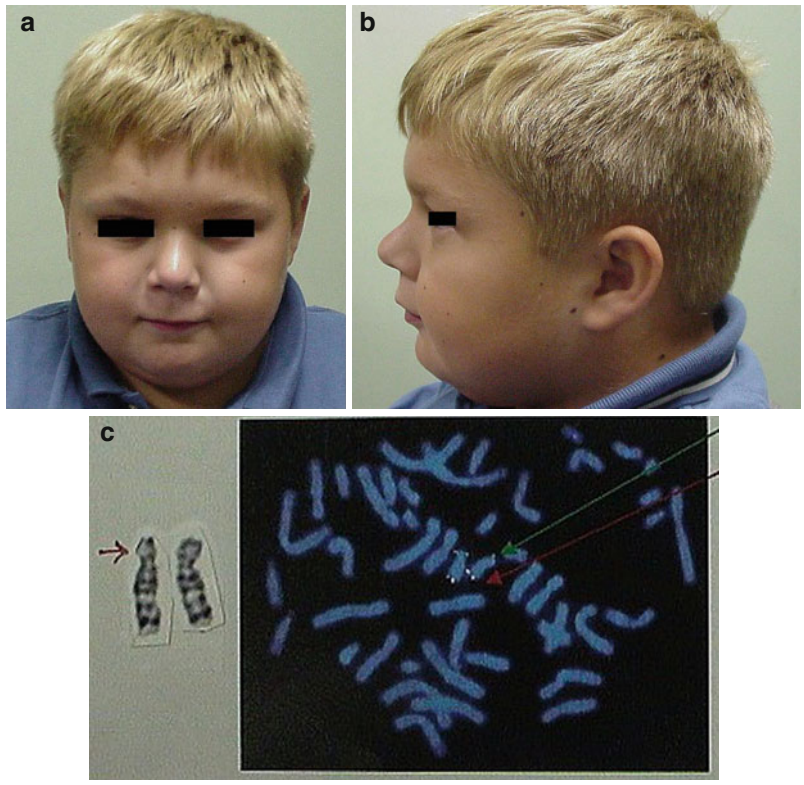

Fig. 3 (**a–c**) An 11-year-old boy with del(18p). He has short stature, mild mental retardation, IgA deficiency, a round face, tricuspid/mitral regurgitation, glandular hypospadias, and small hands and feet. A partial karyotype with FISH is illustrated here

Fig. 4 A young girl with monosomy 18p syndrome [Del(18p)-Del(18)(qter-p111)]. In addition to developmental and speech delay, the patient has a round face, short upper lip, broad philtrum, everted lower lip, and protruding ears

Del(22q11.2) Syndrome

The 22q11.2 deletion syndrome is one of the most common multiple anomaly syndrome and the most common microdeletion syndrome. It is the most common syndrome associated with palatal clefts and congenital velopharyngeal dysfunction (Kirschner 2005) and the second most common cause of developmental delay accounting for about 2.4% of affected individuals. The occurrence is approximately 1 in 4,000 live births (Botto et al. 2003; Óskarsdóttir et al. 2005).

Synonyms and Related Disorders

22q11.2 Microdeletion Syndrome; CATCH-22 syndrome; Cayler craniofacial syndrome associated with del(22q11.2); Congenital thymic hypoplasia associated with hypocalcemia; DiGeorge syndrome; Takao syndrome; Velocardiofacial syndrome (Shprintzen syndrome)

Historic overviews of the syndromes associated with 22q11.2 deletion:

1. Congenital thymic hypoplasia associated with hypocalcemia (1959)
2. DiGeorge syndrome (DGS) (1972)
   a. Congenital thymic hypoplasia
   b. Hypocalcemia
   c. T-cell dysfunction
   d. Typical facial anomalies
   e. Typical cardiac anomalies
3. Takao syndrome (conotruncal anomaly face syndrome) (1976)
   a. Conotruncal cardiac anomalies
   b. Typical facial appearance
   c. Velopharyngeal insufficiency
   d. Learning disability
4. Velocardiofacial syndrome (VCFS) (Shprintzen syndrome) (1978)
   a. Velophalangeal abnormalities
   b. Cardiac abnormalities
   c. Facial abnormalities
   d. The birth incidence of 1/1,800–1/4,000, making VCFS the second most common cause of congenital heart disease after Down syndrome
5. DiGeorge syndrome speculatively linked to chromosome 22 (1981)
6. Partial monosomy of chromosome 22 (1982)
7. "CATCH-22 syndrome" (1989): not a preferred term
   a. *C*ardiac disease
   b. *A*bnormal facies
   c. *T*hymic hypoplasia
   d. *C*left palate
   e. *H*ypocalcemia
   f. Associated with a deletion in chromosome-*22*
8. Cayler craniofacial syndrome associated with del (22q11.2) (1994)
   a. Asymmetric crying facies
   b. Phenotypic spectrum expanded to include extracardiac anomalies
   c. Associated with del(22q11.2)
9. Some cases of autosomal dominant Opitz G/BBB syndrome (1995)
   a. Hypertelorism
   b. Laryngotracheoesophageal cleft
   c. Cleft palate
   d. Swallowing difficulty
   e. Genitourinary defects
   f. Mental retardation
   g. Congenital heart defects

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Genetics/Basic Defects

1. Inheritance
   a. De novo deletions in the majority of cases (80–90%) (Yamagishi and Srivastava 2003)
   b. The deletion can be transmitted as an autosomal dominant trait.
   c. Familial deletions identified in 7% of probands
2. Cause: hemizygous deletion of 22q11.2
   a. Deletions inherited from an affected parent (<14%)
   b. Up to 89% of patients show a typical phenotype of DiGeorge syndrome.
   c. Occupy roughly 15% of the patients with congenital heart disease
   d. Microdeletions detected by fluorescence in situ hybridization (FISH) probes
3. Molecular/cytogenetic basis
   a. DiGeorge critical region (300–600 kbp containing approximately 25–30 candidate genes), mapped to 22q11.2
   b. Candidate genes (Yamagishi 2002)
      i. Ubiquitin-fusion-degradation-1-like (*UFD1L*) gene, located in the DiGeorge critical region, which is most consistently deleted in patients with DGS (88%) or VCFS (76%). A significant percentage of cardiac patients with conotruncal cardiac malformations have a 22q11.2 deletion.
      ii. Mutation in *TBX1* gene (belongs to the T-box family of transcription factors), located in 22q11.2 region has been suggested as a rare cause of the syndrome (Yagi et al. 2003). *TBX1* haploinsufficiency is likely the major determinant of aortic arch defects in patients with 22q11.2 deletion syndrome.
4. Cardiac embryogenesis and branchial arch abnormalities
   a. Cardiac structures (derived from the cardiogenic cord in the embryonic mesoderm during very early embryogenesis)
   b. Conotruncus (outflow structures of the heart, derived from branchial arches IV and VI, which differentiate into aorta and pulmonary artery respectively). Malalignment of these structures and incomplete septation give rise to the following diverse congenital heart disease associated with DiGeorge syndrome:
      i. Arch abnormalities (interrupted aortic arch, aortic coarctation)
      ii. Conotruncal abnormalities (truncus arteriosus, pulmonary artery atresia)
      iii. Malalignment of the interventricular septum with the conotruncus (VSD, ASD, Tetralogy of Fallot, DORV)
      iv. Valvular or myocardium abnormalities (unusual)
   c. Branchial arches are also the embryological origin of the anterior facial structures, thyroid, thymus, and parathyroids. Their abnormalities are the phenotypic hallmark of the DiGeorge syndrome groups.
5. Heterogeneous etiology of congenital heart defects
   a. Deletion 22q11.2 (the second most common chromosomal cause of significant congenital heart disease)
   b. Aneuploidy (trisomy 21 remains the most common chromosomal cause of significant congenital heart disease)
   c. Single gene disorder
   d. Multifactorial trait
   e. Maternal disease such as diabetes mellitus
   f. Teratogen exposure

Clinical Features

1. Marked variability of phenotype
2. Endocrine abnormalities: common in patients with a 22q11.2 deletion (Weinzimer 2001)
   a. Hypocalcemia (30%)
      i. Invariably due to hypoparathyroidism, documented by aplasia or hypoplasia of the parathyroid glands at surgery or autopsy
      ii. Symptoms of hypocalcemia most likely manifest in the neonatal period, because maternal calcium supply by fetal circulation is abruptly interrupted at birth and the calcium intake within the first few days of life is usually insufficient.
         a) Seizures
         b) Tremors
         c) Tetany

iii. Other signs of hypocalcemia
a) Paresthesias
b) Muscle cramps
c) Rigidity
iv. Prevalence of hypocalcemia by phenotypic characteristics
a) DiGeorge syndrome (69–72%)
b) Velocardiofacial syndrome (13–22%)
c) Conotruncal anomaly face syndrome (10%)
d) 22q11.2 deletion (49–60%)
v. Autoimmune enteropathies
b. Growth disorders
i. Growth hormone deficiency
ii. Short stature
c. Thyroid disorders
i. Congenital hypothyroidism
a) Noted in 7% of patients with VCFS
b) Noted in 5% of patients with DGS
ii. Hyperthyroidism due to Graves disease
3. Immunodeficiency (highly variable) (77%)
a. Primary T-cell dysfunction (decreased production of T cells caused by impaired formation of thymic tissue) (67%)
b. Secondary T-cell functional defects (19%)
c. Humoral immune deficits (23%)
d. IgA deficiency (13%)
e. Associated autoimmune disease
i. Polyarticular juvenile rheumatoid arthritis, a frequency 150 times that of the general population rate
ii. Autoimmune hemolytic anemia
iii. Idiopathic thrombocytopenic purpura
iv. Autoimmune enteropathies (celiac disease)
v. Vitiligo
4. Cardiovascular malformations (75%, the most common structural anomaly)
a. Conotruncal heart defects
i. Tetralogy of Fallot (the most common heart anomaly)
ii. Pulmonary atresia with ventricular septal defect
iii. Truncus arteriosus (25%)
iv. Interrupted aortic arch type B (30%)
v. Atrial septal defect
b. Right-sided, cervical, or double aortic arch/aberrant subclavian artery
c. Pulmonary artery abnormalities
i. Discontinuity of the pulmonary arteries
ii. Diffuse hypoplasia
iii. Discrete stenosis
iv. Defect of arborization
v. Major aortopulmonary collateral arteries
d. Infundibulum abnormalities
i. Malaligned
ii. Hypoplastic
iii. Absent
e. Semilunar valve abnormalities
i. Bicuspid
ii. Severely dysplastic
iii. Insufficient
iv. Stenotic
5. Craniofacial features
a. Palate
i. Velopharyngeal incompetence (27%)
ii. Submucous cleft palate (16%)
iii. Overt cleft palate (11%)
iv. Bifid uvula (5%)
v. Cleft lip/palate (2%)
vi. Suspected velopharyngeal incompetence
vii. Normal
b. Ears
i. Low-set ears
ii. Over-folded helices
iii. Squared off helices
iv. Cupped, microtic, and protuberant ears
v. Preauricular pits/tags
vi. Narrow canals
vii. Chronic otitis media
viii. Conductive hearing loss
c. Nose
i. Prominent nasal root
ii. Bulbous nasal tip
iii. Hypoplastic alae nasae
iv. Nasal dimple/bifid nasal tip
v. Chronic sinusitis
d. Throat
i. Stridor caused by a vascular ring
ii. Laryngomalacia
iii. Laryngeal webs
e. Eyes
i. Tortuous retinal vessels (58%)
ii. Posterior embryotoxon (69%)
iii. Hooding of the upper and/or lower lid (47%)

iv. Ptosis (9%)
v. Epicanthal folds (3%)
vi. Distichiasis (3%)

6. Skeletal abnormalities
   a. Vertebral anomalies (19%)
      i. Coronal clefts
      ii. Hemivertebrae
      iii. Butterfly vertebrae
      iv. Scoliosis
   b. Rib anomalies including supernumerary ribs (19%)
   c. Hypoplastic scapulae
   d. Upper limb anomalies including pre/postaxial polydactyly (6%)
   e. Lower limb anomalies (15%)
      i. Postaxial polydactyly
      ii. Club foot
      iii. Over-folded toes
      iv. 2, 3 syndactyly
   f. Craniosynostosis
7. Renal abnormalities (37%)
   a. Calculi
   b. Single kidney
   c. Small kidneys
   d. Echogenic kidney
   e. Horseshoe kidney
   f. Bladder wall thickening
   g. Multicystic dysplastic kidney
   h. Duplicated collecting system
   i. Renal tubular acidosis
8. Neuromuscular development
   a. Developmental delays
   b. Hypotonia
   c. Feeding disorders
9. CNS manifestations
   a. Mental retardation
   b. Seizures (with or without hypocalcemia)
   c. Asymmetric crying facies
   d. Ataxia
   e. Cerebellar hypoplasia
   f. Enlarged Sylvian fissures
   g. Pituitary abnormalities
   h. Polymicrogyria
   i. Mega cisterna magna
   j. Neural tube defects
10. Behavior phenotype
    a. Attention deficit/hyperactivity disorder
    b. Autism spectrum disorder
    c. Nonverbal learning disability
    d. Language deficits
    e. Social/emotional concern
    f. Schizophrenia
11. Adult phenotype
    a. Lower rates of congenital heart defects
    b. Higher rates of palate anomalies, learning disabilities/mental retardation, and psychiatric disorders

Diagnostic Investigations

1. Cytogenetic studies
   a. High-resolution chromosome analysis to detect del(22q11.2)
   b. Fluorescence in situ hybridization (FISH) for the chromosome region 22q11 to detect submicroscopic deletion
2. Parental cytogenetic studies are warranted in all families with an affected child in order to identify mildly affected parents, as well as, to rule out low level mosaicism (McDonald-McGinn and Zackai 2008).
3. Molecular analysis: polymerase chain reaction (PCR)–based assays for detection of deletions of 22q11.2
4. Echocardiography for cardiovascular anomalies
5. Chest X-ray
   a. Presence of a heart defect
   b. Absence of thymus shadow
6. Renal ultrasound examination at irregular intervals for the development of renal stones
7. MRI of the brain: detects high prevalence of brain abnormalities that are most likely neurodevelopmental and may partially explain the high prevalence of learning disability and psychiatric disorder
   a. Cerebellar atrophy
   b. Agenesis of the corpus callosum
   c. White matter hyperintensities
   d. Cavum septum pellucidum
   e. Cerebral atrophy
   f. Widespread differences in white matter bilaterally
   g. Regional-specific differences in gray matter in the left cerebellum, insula, and frontal and right temporal lobes
8. Blood calcium levels
9. Immunological studies
   a. Impaired formation of thymic tissue
   b. Decreased production of T cells
   c. Secondary T-cell functional defects, humoral deficits, or both

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Low recurrence risk, provided parents are phenotypically normal and neither one is a carrier of del(22q11.2)
      ii. A higher recurrence risk in case of a parent with germline mosaicism for a microdeletion syndrome
      iii. A 50% recurrence risk if a parent is also found to have the 22q11.2 deletion syndrome
   b. Patient's offspring: 50% affected
2. Prenatal diagnosis
   a. Indications for prenatal testing for the 22q11.2 deletion
      i. A previous child with a 22q11.2 deletion or DiGeorge/velocardiofacial syndrome
      ii. An affected parent with a 22q11.2 deletion
      iii. In utero detection of a fetus with a conotruncal cardiac defect
   b. Prenatal ultrasonography and fetal echocardiography for a fetus at risk for the 22q11.2 deletion
      i. Conotruncal cardiac defect with associated anomalies
      ii. Conotruncal cardiac defect without associated anomalies
      iii. Aplasia or hypoplasia of the fetal thymus in the presence of conotruncal cardiac anomalies: very specific for deletion 22q11.2
      iv. Cardiac lesions with the deletion
         a) Interrupted aortic arch (50–80%)
         b) Truncus arteriosus (35%)
         c) Tetralogy of Fallot (15%)
         d) Rare in double outlet right ventricle and transposition of the great vessels
      v. Sensitivity of different sonographic features allowing discrimination of a subgroup likely to be associated with microdeletion 22q11.2
         a) Nuchal translucency (12%)
         b) Polyhydramnios (20%)
         c) IUGR (8%)
         d) Extracardiac anomalies (36%)
   c. Prenatal diagnosis of 21q11.2 deletion by amniocentesis or CVS
      i. Fluorescence in situ hybridization (FISH) analysis with probes from the DiGeorge chromosomal region (DGCR)
      ii. Preimplantation genetic diagnosis by FISH reported in an at-risk mother with a 22q11.2 deletion
      iii. Occasional detection of an unbalanced translocation or an interstitial deletion of 22q11.2 by cytogenetic analysis
      iv. Molecular genetic analysis
         a) Demonstrate failure to inherit a parental allele or hemizygosity in the deleted region
         b) Restriction fragment length polymorphism (RFLP) analysis and quantitative hybridization
         c) PCR assays using short tandem repeat polymorphisms (STRs) within the DGCR
      v. Limitations of prenatal testing for the 22q11.2 deletion
         a) DGS/VCFS, a heterogeneous disorder in which 10–15% of patients do not have the deletion. Therefore, FISH analysis is of limited value in couples who have had a previously affected child without a deletion.
         b) Atypical deletions of 22q11.2, unbalanced chromosomal translocations, deletions involving other chromosomes have not been detected by FISH using commercially available probes.
         c) Consider other causes of congenital heart defects such as aneuploidy, single gene defects, maternal diseases such as diabetes, and exposure to teratogens.
         d) Inability to predict accurately the phenotype prenatally
   d. Preimplantation genetic diagnosis: available for families in which the diagnosis of the 22q11.2 deletion syndrome has been established in an affected family member
3. Management (Sullivan 2008)
   a. Medical care
      i. Manage the feeding problems
         a) Modification of spoon placement when eating
         b) Treat gastroesophageal reflux with acid blockade, prokinetic agents, postural

therapy, and medication to treat gastrointestinal dysmotility and to facilitate bowel evacuation

ii. Early intervention programs including speech therapy for developmental delay

iii. Management of psychiatric disorder

iv. Hypocalcemia
   a) Asymptomatic hypocalcemia: treat with oral calcium supplements
   b) Severe symptomatic hypocalcemia: treat with prompt administration of parenteral calcium
   c) Goal of treatment: maintain calcium in the low-normal range (8–9 mg/dL) to minimize hypercalcinuria
   d) Over supplementation of calcium leads to nephrocalcinosis

v. Management of immunodeficiency
   a) Most patients have diminished T-cell numbers as a consequence of thymic hypoplasia.
   b) Most patients do not demonstrate a susceptibility to opportunistic infections.
   c) Risk of using live viral vaccines in infants seems to be low except for patients who have thymic aplasia and/or very low T-cell counts (McDonald-McGinn et al. 1999).
   d) Both the measles, mumps, rubella and the varicella vaccine are found to be safe and efficacious in children who had the deletion and who had mild to moderate T-cell compromise (Junker and Driscoll 1995; Pierdominici et al. 2003).
   e) Management of thymic aplasia: A thymus transplant, fully matched peripheral blood transplant, or donor lymphocyte infusions are required.

vi. Thyroid hormone for hypothyroidism

vii. Growth hormone therapy in growth hormone–deficient children with a 22q11.2: associated with sustained improvements in height and growth velocity

b. Surgical care

i. Congenital heart diseases
   a) Palliative operation
   b) Corrective operation

ii. Velopharyngeal dysfunction
   a) Pharyngoplasty
   b) Plastic surgery of cleft lip/palate

iii. Surgery
   a) Gastrointestinal anomalies
   b) Renal anomalies
   c) Musculoskeletal anomalies

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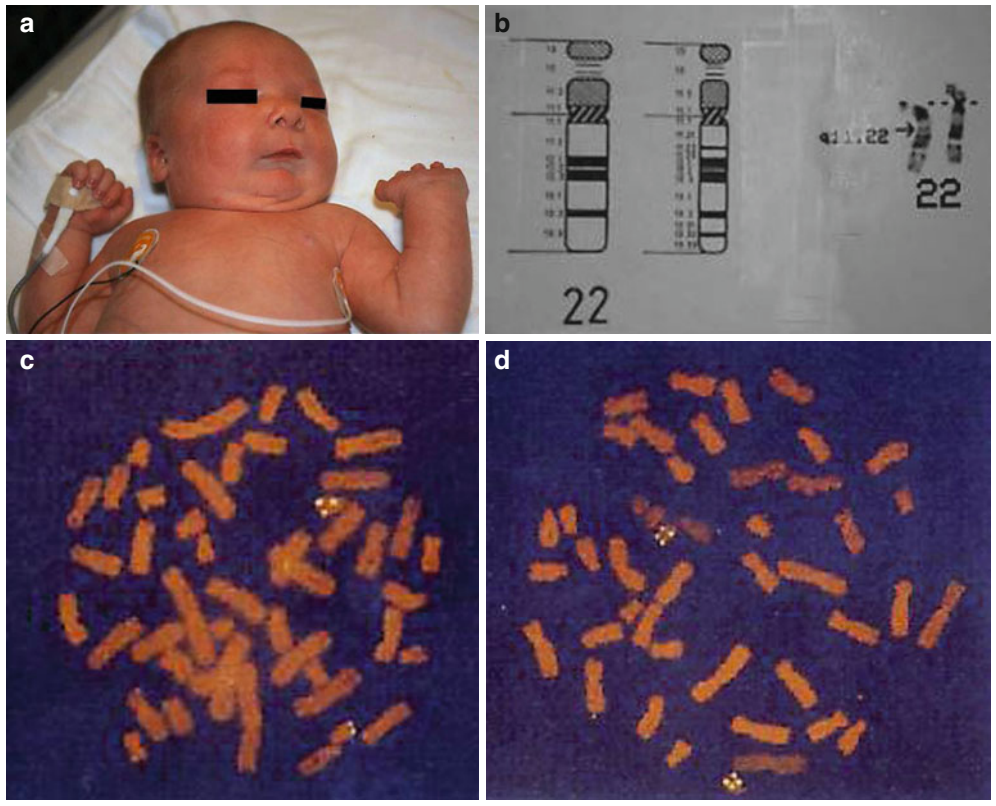

Fig. 1 An infant (**a**) with DiGeorge syndrome. The deletion of 22q11.2 was shown by partial karyotype with ideogram (**b**) and FISH with DiGeorge cosmid probe (**c**). The FISH in (**d**) is a control

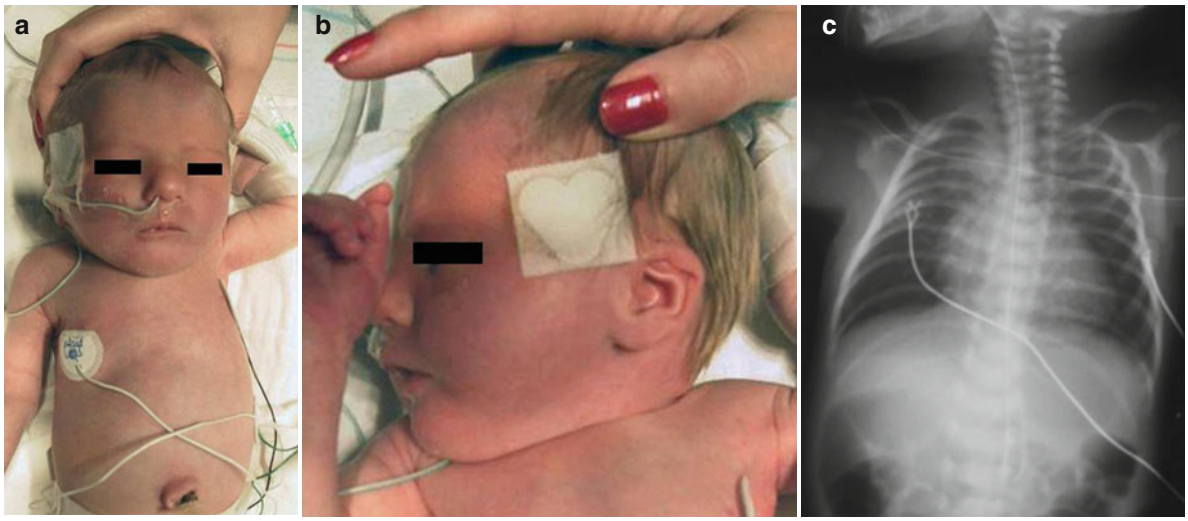

Fig. 2 (**a**–**c**) A newborn infant with conotruncal anomaly facies syndrome. The radiograph shows a conotruncal heart anomaly and absent thymus

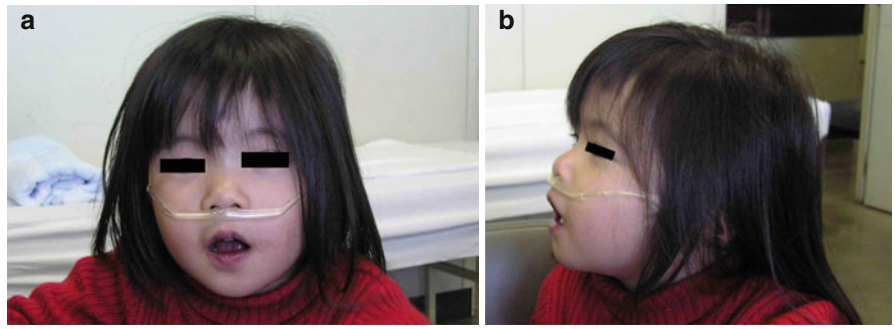

Fig. 3 (**a**, **b**) A 4 years and 6 months old girl with tetralogy of Fallot, growth retardation, developmental delay, and del(22q11.2)

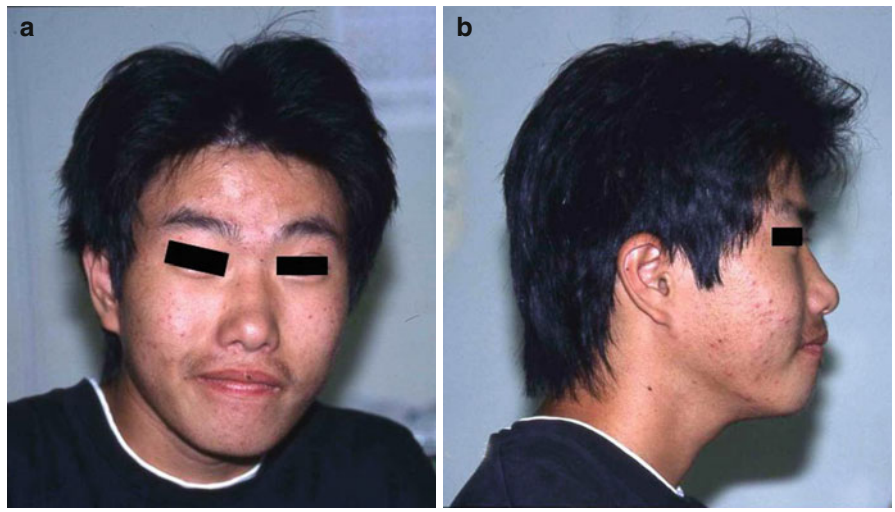

Fig. 4 (**a**, **b**) A 16-year-old boy with tetralogy of Fallot, inguinal hernia, developmental delay, bilateral conductive hearing loss (late onset at 15 years of age), and del(22q11.2) shown in the next figure

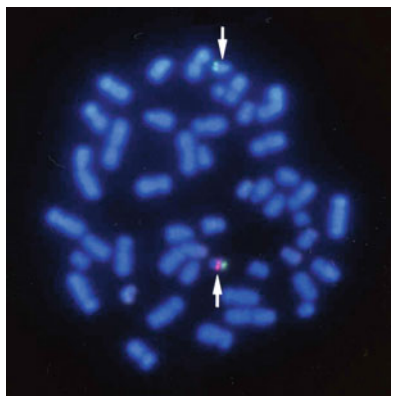

Fig. 5 FISH of the patient in the Fig. 1d. showing two green signals (a probe for 22q13 ARSA) and only one red signal (a probe for 22q11.2; TUPLE1) demonstrating del(22q11.2)

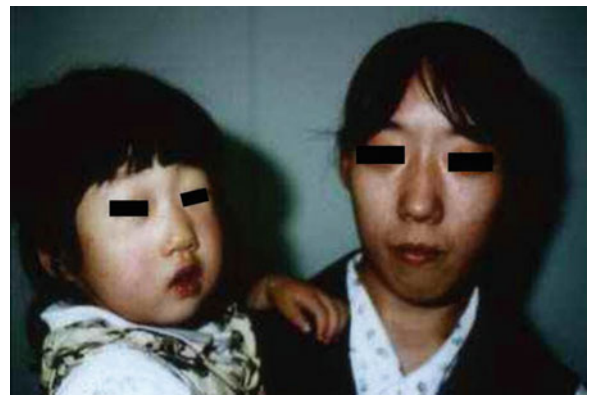

Fig. 6 A mother and daughter both have deletion 22q11.2

Del(Yq) Syndrome

In 1976, Tiepolo and Zuffardi first recognized the deletions of the long arm of the Y chromosome, large enough to be recognized by light microscopy, in six azoospermic men. Large structural rearrangements of the Y chromosome are known to be commonly associated with a 45,X/46,XY chromosomal mosaicism (Siffroi et al. 2000). Majority of Yq deletions are microdeletions and, therefore, require analysis by molecular means (Martin 2008).

Synonyms and Related Disorders

Chromosome Yq deletion syndrome

Genetics/Basic Defects

1. Role of Yq deletions in male infertility (Ma et al. 2000)
   a. Factors controlling human spermatogenesis: postulated to be located on the distal portion of the euchromatin segment of the long arm of the Y chromosome, Yq11 (Tiepolo and Zuffardi 1976)
   b. This spermatogenesis locus at Yq11.23, as demonstrated with high-resolution banding techniques, has since come to be known as the "azoospermia factor" or "AZF" (Bühler 1985).
   c. Further molecular investigations into genotype–phenotype correlation in azoospermic men led to the localization of the *AZF* locus to interval 6 of the Y chromosome (Vergnaud et al. 1986; Affara et al. 1986; Andersson et al. 1988).
   d. Microdeletions of the long arm of the Y chromosome
      i. Represents the most frequent molecular genetic cause of severe male infertility (Ferlin et al. 2006; Krausz and Degl'Innocenti 2006)
      ii. The first solid molecular evidence that failure of spermatogenesis may be caused by cytologically undetectable deletions on the Y chromosome: identification of two nonoverlapping microdeletions mapped to the distal region of intervals 5 and 6, carried by two azoospermic otherwise normal men (Ma et al. 1992)
      iii. Further studies led to the proposal of the existence of three *AZF* subregions termed *AZFa* (formerly JOLAR region), *AZFb*, and *AZFc* (formerly KLARD region) respectively (Vogt et al. 1996).
         a) Deletion of AZFa: associated with lack of germ cells or Sertoli cell-only syndrome.
         b) Deletion of *AZFb*: associated with spermatogenesis arrest.
         c) *AZFc* gene products: involved in the maturation process of postmeiotic germ cells (Vogt et al. 1996).
         d) The above hypothesis remains controversial and it is generally accepted that the completion of spermatogenesis requires multiple genes not only on the Y chromosome but elsewhere as well.
      iv. Recent description of another *AZF* subregion further complicated the issue: *AZFd*: localized between *AZFb* and *AZFc* (Kent-First et al. 1999).

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v. The discovery of the two separate microdeletions on the Yq in infertile men subsequently led to the identification of four candidate gene families for *AZF*:
a) RNA-binding motif (*RBM*), previously named Y-linked RNA recognition motif (*YRRM*) (Ma et al. 1993)
b) Deleted in azoospermia (*DAZ*) (Reijo et al. 1995)
c) *Drosophila* fat facets related Y (*DFFRY*) (Brown et al. 1998)
d) *C*hromodomain Y (*CDY*) (Lahn and Page 1999)

e. Male infertility: most likely result from deletions and/or mutations of one or more of the myriad of genes necessary for spermatogenesis

2. 45,X cell line associated with large cytogenetically visible Yq deletions (Hwa et al. 2004; Cui et al. 2007)
a. Structural aberrations of the Y chromosome, such as large cytogenetically visible deletions of the long arm, ring Y, *iso*- or isodicentric short arm, are unstable and usually lost during mitosis, leading to mosaic 45,X (Hsu 1994; Kirsch et al. 2000; Siffroi et al. 2000; Bertini et al. 2005).
b. In the presence of a 45,X cell line, a fetus has a risk of being a phenotypic female with Turner syndrome manifestations or to have ambiguous external genitalia, whether the other cell line is Yp, Yq, Yp plus Yq, or even a free Y chromosome (Hsu 1994).
c. Patients with Turner syndrome with a Y-derived marker have milder phenotypic abnormalities than those with an X-derived marker. In general, patients with a Y-derived marker are not as short as, and have fewer somatic abnormalities than, patients with an X-derived marker chromosome (Schwartz et al. 1997).

Clinical Features

1. Deletion/microdeletion of the long arm of the Y chromosome
a. Men with deletions, in general, are infertile and therefore deletions are not transmitted to sons unless in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are performed.
b. Associated with severe oligozoospermia

2. Phenotype–genotype correlative analyses (Cram et al. 2000)
a. Identified four subregions within AZF, called AZFa, -b, -d, and -c
b. Most deletions observed in infertile men occur in the AZFc region: associated with severe oligospermia or azoospermia and occasionally oligozoospermia
c. Men with more extensive deletions in the AZFb region that extend into the AZFa region: commonly exhibit histologic phenotypes such as germ cell arrest or Sertoli cell-only syndrome and as a result are usually azoospermic
d. Men with deletions localized exclusively to AZFd: present with mild oligozoospermia or even normal sperm counts associated with abnormal sperm morphology (Kent-First et al. 1999)

3. Phenotypes of 45,X/46,X,del(Y)(q11) (Hwa et al. 2004)
a. Phenotypic males (34.2%): Small testes, short stature, small penis, hypospadias, azoospermia, Turner syndrome, and gonadoblastoma (Hsu 1994).
b. Intersex (47.4%).
c. Phenotypic females (18.4%).
d. Only a few cases of mos45,X/46,X,del(Y) reported with normal male external genitalia (Bühler 1980; Hoshi et al. 1998).
e. The deletions of Y chromosomes are associated with abnormalities of the external genitalia, secondary sexual characteristics, and/or gonadal function.
f. These phenotypic differences are related not only to the presence or absence of the *SRY* gene on Yp, but also to the proportion of 45,X line in gonadal tissue.
i. A sufficient SRY transcript level is necessary to trigger testes formation: Once testes differentiate, male endocrine function is responsible for the rest of the events involving male phenotypic sexual differentiation.
ii. When the 45,X line is predominant in gonadal tissue, the phenotype of Turner syndrome would appear.

4. A case of Y chromosome with terminal deletion associated with nondisjunction, leading to mosaicism of three cell lines, has been reported (Cui et al. 2007): an azoospermic male with complete masculinization associated with karyotype 45,X/46,X,del(Y)/47,X,del(Y),del(Y)

Diagnostic Investigations

1. Diagnostic investigations of all infertile men (Bhasin 2007)
   a. Several semen analyses
      i. Sperm count
      ii. Sperm motility
      iii. Sperm morphology
   b. Hormone measurements (testosterone, LH, and FSH levels) to help determine:
      i. Low testosterone and low or inappropriately normal LH and FSH: gonadotropin deficiency: hypogonadotropic hypogonadism (Gnoth et al. 2005)
      ii. Low testosterone, elevated LH and FSH: obtain karyotype: primary testicular failure
      iii. Normal testosterone and LH, elevated FSH: spermatogenic failure, test for Yq microdeletion
      iv. High testosterone, elevated LH: androgen resistance
      v. Normal testosterone, normal LH, and FSH (Templeton 2000)
         a) Majority of infertile men: have normal testosterone, LH, and FSH levels
         b) Azoospermia: rule out obstruction by post-ejaculatory urine and seminal fructose and screen for Yq microdeletions
         c) Oligo/asthenozoospermia: exclude antisperm antibodies
2. Genetic testing of infertile couples and the offspring: important, especially in couples who are being considered for ICSI
   a. All infertile men with nonobstructive azoospermia, severe oligozoospermia, or very small testes should be offered a karyotype (Simpson and Lamb 2001; Allen et al. 2006).
   b. Screen infertile men with azoospermia or severe oligozoospermia for Yq microdeletions (Cram et al. 2006; Ferlin et al. 2007).
   c. Azoospermic men with at least one absent vas deferens or with evidence of normal spermatogenesis should be tested for CFTR mutations (Anguiano et al. 1992).
   d. Consider CREM mutations in men with postmeiotic maturation arrest (Blendy et al. 1996; Peri et al. 1998; Weinbauer et al. 1998).
   e. Genetic testing is indicated in men in whom personal or family history suggests disorders that have a genetic basis such as hemoglobinopathies and myotonic dystrophy (Takeda and Ueda 1977; Kletzky et al. 1979; Marchini et al. 2000); these patients also need genetic counseling.
3. Yq microdeletions are detected by PCR-based mapping of several conserved molecular markers or genes located within and outside the AZF region; these tests are available from commercial laboratories. With the availability of precise Y chromosome maps, more specific molecular markers have been developed, and guidelines for standardized testing of Yq microdeletions have been published by the European Molecular Genetics Network (Simoni et al. 2004). Array-comparative genomic hybridization (CGH) has emerged as a powerful new molecular tool for the high resolution for the detection of Yq deletions (Osborne 2007).

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Father without Yq deletion: Since most Yq microdeletions occur de novo, the recurrence risk to the male sibling is not significantly increased.
      ii. Father with Yq deletion: Father's Yq deletion will be transmitted to the male sibling.
   b. Patient's offspring
      i. The genetic defects responsible for infertility in the parent may be transmitted to the offspring through ICSI: Yq deletions will be transmitted to male offspring (Page et al. 1999; Cram et al. 2000; Simpson and lamb 2001; Ferlin et al. 2007).
      ii. Children born through ICSI have increased risk of sex chromosome aneuploidy (45,X and 47,XXY embryos) (Palermo et al. 1999; Ferlin et al. 2007).
      iii. Children born through ICSI to infertile couples may have a higher risk of being infertile or subfertile (Cram et al. 2006): may need counseling upon reaching adulthood and surveillance of their reproductive function.

2. Prenatal diagnosis
   a. Prenatal testing, including chorionic villous sampling, may be appropriate in some couples undergoing ICSI.
   b. A fetus with a prenatally diagnosed mosaic 45,X/46,X,del (Y)(q11.2) karyotype from amniotic fluid, in which the deletion was defined by polymorphic microsatellite markers analysis and multiplex STS-PCR.
3. Management (Krausz and Degl'Innocenti 2006; Bhasin 2007)
   a. Gonadotropin therapy: highly effective in gonadotropin-deficient men
   b. Intracytoplasmic sperm injection (ICSI): emerges as the treatment of choice for idiopathic male factor infertility
      i. Expensive
      ii. Associated with the following higher risks compared to naturally conceived pregnancies:
         a) Multiple gestation
         b) Low birth weight
         c) Preterm delivery
         d) Perinatal complications
         e) Chromosome aneuploidy
   c. Men with Yq microdeletions considering ICSI should be offered:
      i. Karyotyping
      ii. Yq microdeletion testing
      iii. Genetic counseling
         a) Obligatory transmission of Yq deletion to male offspring
         b) The phenotype of son: varies substantially and the extent of spermatogenic failure cannot be predicted entirely due to different genetic background and the presence or absence of environmental factors with potential toxicity to reproductive function
         c) A significant proportion of spermatozoa from men with Y microdeletion are nullisomic for sex chromosomes (Siffroi et al. 2000; Jaruzelska et al. 2001), indicating a potential risk for the offspring to develop 45,X Turner syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia.
         d) Screening for Y chromosome microdeletions in patients bearing a mosaic 45,X/46,XY karyotype with sexual ambiguity and/or Turner stigmata has shown a relatively high incidence of AZFc deletions (33%) (Patsalis et al. 2002).
         e) Yq microdeletions could be associated with an overall Y chromosomal instability leading to the formation of 45,X cell lines (Le Bourhis et al. 2000; Jaruzelska et al. 2001; Patsalis et al. 2005).
         f) Despite this theoretical risk, the 36 babies (18 male and 18 female) born from fathers affected by Yq microdeletions are phenotypically normal (Krausz et al. 2003). This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortions of embryos bearing a 45,X karyotype.
         g) In order to avoid the transfer of embryos with sex chromosome mosaicism, preimplantation diagnosis could be offered to the couple. This analysis, together with the abortion rate would provide a more realistic estimation about the real risks of 45,X/46,XY mosaicism and Turner syndrome.
   d. The screening for Yq deletions: of additional clinical utility in azoospermic men in which the type of deletion may have prognostic value for testicular sperm retrieval
   e. Testicular sperm extraction (TESE): not recommended for complete AZFa or AZFb deletions since the probability of the presence of mature sperm is virtually zero
   f. Advise cryoconservation of sperm as a preventive therapy since it is a noninvasive procedure.

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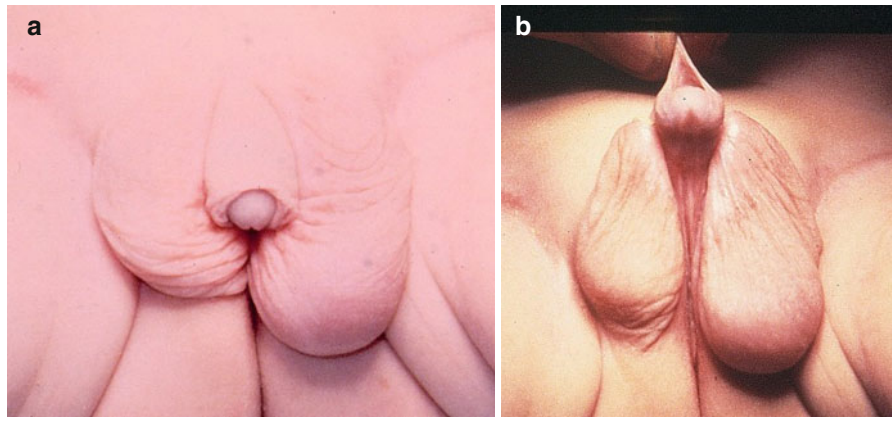

Fig. 1 (**a**, **b**) An infant with del(Yq) showing ambiguous genitalia with a palpable gonad in the left scrotal sac

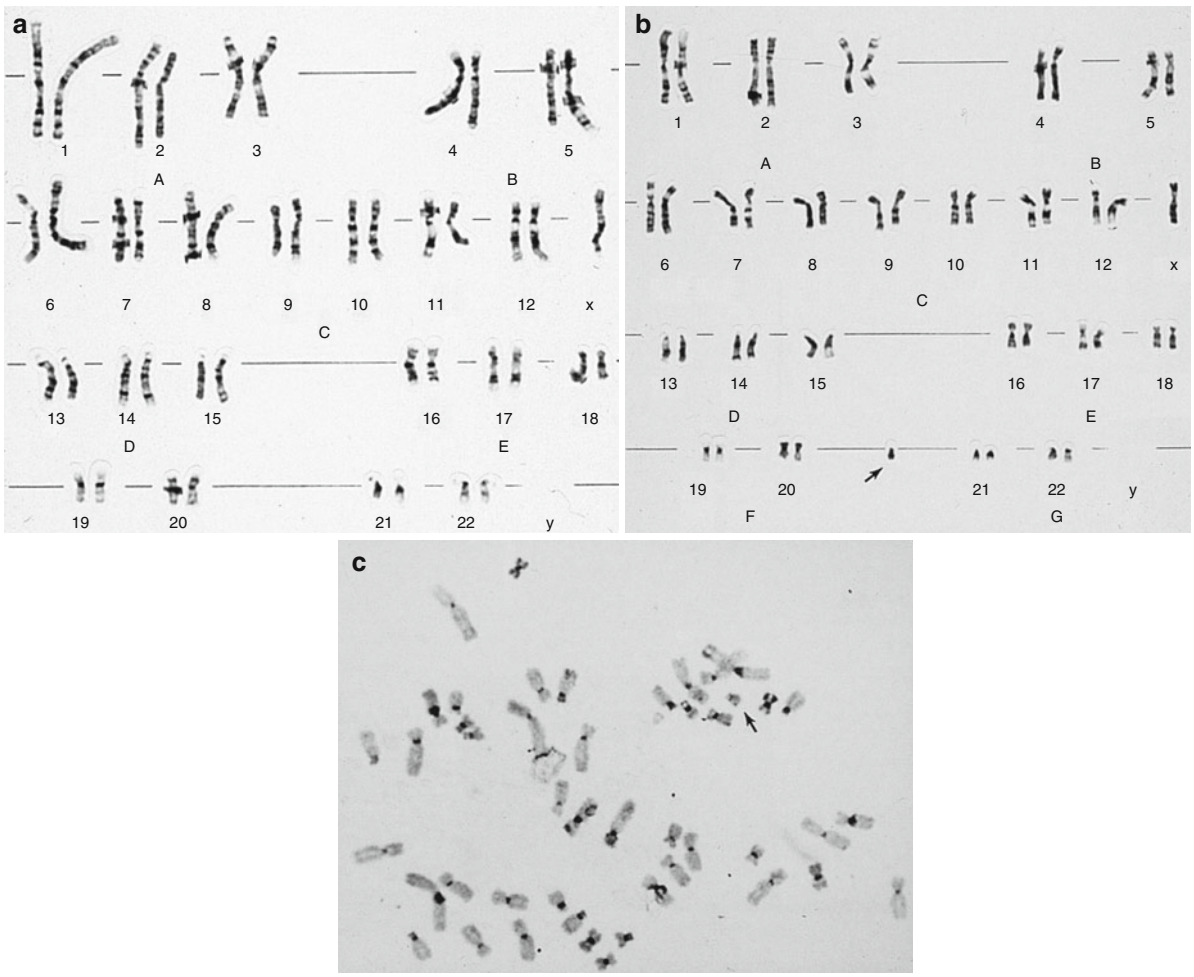

Fig. 2 (**a**–**c**) G-banding karyotypes showed mosaic 45,X/46,X,del(Yq). The del(Yq) (*arrow*) is shown in a C-banded metaphase

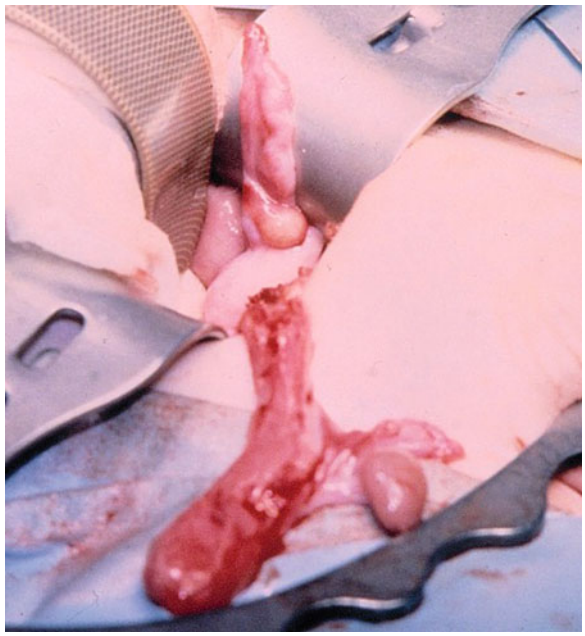

Fig. 3 A gonad is noted at the surgery

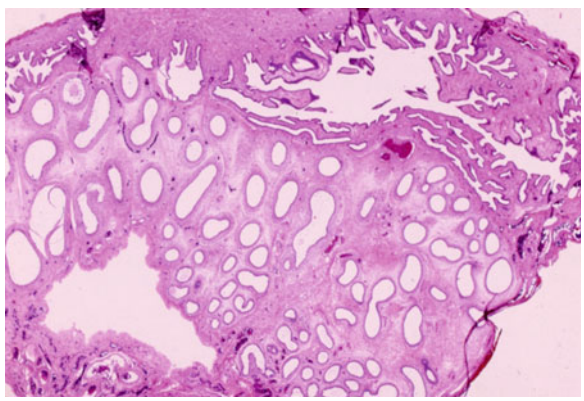

Fig. 4 Fallopian tube-epididymus is shown here on the histologic examination of the specimen

Fig. 5 (**a**, **b**) Successful vaginal reconstruction surgery

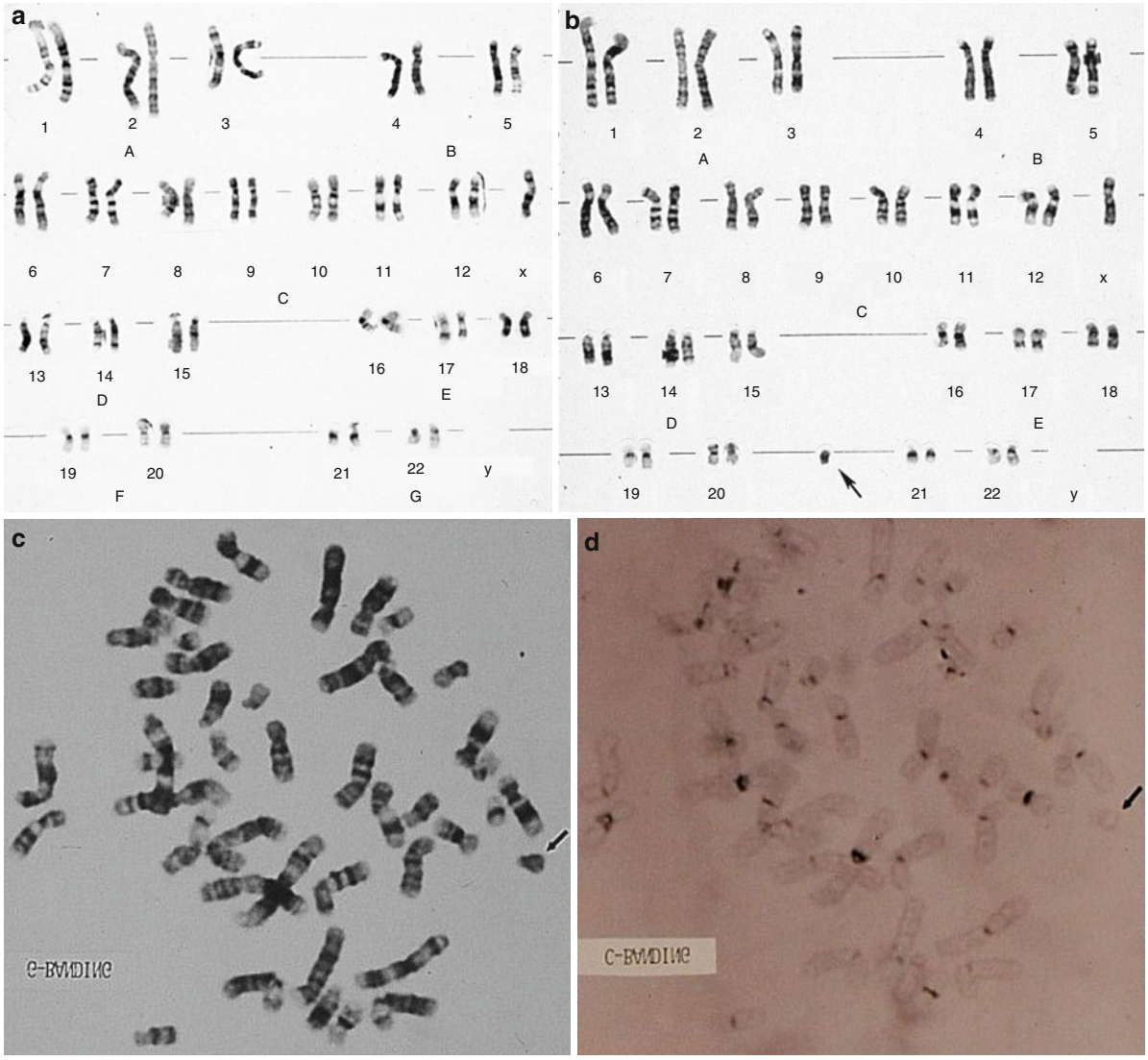

Fig. 6 (**a**–**d**) Another patient with del(Yq) with G- and C-bands showing 45,X/46,X,del(Yq)

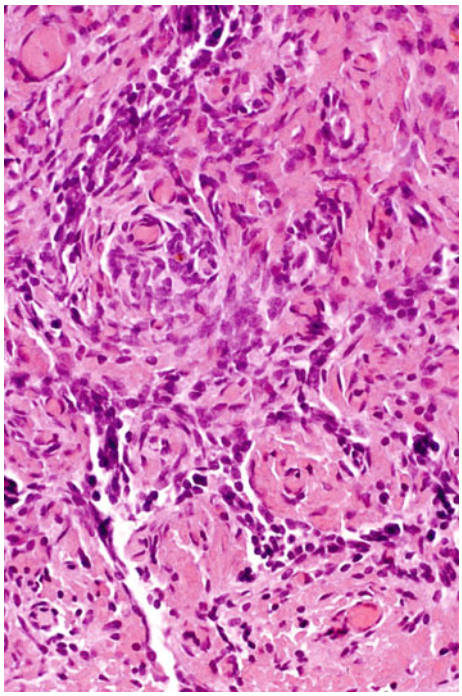

Fig. 7 Dysplastic ovary is shown here

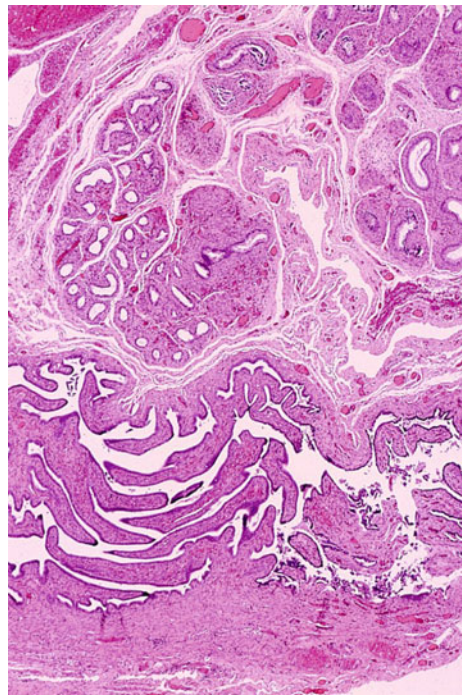

Fig. 8 Epididymus-fallopian tube is shown here

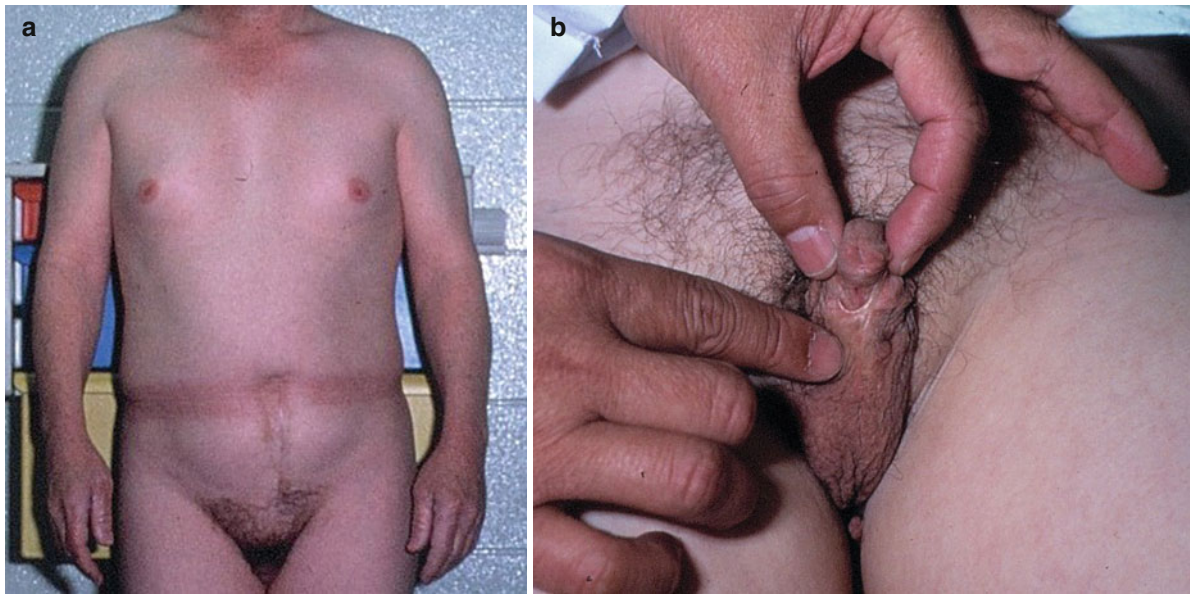

Fig. 9 (**a**, **b**) Another adult male patient with del(Yq) showing short stature, female distribution of the pubic hair, and ambiguous genitalia

Diabetic Embryopathy

Maternal diabetes adversely affects the fetus during pregnancy. The risk of developing congenital malformations has been well documented (Reece and Homko 2000; Correa et al. 2008). The frequency of congenital anomalies among insulin-dependent diabetic offspring is estimated at 3–6% of all infants at birth, representing a twofold to threefold increase, when compared with nondiabetics (Reece and Hobbins 1986).

Synonyms and Related Disorders

Infant of diabetic mother

Genetics/Basic Defects

1. Teratogenicity of maternal diabetes mellitus in human
   a. Occurring during embryogenesis at the end of blastogenesis and organogenesis between third and seventh weeks of gestation
   b. Leading to a spectrum of malformations known as diabetic embryopathy
2. Diabetic fetopathy
   a. Occurs during fetal development (after the tenth week of gestation)
   b. Not associated with malformations
   c. Fetal hyperinsulinism: the cause of macrosomia and numerous other postnatal complications
3. Potential pathogenetic mechanisms of diabetic embryopathy: most likely multifactorial (Chugh et al. 2003)
   a. Oxidant stress
   b. Perturbed biosynthesis of prostaglandins and DNA
   c. Altered expression of some of the morphogenetic regulatory molecules
      i. Extracellular matrix (ECM) proteins
      ii. Transcription factors
      iii. Proto-oncogen

Clinical Features

1. General features of infants of diabetic mothers
   a. Higher rate of congenital malformations
   b. Signs of diabetic fetopathy (Kousseff 1999b)
      i. Macrosomia (increase in adipose tissue and organomegaly) (Tyrala 1996)
         a) Classic appearance: a large, ruddy, puffy, fat, and often limp infant, with legs held in a flexed and abducted position
         b) Presence of prominent fat pads over the upper back and around the lower jaw to produce the image of a round cherubic face.
         c) A predisposing factor for the occurrence of a variety of birth trauma–related injuries
      ii. Birth trauma–related injuries due to difficult vaginal delivery secondary to shoulder dystocia
         a) Cephalohematoma
         b) Subdural hemorrhage
         c) Clavicular fracture
         d) Cranial nerve palsies
         e) Brachial plexopathy (palsy)
      iii. Hypoglycemia (hyperinsulinemia)
      iv. Polycythemia
      v. Hypomagnesemia
      vi. Hyperbilirubinemias (jaundice)

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vii. Hypocalcemia
viii. Cardiomyopathy (thickened interventricular septum)
ix. Renal vein thrombosis

c. Other features
i. Large for gestational age
ii. Higher fetal death rate
iii. Fetal growth retardation in diabetic women with vasculopathy
iv. Higher risk of respiratory distress (hyaline membrane disease)
v. Asphyxia
vi. Acidosis
vii. Apneic spells
viii. Sepsis
ix. Intracranial bleeding
x. Neuromuscular excitability
xi. Single umbilical artery
xii. Small left colon syndrome
xiii. Transient hematuria
xiv. Abnormal vernix caseosa
xv. Hirsutism

2. Spectrum of diabetic embryopathy: Malformations vary in extent and severity.
a. CNS abnormalities (Reece and Hobbins 1986)
i. Neural tube defects: a higher incidence of 19.5 per 1,000 in the diabetic gestation, compared with 1–2 per 1,000 in the general population
ii. Anencephaly
a) The most common anomaly affecting the CNS.
b) An incidence of 0.57% in the diabetic pregnancy, representing a threefold increase over the general population.
iii. Holoprosencephaly
iv. Hydrocephalus
v. Absent corpus callosum
vi. Arnold-Chiari anomaly
vii. Schizencephaly
viii. Microcephaly
ix. Macrocephaly
x. Agenesis of olfactory tracts
xi. Intracranial lipoma
xii. Facial nerve palsy
xiii. Calcified falx cerebi
xiv. Bizarre undergrowth or overgrowth of the brain
xv. Postnatal developmental delay

b. Facial features (85%)
i. Hemifacial microsomia (oculoauriculovertebral anomalies)
ii. Macrostomia/lateral facial cleft
iii. Cleft lip/palate
iv. Micrognathia
v. Branchial cleft cyst
vi. Frontonasal dysplasia
vii. Choanal atresia
viii. Short nose
ix. Nasal milia
x. Fat pad across nose
xi. Facial skin tags

c. Eye anomalies (48%)
i. Lens opacity
ii. Cataracts
iii. Microophthalmia/optic nerve hypoplasia
iv. Colobomas of iris or chorioretina
v. Anterior chamber dysgenesis
vi. Epibulbar dermoid/oculolipoma
vii. Laterally displaced inner canthi
viii. Tear duct obstruction

d. Ear anomalies (95%)
i. Microtia
ii. Sensorineural/conductive hearing loss
iii. Preauricular tags
iv. Anotia
v. Atretic ear canal
vi. Additional ear malformations

e. Cardiovascular anomalies
i. Complex transposition of the great vessels
ii. Single ventricle
iii. Hypoplastic left heart
iv. Tricuspid atresia
v. Tetralogy of Fallot
vi. Ventricular septal defect
vii. Atrial septal defect
viii. Double outflow right ventricle
ix. Pulmonary atresia
x. Coarctation of the aorta
xi. Subaortic stenosis
xii. Right aortic arch
xiii. Tricuspid regurgitation
xiv. Cleft mitral valve
xv. Symmetric hypertrophy of interventricular septum
xvi. Hypertrophic cardiomyopathy

f. Gastrointestinal anomalies

i. Situs inversus
ii. Pyloric stenosis
iii. Duodenal atresia
iv. Small bowel atresias
v. Small left colon (microcolon) syndrome
vi. Rectal atresia
vii. Anal atresia (imperforate anus)
viii. Meckel diverticulum
ix. Diaphragmatic hernia
x. Omphalo-enteric cyst/fistula

g. Genitourinary anomalies (19%)
i. Renal agenesis
ii. Cystic kidneys
iii. Ectopic kidney
iv. Hydronephrosis
v. Ureteral duplication
vi. Ureterocele
vii. Ambiguous genitalia
viii. Hypospadias
ix. Micropenis
x. Cryptorchidism
xi. Uterine agenesis
xii. Hypoplastic vagina

h. Skeletal anomalies (52%)
i. Hand anomalies (limb reduction defects)
a) Radial clubbing
b) Bifid thumbs
c) Hypoplastic/absent thumb
d) Radial hypoplasia
ii. Polysyndactyly
iii. Contractures
iv. Costovertebral anomalies
a) Fused cervical vertebrae
b) Hemivertebrae
c) Torticolis
d) Bifid/fused ribs
v. Hip dislocation
vi. Femoral hypoplasia
vii. Caudal regression (sirenomelia): very rare but it is one of the most unique and commonly associated lesion with maternal diabetes (occurring in 0.2–0.5% of infants of diabetic pregnancies, a 200-fold increase over the general population) (Reece and Hobbins 1986)
a) Agenesis of sacrum and lumbar spine
b) Hypoplasia of the lower extremities
c) Phocomelia
viii. Craniosynostosis

i. Skin anomalies
i. Aplasia cutis
ii. Cutaneous vascular dysplasia

Diagnostic Investigations

1. Complete blood cell count to detect polycythemia
2. Serum or whole blood glucose concentration to detect neonatal hypoglycemia
3. Serum magnesium concentration (ionized or total levels) to detect hypomagnesemia
4. Serum calcium concentration to detect hypocalcemia
5. Serum bilirubin level (total and unconjugated) to detect hyperbilirubinemia
6. Arterial blood gas to assess oxygenation and ventilation with evidence of respiratory distress
7. Radiography for cardiopulmonary distress and skeletal and vertebral anomalies
8. Echocardiography for detecting cardiomyopathy and congenital heart defects
9. Renal ultrasonography for renal anomalies

Genetic Counseling

1. Risk of congenital malformation in infants of mothers with insulin-dependent diabetes (Hajianpour 1993)
a. Relative risk (per 100 live births)
i. Major malformations: 7.9
ii. Major CNS malformations: 15.5
iii. Cardiovascular malformations: 18.0
b. Absolute risks (per 100 live births)
i. Major malformations: 18.4
ii. Major CNS malformations: 5.3
iii. Major cardiovascular malformations: 8.5
2. Risk of congenital malformation in infants of mothers with gestational diabetes mellitus who required insulin during the third trimester of pregnancy (Hajianpour 1993)
a. Relative risk: 20.6 times more likely to have major cardiovascular system defects than infants of nondiabetic mothers
b. Absolute risk: 9.7%
3. Prenatal diagnosis
a. Determination of glycosylated hemoglobin (HbA_{1c}) of the diabetic mother during the first trimester. There is a significantly higher incidence

of major congenital anomalies in the offspring of diabetic women with elevated first trimester HbA_{1c} values (>8%) (Reece and Hobbins 1986).

b. Maternal serum alpha-fetoprotein determination for the presence of associated neural tube defect.
c. Prenatal ultrasonography (Diabetic forum).
   i. Estimation of gestational age
   ii. Evaluation of congenital malformations
      a) Cardiac anomalies
      b) Skeletal anomalies
      c) CNS anomalies
      d) Renal anomalies
      e) Other anomalies
   iii. Evaluation of fetal growth
      a) Macrosomia
      b) Intrauterine growth retardation
   iv. Assessment of fetal status
   v. Maternal hydramnios
d. Fetal echocardiography for congenital heart defects

4. Management
   a. To reduce the rate of congenital malformations in offspring of mothers with diabetes mellitus (Reece and Hobbins 1986)
      i. Preconceptional care and counseling
      ii. Prepregnant glycemic control to provide endocrine milieu necessary for normal embryogenesis
   b. Plan of delivery
      i. Deliver newborn infant of the diabetic mother between 35th and 37th weeks of gestation
      ii. Anticipate Cesarean section with identification of the macrosomic fetus
   c. Management of respiratory distress
   d. Management of hypoglycemia, hypocalcemia, and hypomagnesemia
   e. Management of cardiomyopathy and heart failure
   f. Management of congenital anomalies

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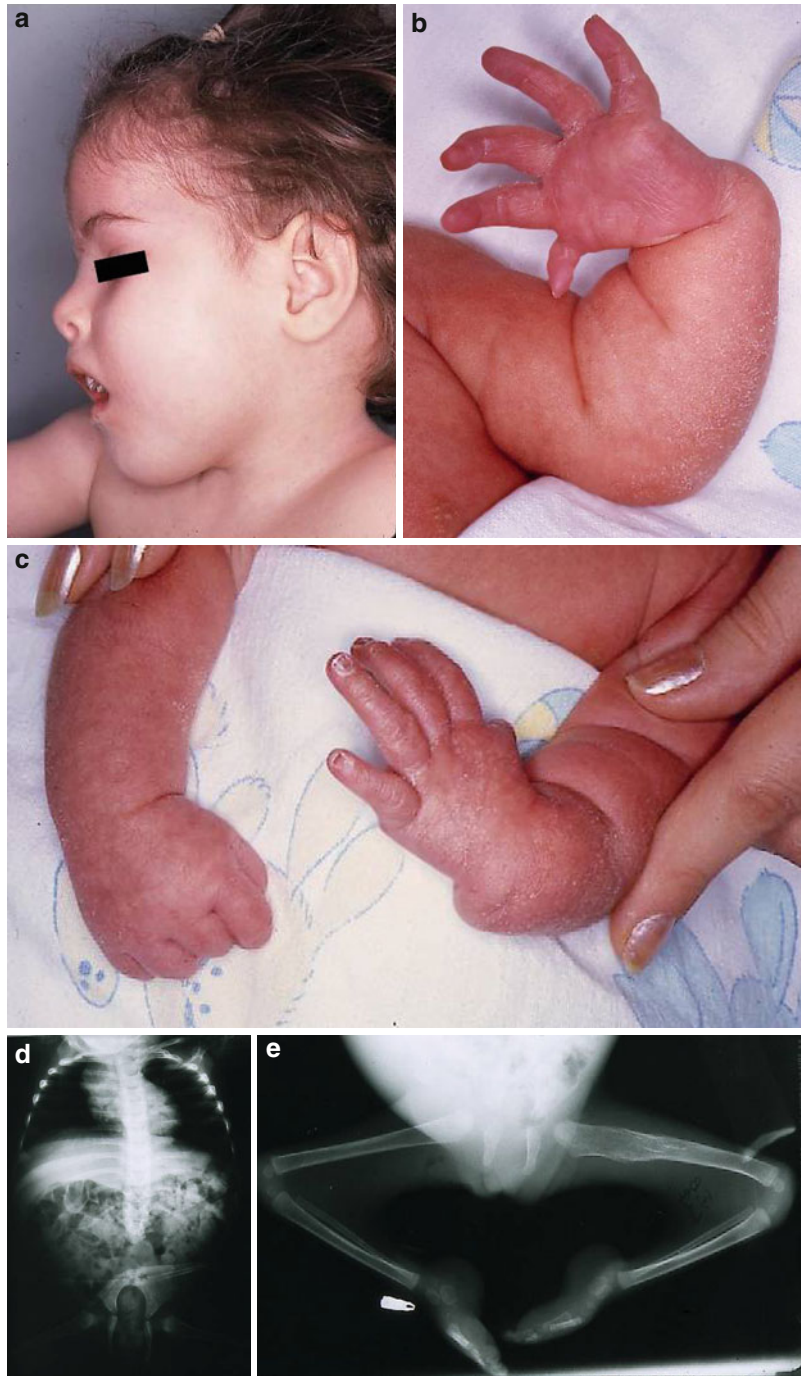

Fig. 1 (**a**–**e**) A 2 years and 9 months old girl with diabetic embryopathy showing left club hand with hypoplastic thumb and sacral agenesis with contractures of knees illustrated by radiographs

Fig. 2 (**a**–**d**) A newborn with diabetic embryopathy showing a large head due to hydrocephalus, depressed nasal bridge, short nose, micrognathia, microtia, right club hand, hemivertebrae, and caudal dysgenesis

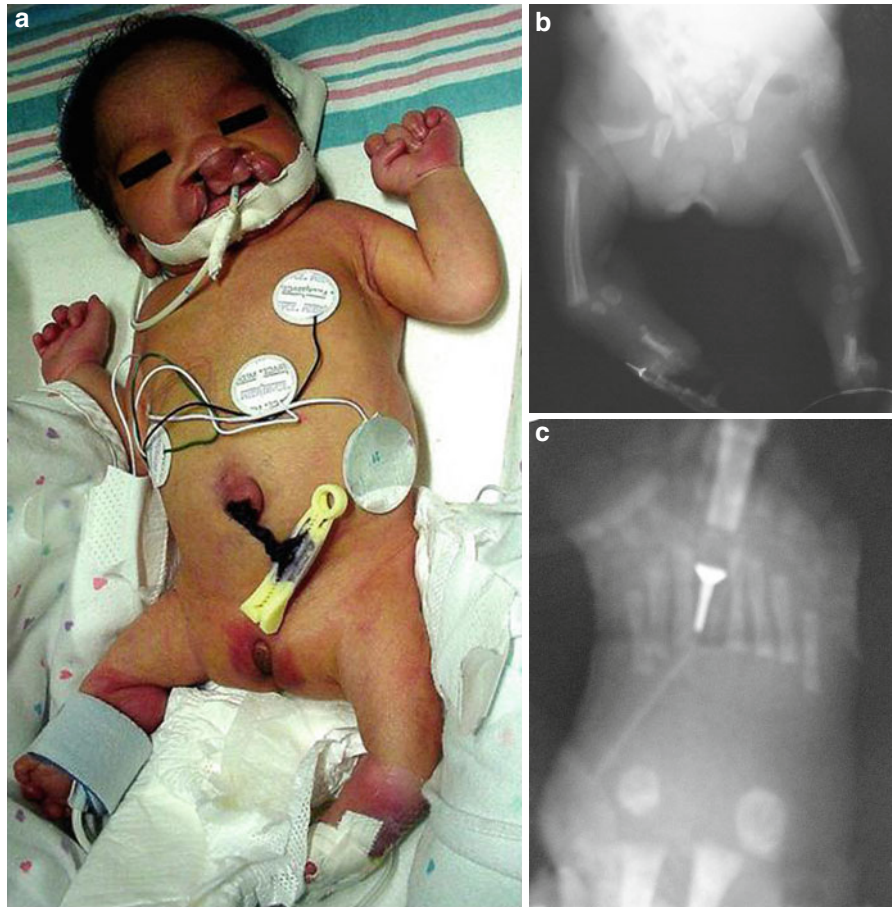

Fig. 3 (**a**–**c**) A newborn with diabetic embryopathy showing cleft lip/palate, caudal regression, femoral hypoplasia, and polydactyly

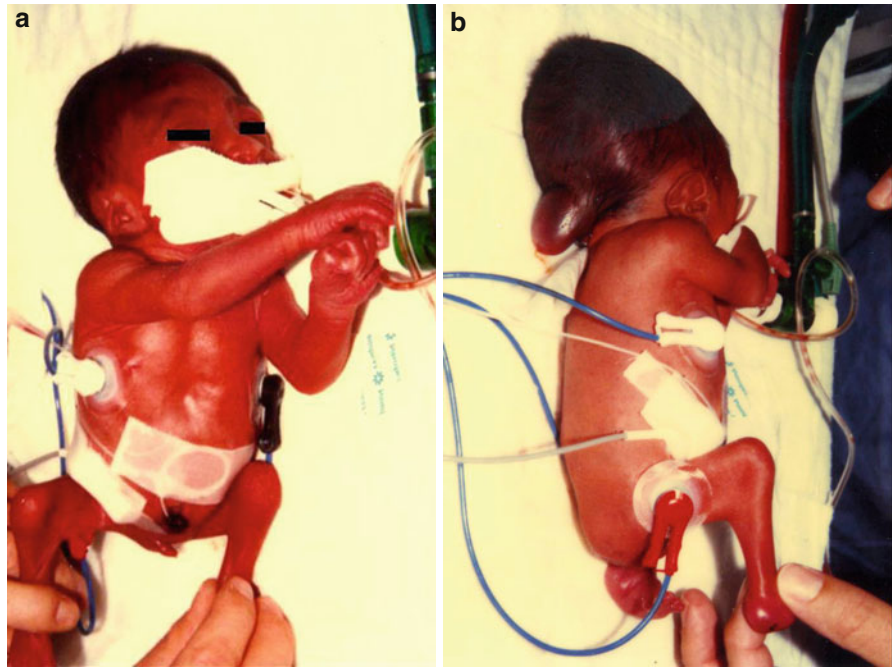

Fig. 4 (**a**, **b**) An infant born to the diabetic mother showing cystic hygroma with multiple contractures and multiple pterygia

Down Syndrome

In 1866, Down described clinical characteristics of the syndrome that now bears his name. In 1959, Lejeune and Jacobs et al. independently determined that Down syndrome is caused by trisomy 21.

Down syndrome is by far the most common, the best-known chromosome disorder in humans and the most common cause of intellectual disability (Peterson and Mikkelsen 2000). Mental retardation, dysmorphic facial features, and other distinctive phenotypic traits characterize the syndrome. Frequency is estimated to be 1 in 800 live births. Approximately 6,000 children are born with Down syndrome annually in the USA (Canfield et al. 2006).

Synonyms and Related Disorders

Trisomy 21 Syndrome

Genetics/Basic Defects

1. Caused by an extra chromosome 21
   a. Affect almost every organ system
   b. Result in a wide spectrum of phenotypic consequences
      i. Life-threatening complications
      ii. Significant alteration of life course (e.g., mental retardation)
      iii. Dysmorphic physical features
      iv. Decreased prenatal viability
      v. Increased prenatal and postnatal morbidity
2. Typical physical phenotype due to an extra copy of the proximal part of 21q22.3
   a. Mental retardation
   b. Characteristic facial features
   c. Hand anomalies
   d. Congenital heart defects
3. 21q22.1-q22.3 region containing the gene(s) responsible for the congenital heart disease observed in Down syndrome
4. Down syndrome critical region (DSCR): the region from 21q21 to 21q22.3 (McCormick et al. 1989; Rahmani et al. 1989)
5. DCR-1: a region with the largest number of associated features, including facial and hand phenotypes and mental retardation (Cold Spring Harbor meeting in 1997)
6. Types of trisomy 21
   a. Full trisomy 21 (94%)
   b. Mosaicism (2.4%)
   c. Translocations (3.3%)
      i. De novo (75%)
      ii. Familial translocation (25%)
   d. Isochromosome 21
7. Origin of nondisjunction: maternal nondisjunction in the first meiotic division (75%, most common)
8. Well-documented risk factor for maternal meiotic nondisjunction: advanced maternal age (Roitzen and Patterson 2003)
9. Down syndrome due to translocation occurs independent of maternal age and may be inherited from either parent (Tolmie 2002)
10. Majority of mosaic cases result from a trisomic zygote with mitotic loss of one chromosome 21

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Clinical Features

1. Growth and development
   a. Short stature
   b. Hypotonia which improves with age
   c. Moderate-to-severe mental retardation with IQ range of 20–85 (mean IQ is approximately 50)
   d. Articulatory problems
   e. Sleep apnea occurring when inspiratory airflow from the upper airway to the lungs is impeded for 10 s or more, often resulting in hypoxemia or hypercarbia
   f. Seizure disorder (5–10%)
      i. Infantile spasms (most common type of seizures seen in infancy)
      ii. Tonic–clonic seizures (most commonly seen in older patients)
   g. Visual and hearing impairments in addition to the presence of mental retardation further limiting the child's overall function and may prevent the child from participating in significant learning processes and obtaining appropriate language development and interpersonal skills
   h. Obesity during adolescence
   i. Premature aging
      i. Decrease in skin tone
      ii. Early graying or loss of hair
      iii. Hypogonadism
      iv. Cataracts
      v. Hearing loss
      vi. Age-related increase in hypothyroidism
      vii. Seizures
      viii. Neoplasms
      ix. Degenerative vascular disease
      x. Loss of adaptive abilities
      xi. Increased risk of senile dementia of Alzheimer type
2. Behavior
   a. Natural spontaneity
   b. Genuine warmth
   c. Cheerfulness
   d. Gentleness
   e. Patience
   f. Tolerance
   g. Anxiety
   h. Stubbornness
3. Psychiatric disorders
   a. Prevalence among children (17.6%)
   b. Prevalence among adults (27.1%)
   c. Children and adolescents at a higher risk for
      i. Autism
      ii. Attention deficit hyperactivity disorder
      iii. Conduct disorder
      iv. Obsessive–compulsive disorder
      v. Tourette syndrome
      vi. Depressive disorder during the transition from adolescence to adulthood
4. Skull
   a. Brachycephaly
   b. Microcephaly
   c. Sloping forehead
   d. Vertical creases on the forehead when crying ("Woolley" sign, named after the late mentor, Dr. Woolley)
   e. Flat occiput
   f. Large fontanels with late closure
   g. Patent metopic suture
   h. Absence of frontal and sphenoid sinuses
   i. Hypoplasia of the maxillary sinuses
5. Eyes
   a. Up-slanting palpebral fissures
   b. Bilateral epicanthal folds
   c. Brushfield spots (speckled iris)
   d. Refractive errors (50%)
   e. Strabismus (44%)
   f. Nystagmus (20%)
   g. Blepharitis (33%)
   h. Conjunctivitis
   i. Tearing from stenotic nasolacrimal ducts
   j. Congenital cataracts (3%)
   k. Pseudopapilledema
   l. Spasm nutans
   m. Acquired lens opacity (30–60%)
   n. Keratoconus
6. Nose
   a. Hypoplastic nasal bone
   b. Flat nasal bridge
7. Mouth
   a. Open mouth
   b. Tendency of tongue protrusion
   c. Fissured and furrowed tongue

d. Mouth breathing
e. Drooling
f. Chapped lower lip
g. Angular cheilitis

8. Teeth
   a. Partial anodontia (50%)
   b. Tooth agenesis
   c. Malformed teeth
   d. Delayed eruption
   e. Microdontia (35–50%) in both the primary and secondary dentitions
   f. Hypoplastic and hypocalcified teeth
   g. Malocclusion
   h. Taurodontism (0.54–5.6%)
   i. Increased periodontal destruction
9. Ears
   a. Small
   b. Over-folded helix
   c. Chronic otitis media
   d. Hearing loss common. Between 66% and 89% of children have hearing loss of greater than 15–20 dB in at least one ear by auditory brainstem response.
10. Neck
    a. Atlantoaxial instability (14%) resulting from laxity of transverse ligaments that ordinarily hold the odontoid process close to the anterior arch of the atlas.
    b. Laxity causing backward displacement of the odontoid process, leading to spinal cord compression
11. Chest
    a. Narrow chest
    b. Decreased internipple distance
12. Congenital heart defects
    a. Common (40–50%)
    b. Frequently seen in hospitalized Down syndrome patients (62%)
    c. Common cause of death in the first 2 years of life
    d. Endocardial cushion defect/atrioventricular canal (43%, most common type): About 70% of all endocardial cushion defects are associated with Down syndrome.
    e. Ventricular septal defect (32%)
    f. Secundum atrial septal defect (10%)
    g. Tetralogy of Fallot (6%)
    h. Isolated patent ductus arteriosus (4%)
    i. Multiple cardiac defects (30%). The most common associated lesions are patent ductus arteriosus (16%) and pulmonic stenosis (9%)
13. Abdomen
    a. Diastasis recti
    b. Umbilical hernia
14. Gastrointestinal (12%)
    a. Duodenal atresia or stenosis
    b. Hirschsprung disease (less than 1%)
    c. TE fistula
    d. Meckel diverticulum
    e. Imperforate anus
    f. Omphalocele
15. Genitourinary
    a. Renal malformations
    b. Hypospadias
    c. Micropenis
    d. Cryptorchidism
16. Skeletal
    a. Atlantoaxial (and atlantooccipital) instability
       i. Occurring in approximately 15% of individuals (<21 years old)
       ii. Mildest asymptomatic form
       iii. Severe symptomatic subluxation or dislocation at the atlantoaxial joint may injure the spinal cord. Neurologic manifestations include:
          a) Easy fatigability
          b) Difficulties in walking
          c) Abnormal gait
          d) Neck pain
          e) Limited neck mobility
          f) Torticollis (head tilt)
          g) Incoordination and clumsiness
          h) Sensory deficits
          i) Spasticity
          j) Hyperreflexia
          k) Clonus
          l) Extensor-plantar reflex
          m) Other upper motor neuron and posterior column signs and symptoms
          n) Rarely progressing to paraplegia, hemiplegia, quadriplegia, or death
    b. Short and broad hands
    c. Clinodactyly of the fifth fingers with a single flexion crease (20%)

d. Hyperextensible finger joints
e. Increased space between the great toe and the second toe
f. Acquired hip dislocation (6%)

17. Endocrine
    a. Thyroid disease
        i. Primarily autoimmune disorder with a lifetime prevalence of 13–63%
        ii. Congenital hypothyroidism: about 28 times more common among infants with Down syndrome than in the general population with an incidence of 1% detected by newborn screening
            a) 0.7% permanent congenital hypothyroidism
            b) 0.3% transient congenital hypothyroidism
        iii. Hypothyroidism in 16–20% of young patients
    b. Diabetes
    c. Decreased fertility
        i. Almost invariably infertile in males
        ii. Decreased fertility in females
18. Hematologic
    a. Neonatal leukemoid reactions (i.e., pseudoleukemia) is common. To distinguish this from true leukemia is frequently a diagnostic challenge.
    b. 10- to 15-fold increased risk of developing leukemia in children with Down syndrome. Approximately 1 in 150 patients develops leukemia.
    c. Uniquely predisposed to clonal disorders affecting the megakaryocyte lineage in children with Down syndrome
        i. Transient myeloproliferative disorder (also known as transient leukemia)
            a) Resolves spontaneously in most cases
            b) Develops acute megakaryoblastic leukemia in up to 30% of cases
        ii. Acute megakaryoblastic leukemia
    d. An increased risk of hepatitis B carrier status if previously institutionalized
19. Immunodeficiency: Patients have about 12-fold increased risk of developing infectious diseases, especially pneumonia, secondary to impaired cellular immunity.
20. Upper airway obstruction
    a. Causes
        i. Large tonsils and adenoids
        ii. Lingual tonsils
        iii. Choanal stenosis
        iv. Glossoptosis
    b. Consequences
        i. Serous otitis media
        ii. Alveolar hypoventilation
        iii. Arterial hypoxemia
        iv. Cerebral hypoxia
        v. Pulmonary artery hypertension
        vi. Cor pulmonale
        vii. Heart failure
21. Skin
    a. Cutis marmorata
    b. Thickened nuchal folds
    c. Xerosis
    d. Localized hyperkeratotic lesions
    e. Elastosis serpiginosa
    f. Alopecia areata (up to 10%)
    g. Vitiligo
    h. Folliculitis
    i. Abscess formation
    j. Recurrent skin infections
22. Dermatoglyphics
    a. Distal axial triradius in the palms
    b. Transverse palmar creases
    c. A single flexion crease in the fifth finger
    d. Ulnar loops (often 10) in the digital patterns
    e. A pattern present in hypothenar and interdigital III regions
23. Significant health problems observed in adults with Down syndrome
    a. Untreated congenital heart anomalies
    b. Acquired cardiac disease
    c. Pulmonary hypertension
    d. Recurrent respiratory infections/aspiration leading to chronic pulmonary interstitial changes
    e. Presenile dementia/Alzheimer-type disease
    f. Adult-onset epilepsy
    g. Osteoarthritic degeneration of the spine
    h. Osteoporosis with resultant fractures of the long bones or vertebral bodies
    i. Untreated atlantooccipital instability
    j. Acquired sensory deficits
    k. Loss of vision due to early onset of adult cataracts, recurrent keratitis or keratoconus
    l. Significant hearing loss
    m. Behavioral problems

24. Prognosis
    a. Life expectancy
        i. Approximately 75% of conceptuses die in embryonic or fetal stage
        ii. Approximately 85% of infants survive up to 1 year
        iii. About 50% can be expected to live beyond the age 50 years
    b. Mobility and mortality
        i. Presence of congenital heart disease (most significant factor that determines survival)
        ii. Esophageal atresia with or without TE fistula, Hirschsprung disease, duodenal atresia, infection, and leukemia adding to mortality
        iii. Higher mortality rate later in life secondary to premature aging
    c. Phenotype of mosaic individuals: depends on the frequency and distribution of trisomic cells, with typical Down syndrome as the worst phenotype

Diagnostic Investigations

1. Serum triple screen
    a. Alpha-fetoprotein
    b. Unconjugated estriol
    c. Human chorionic gonadotrophin
2. Cytogenetic studies
    a. Clinical diagnosis should be confirmed with cytogenetic studies
    b. Karyotyping is essential for determination of recurrence risk
        i. Free trisomy 21 (93–96%)
        ii. Robertsonian translocation (2–5%)
        iii. Reciprocal translocation (<1%)
        iv. Isochromosome (<1%)
        v. Mosaicism (2–4%)
    c. In translocation or isochromosome Down syndrome, karyotyping of the parents and other relatives is required for proper genetic counseling
3. Interphase fluorescence in situ hybridization (FISH)
    a. Used for rapid diagnosis
    b. Successfully applied to both prenatal diagnosis and diagnosis in the newborn period
4. Extraction of fetal cells from maternal circulation: After fetal nucleated red blood cells have been sorted using different cell transferrin and glycophorin-A receptors on the cell surface, interphase FISH can determine chromosome constitution. Chromosome-specific probes for X, Y, 13, 18, and 21 permit diagnosis. The FISH finding should be confirmed by standard cytogenetic techniques
5. Thyroid function tests: TSH and T4 should be obtained at birth and annually thereafter.
6. Measurement of IgG
    a. Used to identify deficiency of IgG subclasses 2 and 4
    b. A significant correlation between decreased IgG subclass 4 and bacterial infections
    c. Cellular immunity deficits documented in individuals with gingivitis and periodontal disease
7. Skeletal radiography
    a. Craniofacial anomalies include
        i. Brachycephalic microcephaly
        ii. Hypoplastic facial bones and sinuses
    b. Cervical spine X-rays (lateral flexion and extension views)
    c. Required to measure the atlanto-dens distance for excluding atlantoaxial instability at 3 years of age
    d. Used prior to anesthesia if there are signs suggesting spinal cord compression
    e. Reduced iliac and acetabular angles in the young infant
    f. Short hands with shortened digits and clinodactyly due to hypoplastic middle phalanx of the fifth finger
8. Echocardiography: This test should be performed on all infants with Down syndrome for identification of congenital heart disease, regardless of findings on physical examination.
9. Auditory brainstem response (ABR), also known as brainstem auditory evoked response (BAER), to demonstrate hearing loss. Evaluation of ABR in 47 unselected children with Down syndrome, aged between 2 months and 3 1/2 years, demonstrated some degree of hearing loss in 66% of the children examined (28% unilateral, 38% bilateral).
10. Speech evaluation
11. Pediatric vision screening for ophthalmologic disorders
12. Modified Denver Developmental Screening Test chart for non-institutionalized children for assessing the developmental milestones

13. Growth charts available for children with Down syndrome
14. Prenatal ultrasonography
    a. Thickened nuchal fold (major marker)
    b. Cystic hygroma
    c. Slightly shortened femora
    d. Hyperechogenic bowel
    e. Pyelectasis
    f. Echogenic intracardiac focus
    g. Wider lateral flare of the iliac bones
    h. Other subtle sonographic signs
        i. Short ears
        ii. Hypoplasia of the middle phalanx of the 5th fingers (clinodactyly)
        iii. Choroid plexus cyst
        iv. Delayed fusion of the amnion and chorion
        v. Simian crease of the hand
        vi. Separation of the great toe ("sandal gap foot")

Genetic Counseling

1. Recurrence risk (Chen 2010)
    a. Patient's sib
        i. Non-disjunction type: about 1% for younger women and approximates the age-related risk for older women (Nussbaum et al. 2004)
        ii. De novo Robertsonian translocation type: 2–3%
    b. Familial Robertsonian translocation type
        i. Theoretical recurrence risk for a Robertsonian carrier parent to have a live-born Down syndrome offspring: 1 in 3
        ii. The actual risks to future offspring depend on parental sex:
            a) Mother with rob(Dq;21q): 10–11%
            b) Father with rob(Dq;21q): 2.4%
            c) Mother with rob(21q;22q): 14%
            d) Father with rob(21q;22q): 1–2%
    c. A carrier parent with a 21q21q translocation or isochromosome: a 100% recurrence risk
    d. Gonadal mosaicism postulated for having more than one trisomic child in the family with apparently normal parents
    e. Patient's offspring
        i. Affected individuals rarely reproduce
        ii. Females with trisomy 21: About 15–30% are fertile and have a 50% risk of having an affected child
        iii. Males with trisomy 21: no evidence of fathering a child
2. Prenatal screening
    a. Advanced maternal age
        i. The first prenatal diagnosis of Down syndrome made in 1968
        ii. Gradual introduction of screening women on the basis of advanced maternal age with amniocentesis into medical practice
    b. Maternal serum biochemical markers
        i. Low maternal serum alpha-fetoprotein (MSAFP) shown to be associated with Down syndrome in 1983
        ii. Later, elevated human chorionic gonadotropin (hCG) and low unconjugated estriol (uE3) found to be the additional markers for Down syndrome
        iii. By 1988, the three biochemical markers, together with maternal age were accepted as a method of prenatal screening for Down syndrome in the general population
        iv. Estimated detection rate when ultrasound is used to estimate gestational age: 20% when using only the MSAFP test, 59% using the double test (MSAFP and hCG), and 69% using the triple test (MSAFP, hCG, uE3). The false positive rate is 5%. Other factors for adjustment are maternal age and weight, insulin-dependent diabetes mellitus, multiple pregnancy, ethnic origin, previous Down syndrome pregnancy, and first or repeat test in a pregnancy. A positive screening test suggests only an increased risk for having a Down syndrome fetus and that definitive testing by amniocentesis with chromosome analysis is indicated
    c. First-trimester free beta-hCG and pregnancy-associated plasma protein A retrospective screening study achieved rates as high as those associated with MSAFP, hCG, or uE3 in the second trimester. Prospective studies are needed to further assess first-trimester screening
3. Prenatal diagnosis
    a. Ultrasonography
        i. Nuchal fold thickening identifies 75% of Down syndrome fetuses
        ii. Shortened humerus or femur length detects 31% of cases

iii. Cystic hygroma
iv. Duodenal atresia or stenosis (double-bubble sign)
v. Cardiac defects
a) Endocardial cushion defect with atrial and ventricular septal defects
b) Abnormal mitral and tricuspid valves
vi. Echogenic bowel
vii. Renal pyelectasis

b. Amniocentesis, CVS, or fetal blood sampling
i. FISH analysis of interphase cells or metaphase spreads
ii. Chromosome analysis

4. Management
a. Medical care
i. Early intervention programs
a) Physical therapy
b) Occupational therapy
c) Speech therapy
d) Special education programs
ii. Hearing evaluation
iii. Thyroid hormone for hypothyroidism
iv. Medical management of congenital heart defects
a) Digitalis and diuretics usually required
b) Subacute bacterial endocarditis prophylaxis
v. Prompt treatment of respiratory tract infections and otitis media
vi. Pneumococcal and influenza vaccines for children with chronic cardiac and respiratory disease
vii. Anticonvulsants for seizures
viii. Provide pharmacologic agents, behavioral therapy, and psychotherapy for behavioral/psychiatric disorders
ix. Treat skin disorders
a) Weight reduction
b) Proper hygiene
c) Frequent baths
d) Application of antibiotic ointment
e) Systemic antibiotics therapy
x. Prevent dental caries and periodontal disease
a) Appropriate dental hygiene
b) Fluoride treatments
c) Good dietary habits
d) Restorative care
xi. Megadoses of vitamins and minerals supplemented with zinc and/or selenium: have not shown benefits in a number of well-controlled studies

b. Surgical care
i. Presence of Down syndrome alone does not adversely affect the outcome of surgery in the absence of pulmonary hypertension
ii. Timely surgery of cardiac anomalies necessary to prevent serious complications
iii. Prompt surgical repair of the following gastrointestinal anomalies:
a) TE fistula
b) Pyloric stenosis
c) Duodenal atresia
d) Annular pancreas
e) Aganglionic megacolon
f) Imperforate anus
iv. Adenotonsillectomies may be required for obstructive sleep apnea.
v. Surgical intervention may be necessary to reduce the atlantoaxial subluxation and to stabilize the upper segment of the cervical spine if neurologic deficits are significant.
vi. Extract congenital cataracts, which occur in about 3% of children, soon after birth with subsequent correction with glasses or contact lenses to assure adequate vision
vii. Anesthetic airway management
a) Adequate evaluation of the airway and neurological status
b) Cervical spine radiography (flexion and extension views) when any neurologic deficits suggest spinal cord compression
c) Avoid hyperextension of the head during laryngoscopy and intubation
d) Prescribe anticholinergics to control airway hypersecretion
e) Aware of other airway complications (subglottic stenosis and obstructive apnea resulting from a relatively large tongue, enlarged adenoids, and midfacial hypoplasia)

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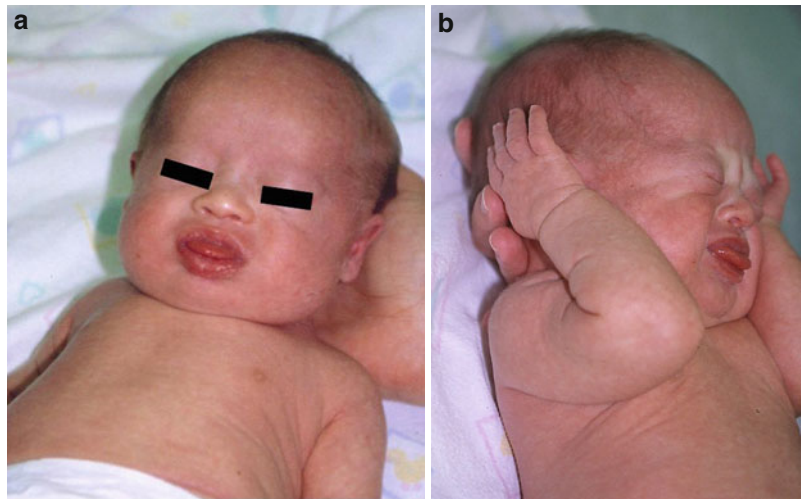

Fig. 1 (**a**, **b**) An infant with Down syndrome showing sloping forehead, upslanting palpebral fissures, "Woolley" sign, flat nasal bridge, small mouth, protruding tongue, narrow chest, and decreased internipple distance

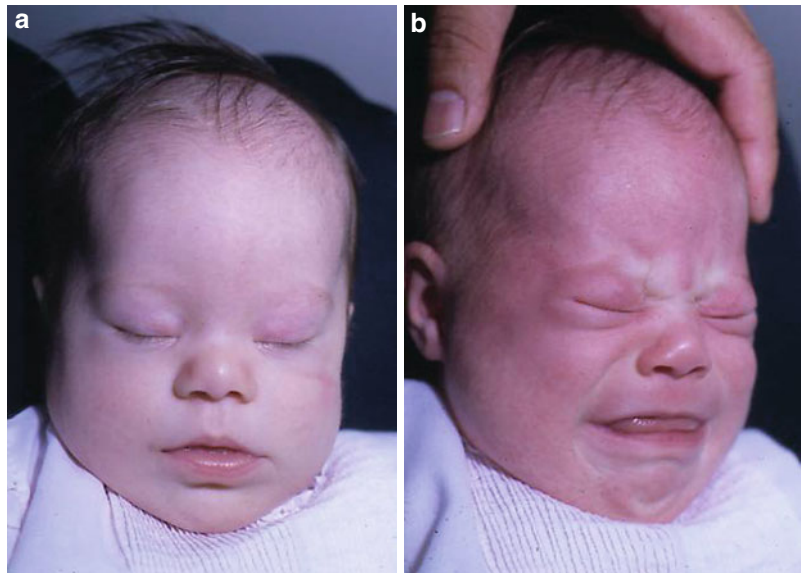

Fig. 2 (**a**, **b**) An infant with Down syndrome showing microcephaly, sloping forehead, upslanting palpebral fissure, and "Woolley" sign

Fig. 3 (**a**, **b**) Two infants with Down syndrome showing severe hypotonia in the neck and back (gibbus)

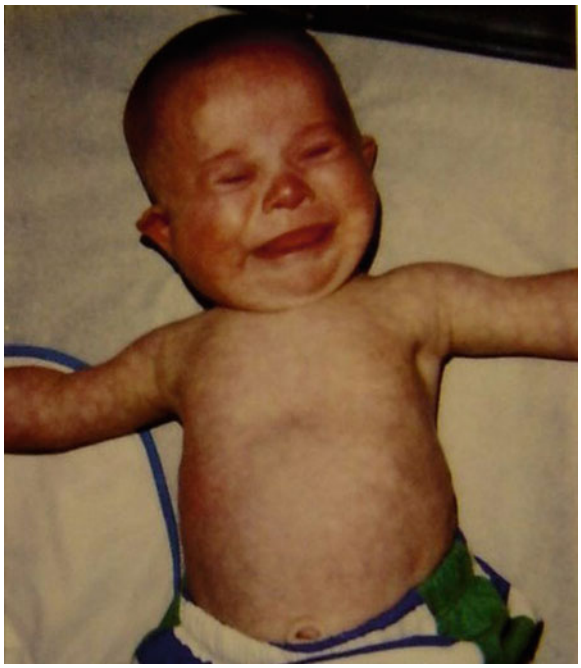

Fig. 4 An infant with trisomy 21 showing typical facial features and cutis marmorata

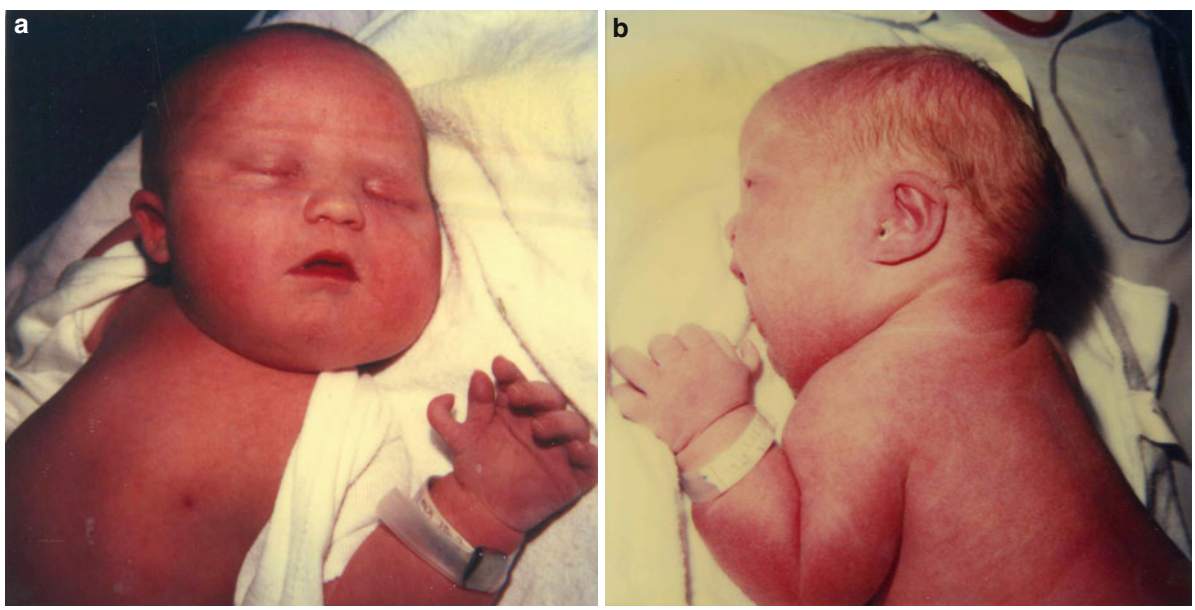

Fig. 5 (**a**, **b**) An infant with Down syndrome showing lymphedema in the cheeks and thickened nuchal fold

Fig. 6 (**a**, **b**) Two children with Down syndrome showing Brushfield spots of the iris

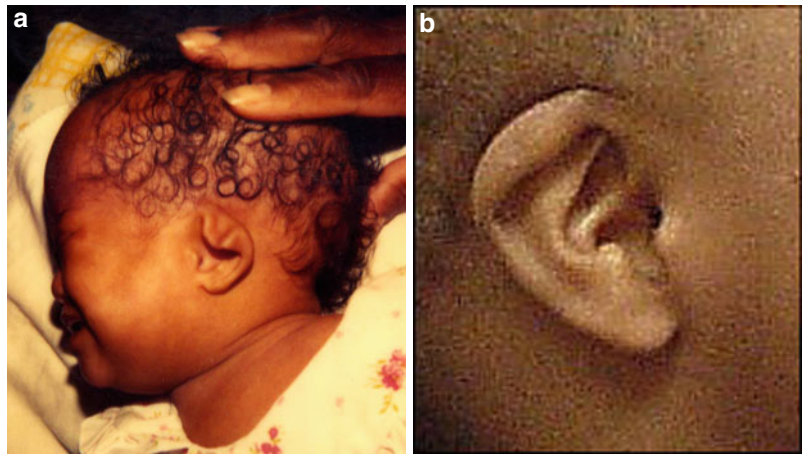

Fig. 7 (**a**, **b**) Two infants with Down syndrome showing typical small ear with overfolded helix

Fig. 8 A neonate with trisomy 21 showing thickened nuchal fold, typical ear, and a transverse palmar crease on the right palm

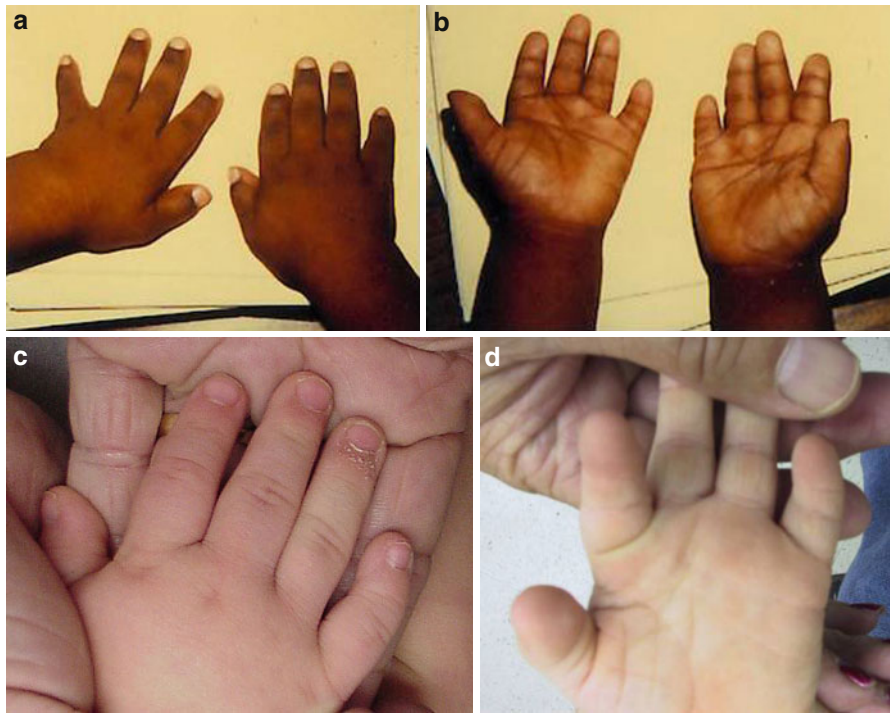

Fig. 9 (**a–d**) Two infants with Down syndrome showing small hands, small fingers, clinodactyly of the 5th finger with a single crease, and transverse palmar creases

Fig. 10 (**a**, **b**) Two infants with Down syndrome showing a widened space between the first and the second toes ("sandal gap" foot)

Fig. 11 An adult patient with Down syndrome showing upslanting palpebral fissure and severe midfacial hypoplasia

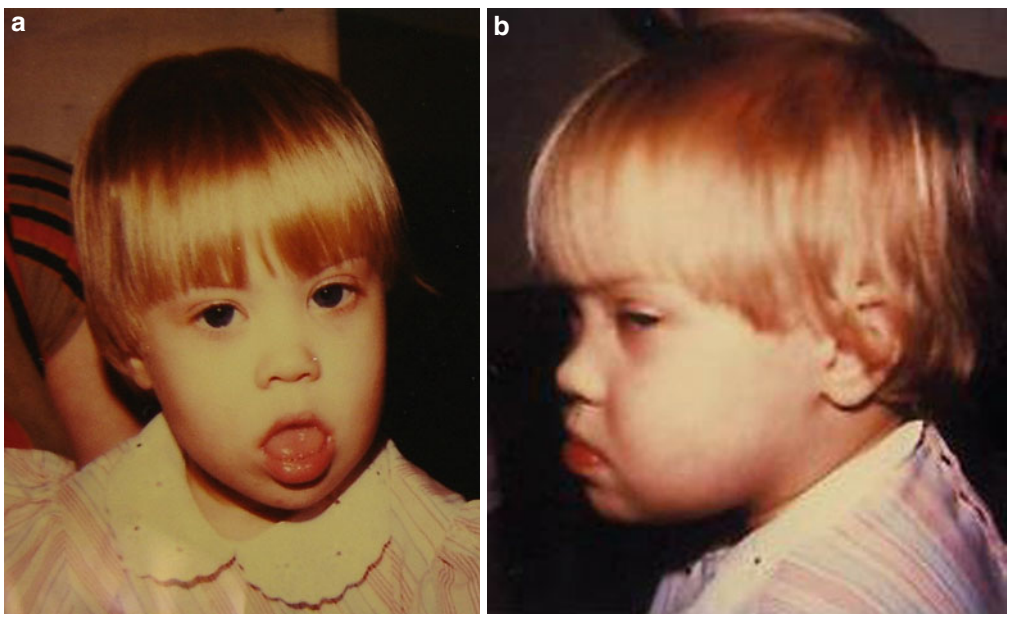

Fig. 12 (**a**, **b**) A girl with mosaic trisomy 21 showing typical Down syndrome phenotype

Fig. 13 (**a**, **b**) An adult patient with mosaic trisomy 21 showing relatively mild phenotype

Fig. 14 A brother and a sister with non-disjunction type of trisomy 21

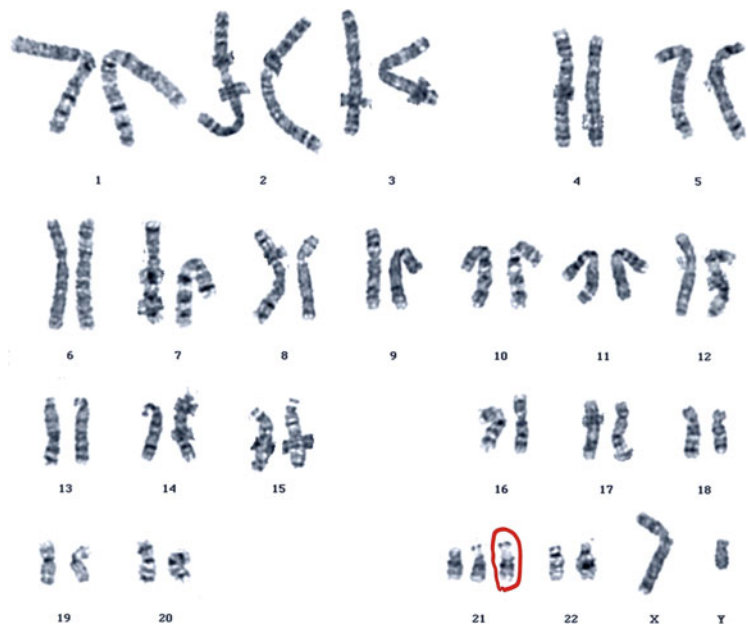

Fig. 15 A G-banded karyotype showing trisomy 21

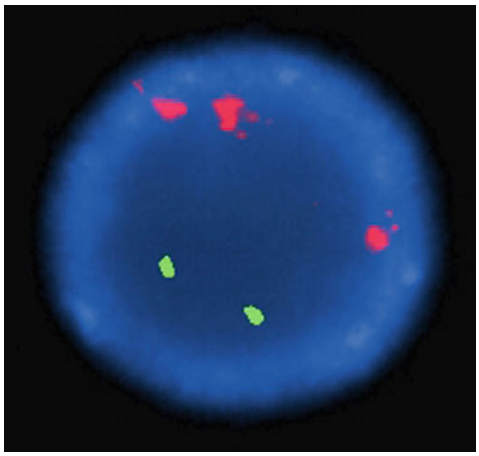

Fig. 16 FISH using a probe cocktail for chromosomes 13 (*green*) and 21 (*orange*) on interphase cells. Three copies of the orange/chromosome 21 signal are seen with only two copies of the green signal/chromosome 13 (AneuVysion LSI 13/21, Vysis/Abbott)

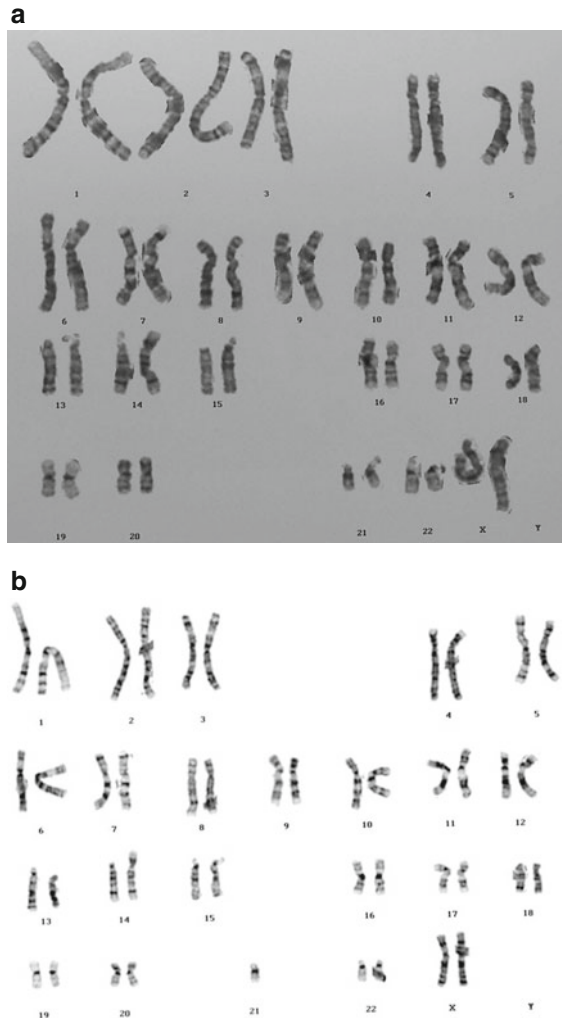

Fig. 17 (**a**, **b**) G-banded karyotypes showing t(14q;21q) trisomy 21 and carrier

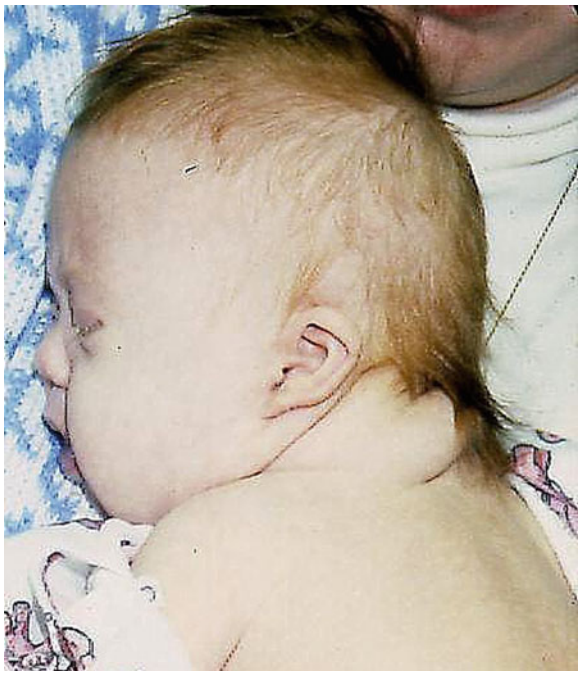

Fig. 18 A neonate with i(21q) trisomy 21 showing typical Down syndrome phenotype including thickened nuchal folds

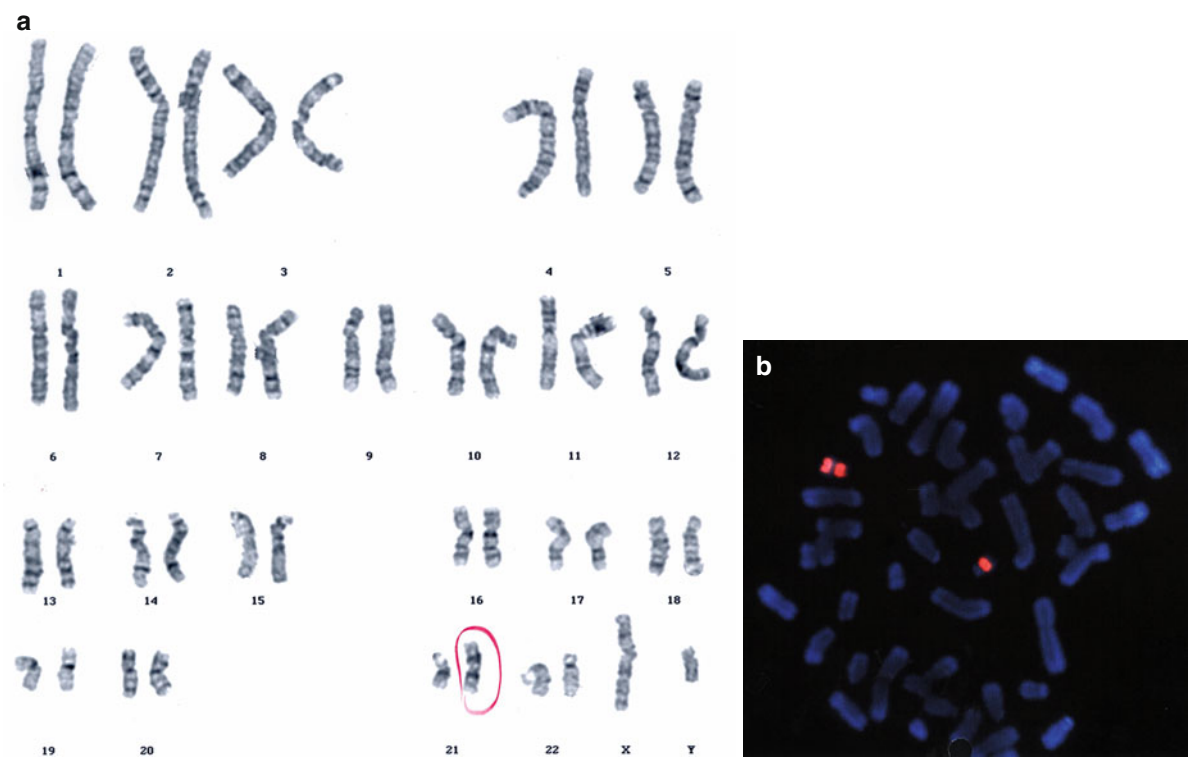

Fig. 19 (**a**, **b**) A G-banded karyotype and FISH showing i(21q) trisomy 21

Duncan Syndrome

In 1975, Purtilo et al. reported the Duncan pedigree in which six of 18 males died of a lymphoproliferative disorder. The boys, aged between 2 and 19 years, exhibited a progressive-combined variable immunodeficiency disease characterized by benign or malignant proliferation of lymphocytes, histiocytosis, and alterations in concentrations of serum immunoglobulins. This condition is now known as Duncan syndrome or X-linked lymphoproliferative syndrome (XLP) which is a rare T and NK cell immune deficiency which most frequently presents as fulminant infectious mononucleosis following infection with the Epstein–Barr virus (EBV) in most affected boys, leading to death in 50% of the cases.

Synonyms and Related Disorders

X-Linked Lymphoproliferative Disease

Genetics/Basic Defects

1. An X-linked recessive disorder.
2. The gene causing XLP, identified and described in 1998, was termed SH2D1A or SAP [signaling lymphocyte activation molecule (SLAM)-associated protein]. The gene encodes a protein which interacts with the SLAM (or CD150, a T-cell surface marker, and self-ligand) and several related receptors.
3. The immune response of XLP patients against EBV.
   a. Not efficient for the control of EBV expansion (in contrary to the coordinated immune response to EBV seen in normal individuals)
   b. Exhibit a dysregulated response characterized by an excessive accumulation of activated CD8+ T cells, natural killer (NK) cells, and macrophages and by the inability to control acute EBV infection.

Clinical Features

1. Diverse phenotype in affected boys
2. Fulminant infectious mononucleosis (FIM) with virus-associated hemophagocytic syndrome (VAHS)
   a. The most common and most dramatic manifestation of XLP with the worst prognosis (over 90% mortality)
   b. Clinically well until EBV infection, leading to a dysregulated and exaggerated immune response with proliferation of cytotoxic T cells, EBV-infected B cells and macrophages in tissues throughout the body
   c. Clinically manifests as pronounced lymphadenopathy and hepatosplenomegaly, resulting in extensive parenchymal damage with accompanying dysregulated cytokine release
      i. Most prominent in the liver, causing fulminant hepatitis and hepatic necrosis, and in the bone marrow, leading to profound marrow hypoplasia
      ii. Infiltration in other tissues
         a) Spleen (white pulp necrosis)
         b) Brain (perivascular mononuclear cell infiltrates)
         c) Heart (mononuclear cell myocarditis)
         d) Kidney (mild interstitial nephritis)

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e) Postmortem hemophagocytosis observed in various tissue in 90% of XLP boys presenting with FIM

3. Dysgammaglobulinemia
   a. Extensive necrosis and lymphoid depletion throughout the lymphoreticular system that follows acute EBV infection
   b. Abnormal immunoglobulin (Ig) production after EBV infection: ranging from decreased levels of IgG to panhypogammaglobulinemia
   c. Humoral dysfunction may accompany cellular T and natural killer (NK) defects in more severe cases
4. Malignant lymphoma
   a. Found in approximately one third of boys with XLP, with B-cell lymphoma being the most common lymphoproliferative disorder observed
   b. Median age: 4–6 years
   c. Extranodal lesions: approximately 75% in ileocecal region and a smaller number in central nervous system, liver, and kidneys
   d. Almost all the lymphomas were of B-cell origin but tumors with a T-cell phenotype have also been described
   e. Lymphomas can be histologically classified as:
      i. Burkitt's lymphomas (53% of all B-cell lymphomas)
      ii. Immunoblastic lymphomas (12% of all cases)
      iii. Small cleaved or mixed cell lymphomas (12%)
      iv. Unclassifiable lymphomas (5% of all cases) (Harrington et al. 1987)
      v. Four cases of Hodgkin's disease were reported to the XLP registry
   f. Features of lymphomas in XLP: similar to those seen in other primary immunodeficiencies
      i. Extranodal involvement
      ii. High-grade histology
      iii. Evidence of clonality
      iv. Gene rearrangements
   g. Poor survival rate (35%)
   h. Remission can often be achieved with the use of standard pediatric lymphoma chemotherapy protocols but there is a high rate of relapse or development of the other manifestations of XLP
5. Other clinical manifestations
   a. Aplastic anemia can arise as a complication of fulminant infectious mononucleosis with hemophagocytosis, leading to marrow aplasia. However, 3% of all cases can present initially as aplastic anemia.
   b. Lymphoid vasculitis
      i. Another uncommon but well-described complication of XLP
      ii. Histological features: arterial wall destruction with aneurismal dilatation
   c. Accompanied by various degrees of hemophagocytic lymphohistiocytosis
6. Phenotype is likely determined by a number of factors, including the SAP mutation, and environmental and infectious factors on a background of disease modifier genes, as seen in other primary immunodeficiencies
7. XLP without EBV infection: at least 10% of cases of XLP are driven without EBV infection
8. Posttransplant lymphoproliferative disorder (PTLD)
   a. Related to EBV infection
   b. Estimated to occur in 2–5% of all transplant recipients
   c. More common in children since many children are EBV-naive at the time of transplant
   d. Protean manifestations of PTLD
      i. Local disease, such as graft dysfunction
      ii. Systemic disease, such as viral illness
   e. Mortality rates reported for children who develop PTLD: high and range from 36% to 69%
9. Diagnostic criteria for XLP (Conley et al. 1999)
   a. Definitive: male patients with a mutation in SAP
      i. Lymphoma/Hodgkin's disease
      ii. Fatal EBV infection
      iii. Immunodeficiency
      iv. Aplastic anemia or lymphohistiocytic disorder
   b. Probable
      i. Male patients experiencing lymphoma/Hodgkin's disease, immunodeficiency, plastic anemia or lymphohistiocytic disorder, resulting in death, following acute EBV infection
      ii. Maternal cousins, uncles, or nephews with a history of similar diagnoses, following acute EBV infection
   c. Possible: male patients with lymphoma/Hodgkin's disease, immunodeficiency, plastic anemia, or lymphohistiocytic disorder, resulting in death, following acute EBV infection

Diagnostic Investigations

1. Identification of SAP as the defective gene in XLP now allows unambiguous diagnosis of the condition
2. Screen all male patients with common variable immunodeficiency (CVID) since some patients previously labeled as having CVID have been shown to have mutations in the SAP gene
3. Prior to an encounter with EBV: no uniform abnormalities are observed on laboratory testing of individuals with XLP. Some individuals may have:
   a. Decreased numbers of lymphocyte subsets including decreased T cells, B cells, and NK cells
   b. Variably decreased NK cell function
   c. Dysgammaglobulinemia, most frequently manifest by low serum concentration of IgG with elevated serum concentration of IgM and/or IgA
4. Evidence of acute EBV infections supported by:
   a. Heterophil antibodies on monospot testing
   b. EBV detection by polymerase chain reaction (PCR)
   c. Detection of EBV-specific IgM antibodies
   d. Atypical lymphocytosis on peripheral blood smear
5. Specific tests suggesting the diagnosis of XLP in males with severe EBV infections:
   a. Markedly elevated liver transaminases
   b. Inverted CD4:CD8 ratio in peripheral blood
   c. Liver biopsy consistent with widespread necrosis during severe EBV infection
   d. Bone marrow biopsy with evidence of hemophagocytosis during severe EBV infection
   e. Positive EBV viral capsid antigen (VCA) titer, but negative Epstein–Barr virus nuclear antigen (EBNA) titer
6. Molecular genetic testing: clinically available
   a. Sequence analysis of the entire coding region of *SH2D1A* and exon/intron boundaries identifies nucleotide substitutions, small deletions, small insertions, small insertions/deletions, and small inversions
   b. PCR-based sequencing can detect about 97% of *SH2D1A* mutations in affected males who have two or more maternally related family members with an XLP phenotype and about 75% of mutations in obligate carrier females
   c. Large deletions account for about 25% of mutations in families with XLP
   d. Because males have one X chromosome, the absence of amplification of a region of a gene under stringent laboratory conditions implies that a large deletion or rearrangement is present and because females have two X chromosomes, amplification of a region occurs even in the presence of a large deletion because of the contribution of the second X chromosome; thus, PCR-based sequencing does not accurately detect a large deletion.
7. Carrier detection of at-risk female relatives: available on a clinical basis when the mutation has been identified in the proband or family relative

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: The risk to sibs depends upon the carrier status of the mother
      i. Mother is a carrier: the chance of transmitting the disease-causing mutation in each pregnancy is 50%
      ii. Male sibs who inherit the mutation will be affected
      iii. Female sibs who inherit the mutation will be carriers but asymptomatic and have no immunologic or biochemical markers of the disorder
      iv. Presence of germline mosaicism of the mother: even if the disease-causing mutation has not been identified in DNA extracted from the mother's leukocytes, her offspring are still at increased risk
   b. Patient's offspring
      i. Affected males will likely live to reproduce in the near-future following bone marrow transplantation and that the chemotherapy regimen used prior to BMT will not render them infertile
      ii. Males will pass the disease-causing mutation to all of their daughters and none of their sons
2. Prenatal diagnosis
   a. Fetal karyotyping to determine male fetus (46,XY)
   b. DNA extracted from fetal cells by amniocentesis or CVS analyzed for known gene mutation

3. Management
   a. All identified males receive immunoglobulin replacement to prevent bacterial and viral infections
   b. Allogeneic hematopoietic stem cell transplantation (HSCT): the only definitive cure for XLP, and prevention of EBV and non-EBV complications at present
   c. Treatment is difficult during the acute FIM phase of XLP, as demonstrated by the high mortality rate
      i. Treatment using antivirals (acyclovir/ganciclovir/foscarnet), high-dose immunoglobulin, immunosuppressive agents, and IFN-a and IFN-c have been disappointing
      ii. The high rate of hemophagocytosis associated with XLP has led to the use of antihistiocytic regimes with etoposide such as HLH 94, for the treatment of boys with XLP, shown to induce long-term remission or to stabilize the patient prior to allogeneic HSCT
      iii. Etoposide has also been included in the conditioning regime in combination with busulphan and cyclophosphamide for some patients
   d. Regular immunoglobulin replacement to prevent recurrent infection and additional bacterial prophylaxis in patients developing hypogammaglobulinemia post-viral infection. This may not prevent subsequent development of malignant lymphoma or aplastic anemia. Patients with lymphoma have been treated according to standard chemotherapy protocols but there is a high rate of relapse and patients may also develop other phenotypes of XLP.
   e. Prospect of gene therapy as a future treatment option with the identification of the XLP gene
      i. Recent success of gene therapy for the treatment of two forms of severe combined immunodeficiency offers hope for other immunodeficient conditions
      ii. Gene therapy for XLP is attractive in that the cellular defects are primarily confined to T and NK cells, both of which are readily accessible and can be efficiently transduced

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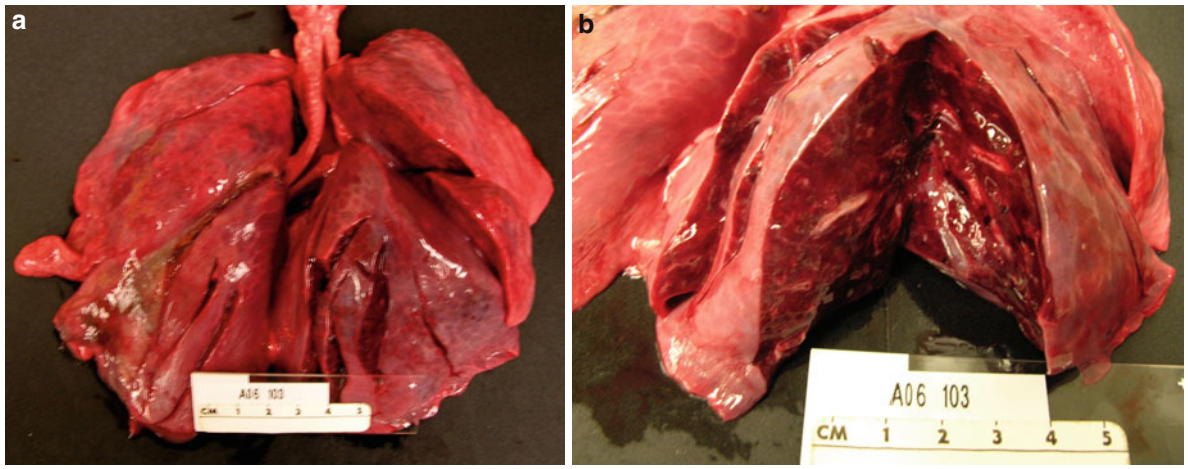

Fig. 1 (**a**, **b**) The deceased patient was a 4-year-old boy complained of fever, anemia, neutropenia, thrombocytopenia, and lymphadenopathy. He was noted to have cervical, axillary, and inguinal lymphadenopathy and hepatosplenomegaly. DNA analysis revealed a nonsense mutation, 172 C > T (Q56X), in the coding sequence of *SH12D1A* gene which confirmed the diagnosis of X-linked lymphoproliferative disease. A maternal first cousin is also affected with Duncan disease. On necropsy, both lungs appeared congested and the cut surface of both lungs was dark and airless with diffuse atelectasis

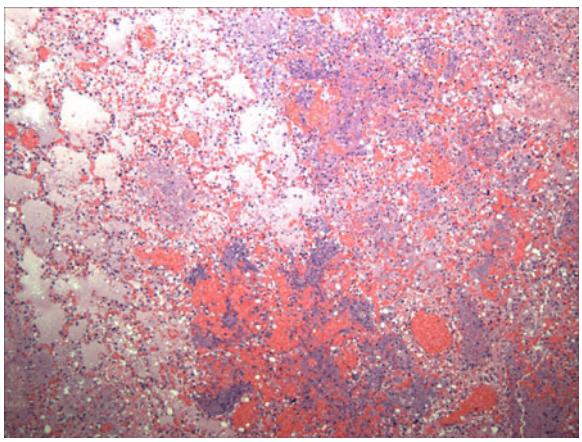

Fig. 2 Microscopic examination of the lungs showed congestion, hemorrhage, and edema with extensive gram-negative bacterial growth

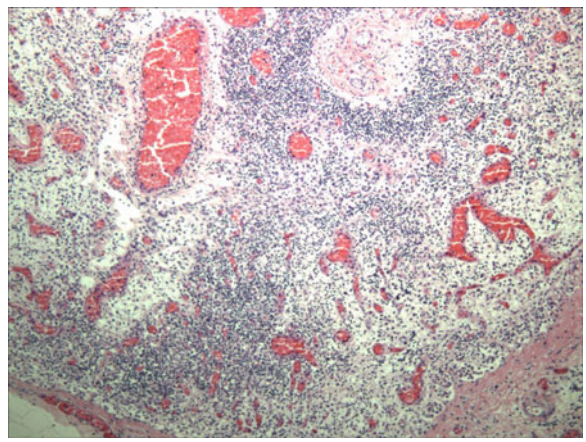

Fig. 3 The microscopic examination of the lymph nodes showed absence of germinal centers, depletion of the lymphocytes, sinus histiocytosis, and vascular congestion

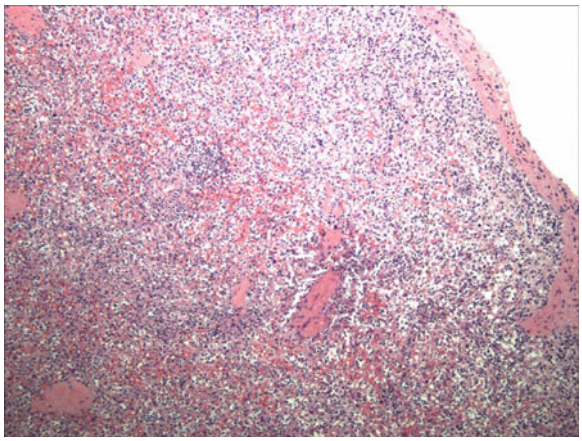

Fig. 4 Microscopic examination of the spleen showed lymphocyte depletion and rare megakaryocytes

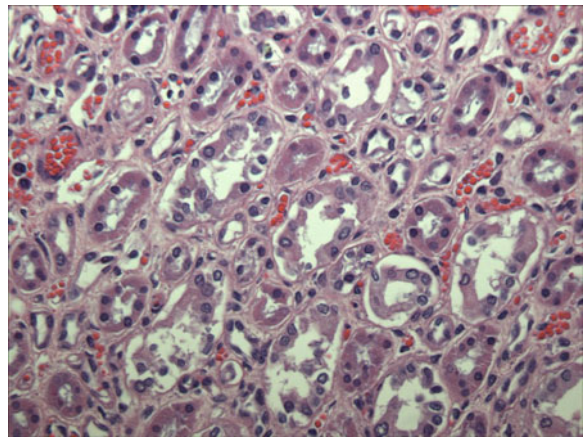

Fig. 7 Proximal tubules of the kidney were necrotic, consistent with ischemic changes

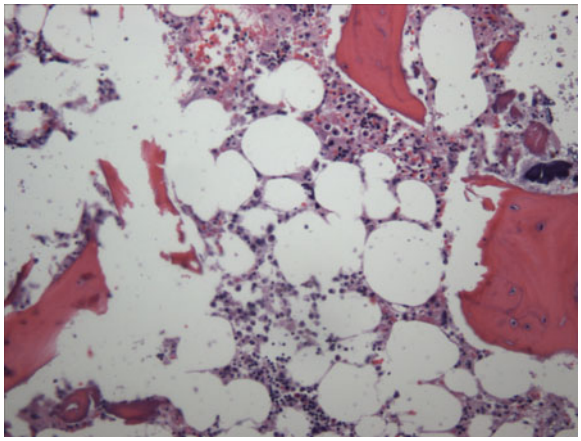

Fig. 5 Bone marrow was hypocellular with fat to cell ratio of 90:10 and very few mature lymphocytes

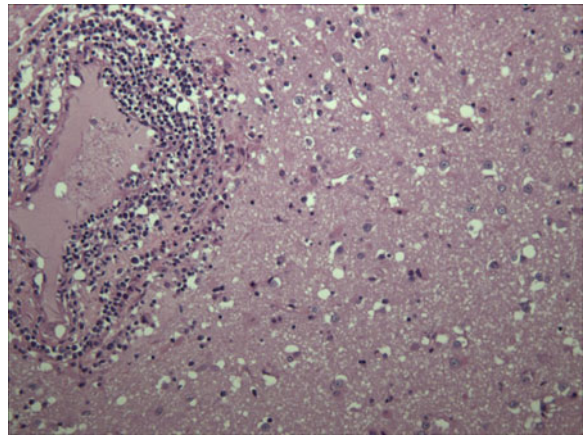

Fig. 8 The brain showed intense perivascular and mild patchy parenchymal infiltration with atypical reactive lymphocytes

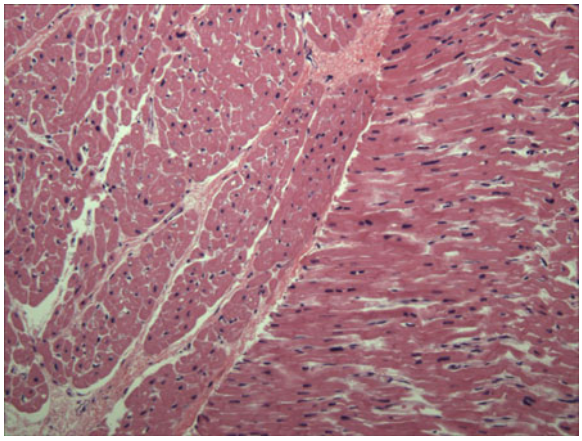

Fig. 6 Nuclei of heart muscles were enlarged, consistent with moderate hypertrophy

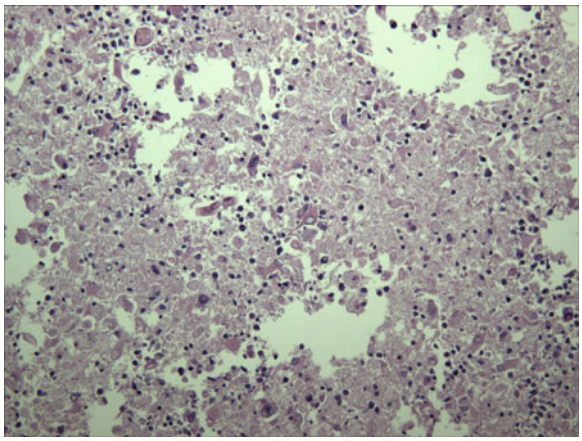

Fig. 9 The liquefied areas of the brain contained numerous foamy macrophages and the surrounding tissue contained numerous gemistocytes (active gliosis), in the RSFG, left corpus striatum, brain stem, and cerebellum

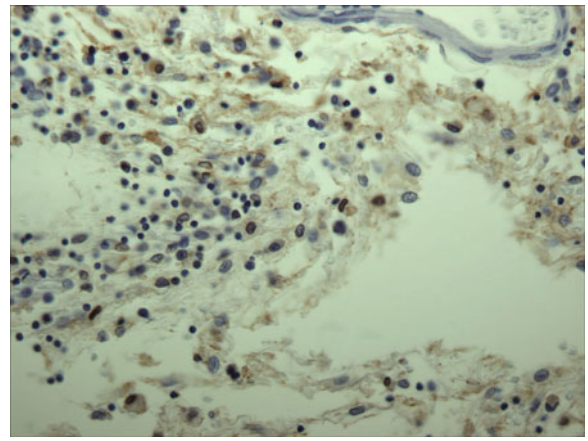

Fig. 10 Some cells in the infiltrate were positive for EB virus by FISH analysis

Dyschondrosteosis

Dyschondrosteosis is an autosomal dominant form of mesomelic dysplasia, first described by Leri and Weill in 1929. Langer mesomelic dysplasia, also called mesomelic dwarfism of the hypoplastic ulna, fibula, and mandible type, is a more severe form (homozygous state) of Leri–Weill dyschondrosteosis.

Synonyms and Related Disorders

Langer mesomelic dysplasia; Leri–Weill syndrome

Genetics/Basic Defects

1. Inheritance
   a. Dyschondrosteosis: autosomal dominant
   b. Langer mesomelic dysplasia: psuedoautosomal recessive
2. Molecular basis (Zinn et al. 2002)
   a. Caused by mutations and deletion of *SHOX* (short stature homeobox-containing) gene
      i. The *SHOX* gene is mapped to Xp22.3, based on the observation of unbalanced translocation involving the pseudoautosomal region of the short arm of the X and Y chromosomes (PAR1) in dyschondrosteosis patients and of some degree of Madelung deformity in Turner syndrome patients.
      ii. The Xp22.3 region encompasses the pseudoautosomal *SHOX* gene, which encodes isoforms of a homeo-domain transcription factor expressed in developing human limbs.
      iii. The gene in the Xp22.3 region escapes X-inactivation in females and participates in obligate recombination during male meiosis. Consequently, dyschondrosteosis segregates as an apparently "autosomal" dominant disorder.
   b. Haploinsufficiency of the *SHOX* gene, implicated in the following disorders:
      i. Turner syndrome: *SHOX* is haploinsufficient in females with 45,X Turner syndrome, accounting for approximately 2/3 of the characteristic growth deficit.
      ii. Idiopathic short stature: Observation that a point mutation that cosegregates with idiopathic short stature suggests that *SHOX* haploinsufficiency may also cause growth failure in the patients with normal karyotype. *SHOX* mutations have been found in 2–3% of patients with idiopathic short stature.
      iii. Leri–Weill dyschondrosteosis (including homozygous form of Langer mesomelic dysplasia)
   c. Identification of large-scale deletions or mutations in the *SHOX* gene in the majority of the cases
   d. *SHOX* mutations: causative for mesomelic growth retardation and Madelung deformity in Leri–Weill dyschondrosteosis and Langer mesomelic dysplasia
   e. Leri–Weill syndrome as a part of contiguous gene syndrome with deletion of Xp22.3

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3. Langer mesomelic dwarfism
   a. A homozygous state of dyschondrosteosis gene (Espiritu et al. 1975a, b)
   b. Caused by deletion of both *SHOX* alleles (complete *SHOX* deficiency)
   c. Also associated with compound heterozygous mutations and deletions of the *SHOX* gene, mapped to the pseudoautosomal region 1 (PAR1) of the sex chromosomes Xp22.33 and Y11.32 or the downstream PAR1 where SHOX enhance elements are located
      i. A compound heterozygote with a deletion in the 3′ *SHOX* flanking region in one allele and the loss of the entire *SHOX* gene in the other has been described with a "mild" Langer mesomelic dysplasia phenotype (Fukami et al. 2005)
      ii. Detection of two different deletions in a proband with clinical features of Langer mesomelic dysplasia in the pseudoautosomal 1 region (PAR1) of the X and Y chromosomes: a *SHOX* encompassing deletion inherited from his father and a downstream PAR1 deletion not including *SHOX* inherited from his mother (Campos-Barros et al. 2007)

Clinical Features

1. Dyschondrosteosis
   a. Mesomelic dwarfism (disproportionate short stature)
   b. Phenotypic inter- and intrafamilial heterogeneity, a frequent finding
   c. Much more common and less severe than Langer mesomelic dysplasia
   d. Females more commonly and more severely affected (more severe Madelung deformity) than males
   e. Intelligence: normal
   f. Limbs
      i. Mesomelia (disproportionate forelimb shortening)
         a) Shortened forearms
         b) Shortened forelegs
      ii. A Madelung deformity of the forearms and wrists secondary to bowing of the radius and dorsal subluxations of the distal ulna
      iii. Reduced radiocarpal motion
      iv. Limited elbow and wrist pronation and supernation
      v. Genu varum
2. Langer mesomelic dysplasia
   a. The homozygous form of Leri–Weill syndrome (Espiritu et al. 1975a, b)
   b. Severe disproportionate short stature with marked mesomelic and rhizomelic limb shortening
   c. Parents of some children with Langer mesomelic dysplasia have features of the more common dominantly inherited mesomelic skeletal dysplasia Leri–Weill dyschondrosteosis.
   d. Intelligence: normal
   e. Limb malformations
      i. Aplasia or severe hypoplasia of the ulna and fibula
      ii. Thickened and curved radius and tibia
   f. Hypoplasia of the mandible
   g. A variable degree of Madelung deformity and mesomelic shortening in both parents
3. Prognosis
   a. Minimal disability from the Madelung deformities of the wrists
   b. Secondary arthrosis of the radiocarpal joint
   c. Osteoarthritis of the large joints
   d. Langer mesomelic dysplasia: much more severe phenotype than dyschondrosteosis

Diagnostic Investigations

1. Radiography
   a. Mesomelic dysplasia
   b. Madelung deformity of the wrists
      i. Short forearm
      ii. Bowed radius
      iii. Bowed ulna
      iv. Premature fusion of the ulnar half of the radial epiphysis
      v. A V-shaped deformity of the wrist with slanting at the distal radial contour and dorsal dislocation of the ulna
      vi. Wedging of the carpal bones between the deformed radius and protruding ulna, resulting in a triangular configuration with the lunate at the apex
      vii. Cubitus valgus
   c. Coxa valga

d. Lateral subluxation of the patella
e. Short tibia
f. Exostosis of the proximal medial tibia
g. Langer mesomelic dysplasia
   i. Aplasia or severe hypoplasia of the ulna and fibula
   ii. Thickened and curved radius and tibia

2. Cytogenetic analysis (Munns and Glass 2008)
   a. Rare patients with Leri–Weill dyschondrosteosis
      i. A contiguous gene syndrome caused by deletion in distal Xp22.3 (Ballabio et al. 1989; Spranger et al. 1999)
      ii. An unbalanced X;Y translocation (Shears et al. 1998)
      iii. Complex sex chromosome abnormalities (Wei et al. 2001)
   b. Submicroscopic deletions of SHOX causing the SHOX-related haploinsufficiency disorders: not usually detectable by G-banded karyotyping
3. Molecular genetic analysis
   a. *SHOX* deletions detected by FISH analysis using cosmid probe for *SHOX*
   b. MLPA for PAR1 deletions
   c. High-resolution melting (HRM), dHPLC and/or DNA sequencing for point mutations, small deletions and insertions of *SHOX*

Genetic Counseling

1. Recurrence risk
   a. Patient's sibs
      i. Leri–Weill dyschondrosteosis
         a) Neither parent is affected: not increased
         b) One parent is affected with Leri–Weill dyschondrosteosis: 50% affected with Leri–Weill dyschondrosteosis and 50% unaffected
         c) Two parents are affected with Leri–Weill dyschondrosteosis: 50% affected with Leri–Weill dyschondrosteosis, 25% affected with Langer mesomelic dysplasia, and 25% risk of having neither conditions
      ii. Langer mesomelic dysplasia (both parents with Leri–Weill dyschondrosteosis): 50% affected with Leri–Weill dyschondrosteosis, 25% affected with Langer mesomelic dysplasia, and 25% unaffected
   b. Patient's offspring
      i. Leri–Weill dyschondrosteosis
         a) Spouse is normal: 50% affected and 50% unaffected
         b) Spouse is affected with Leri–Weill dyschondrosteosis: 50% affected with dyschondrosteosis, 25% affected with Langer mesomelic dysplasia, and 25% having neither condition
      ii. Langer mesomelic dysplasia
         a) Spouse is normal: All children will be affected with Leri–Weill dyschondrosteosis
         b) Spouse is affected with Leri–Weill dyschondrosteosis: 50% affected with Langer mesomelic dysplasia and 50% affected with Leri–Weill dyschondrosteosis
2. Prenatal diagnosis possible for at-risk families
   a. Prenatal ultrasonography of skeletal features compatible with mesomelic dwarfism
   b. Molecular analysis of previously identified disease-causing *SHOX* mutations in the proband or a parent from the fetal DNA obtained from amniocentesis or CVS
   c. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified
3. Management
   a. Medical therapy of Madelung deformity
      i. May be helpful in skeletally mature individuals with Madelung deformity who have mild-to-moderate short-term wrist pain
      ii. Splints to relief joint pain
      iii. Decrease manual activity levels to manage symptoms without surgery
   b. Surgical therapy of Madelung deformity
      i. Primary goals: pain relief and cosmetic improvement of Madelung deformity
         a) Minimal improvement of range of motion, especially in pronation and supination
         b) Release of the Vickers ligament alone or in combination with an osteotomy
      ii. Osteotomy of radius
      iii. Radioulnar length adjustment
      iv. Ulnar resection
   c. Tibial osteotomy and lengthening combined with epiphyseodesis of the distal fibular epiphysis for the tibiofibular disproportion

d. Ongoing clinical trial with growth hormone therapy in patients with short stature due to *SHOX* mutations

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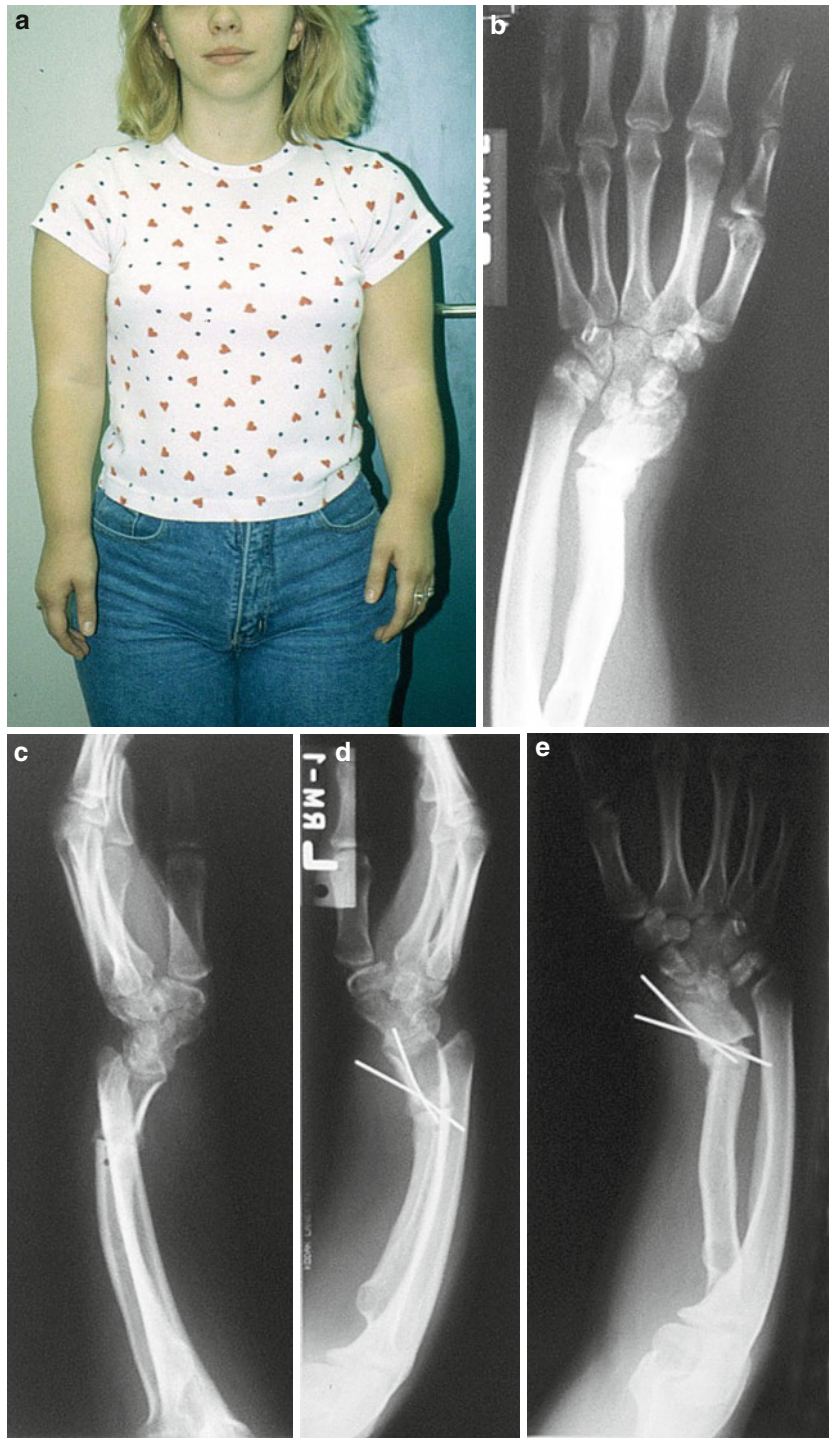

Fig. 1 (**a**–**e**) A young lady with Leri–Weill syndrome showing disproportionate short stature, short forearms and legs, and Madelung deformity of the wrists. Radiographs illustrate typical Madelung deformity (curved radius and ulna with triangular configuration) corrected by surgery

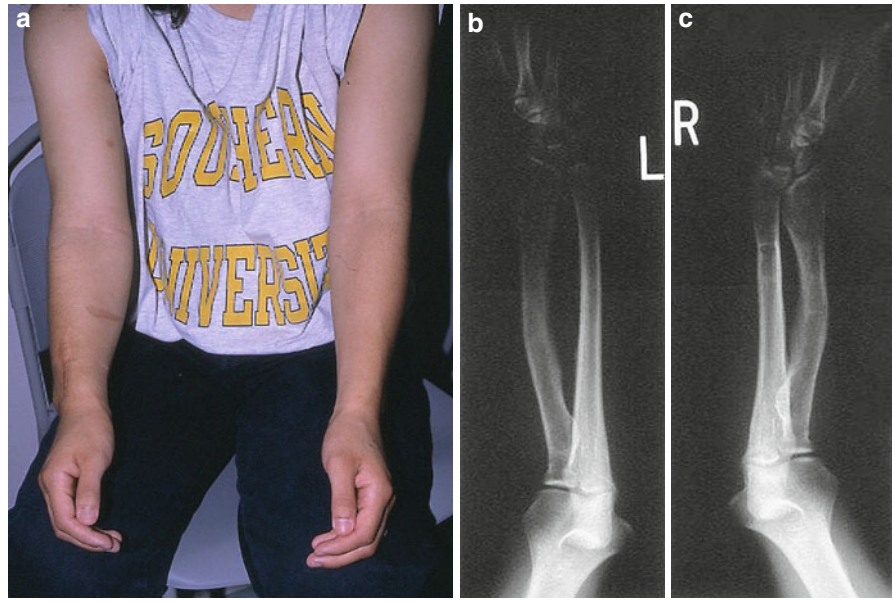

Fig. 2 (**a**–**c**) A young lady with Leri–Weill syndrome with short forearms and Madelung deformity demonstrated by radiographs

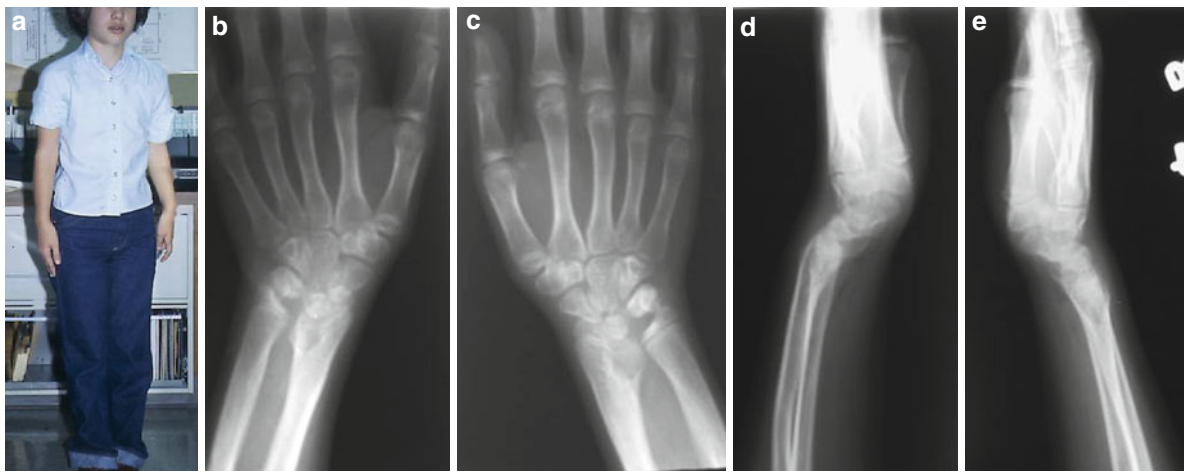

Fig. 3 (**a**–**e**) A young lady with Leri–Weill syndrome showing disproportionate short stature, short forearms and legs, and Madelung deformity illustrated by radiographs

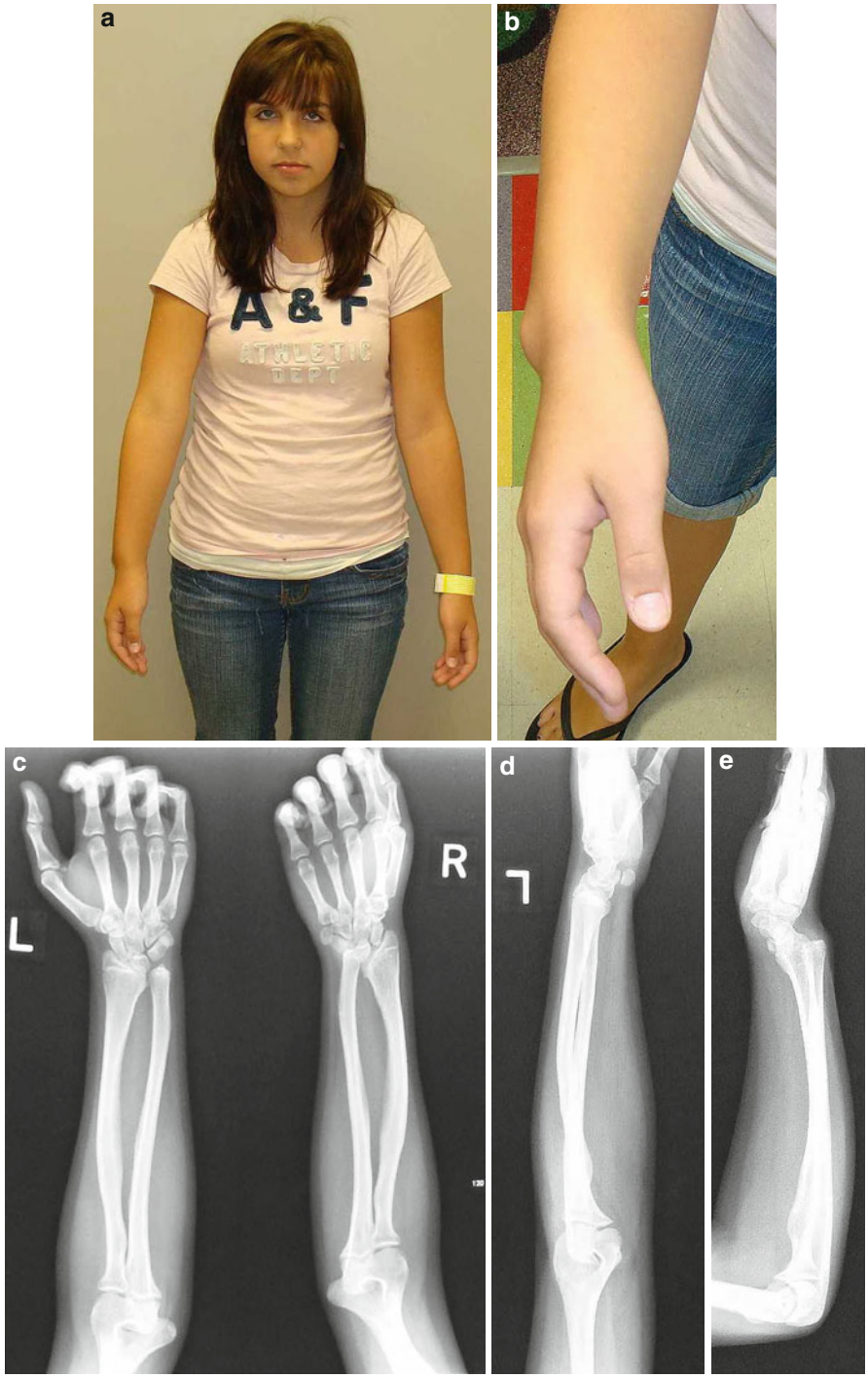

Fig. 4 (**a**–**e**) A 14-year-old girl with Leri–Weill syndrome showing disproportionate short stature, short forearms and legs, and Madelung deformity of the wrists. Radiographs illustrate typical Madelung deformity (curved radius and ulna with triangular configuration)

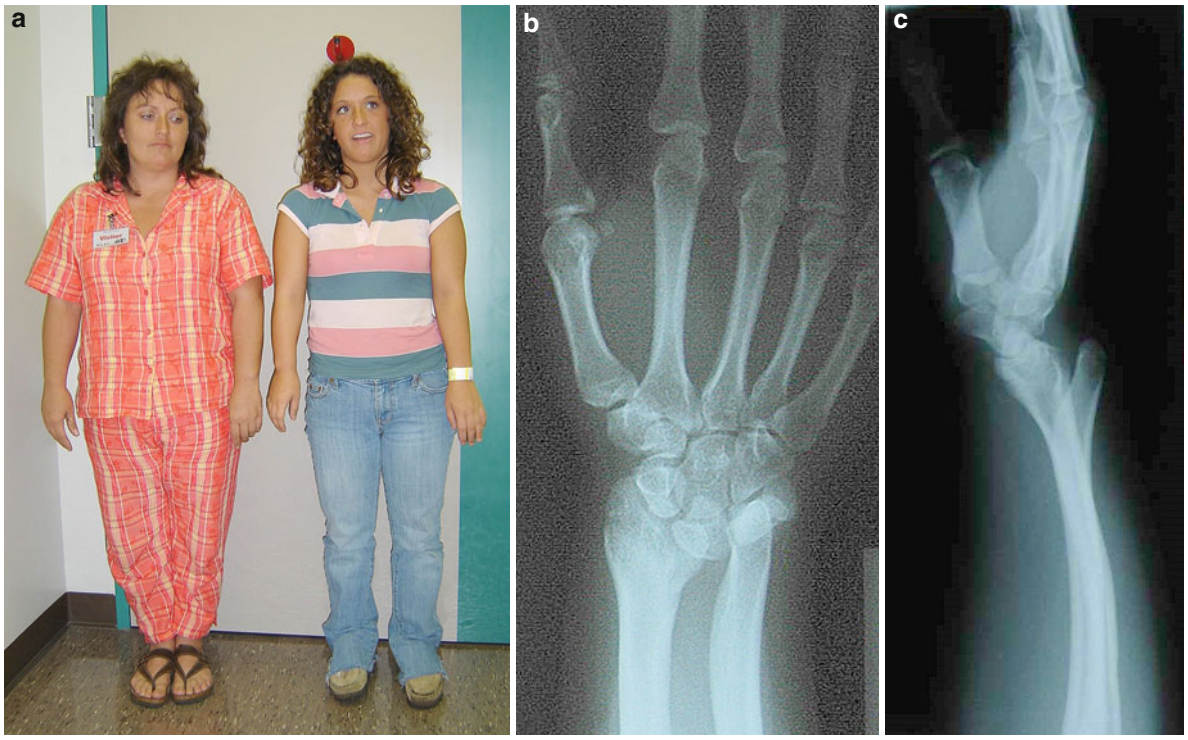

Fig. 5 (**a**–**c**) Mother and daughter with Leri–Weill syndrome with typical phenotype and wrist radiographs

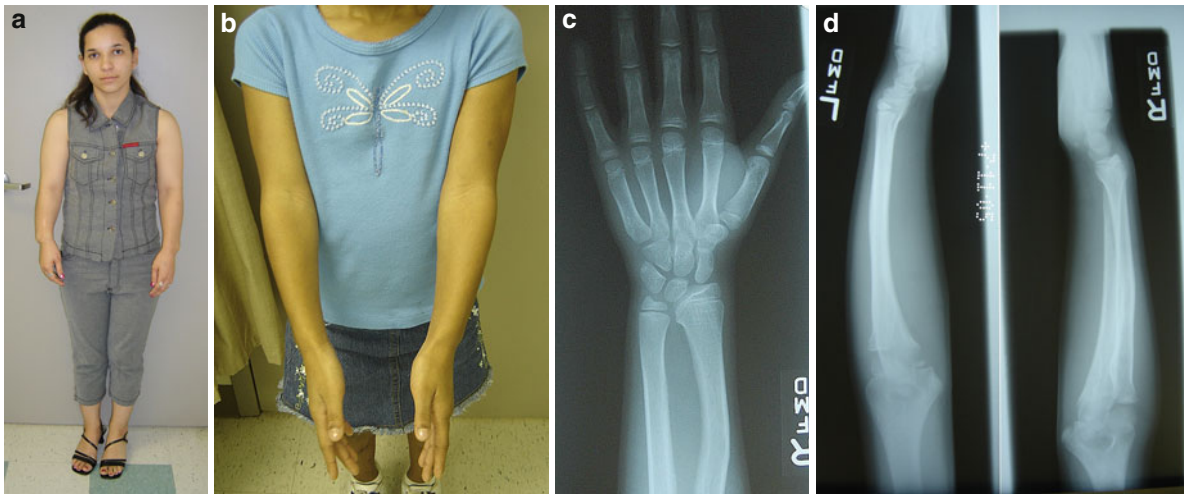

Fig. 6 (**a**–**d**) Another mother and daughter with Leri–Weill syndrome and forearm radiographs of the daughter

Fig. 7 (**a**–**m**) Two sibs with Langer mesomelic dysplasia showing severe mesomelic dwarfism, Madelung deformities, and radiographic features of bowed and foreshortened radius and ulna, hypoplastic/aplastic fibula, and short and thick tibia. Both parents have dyschondrosteosis (Espiritu et al. 1975a, b)

Fig. 8 (**a**, **b**) Radiograph of the mother of above two children showing typical Madelung deformity

Dysmelia

Dysmelia is a widely accepted term used to define a group of malformations in which there is hypoplasia, and partial or total aplasia of the tubular bones of the extremities, ranging from isolated peripheral hypoplasia to complete loss of the extremity. The condition is commonly known as limb deficiency or limb reduction defect. The prevalence rate for all types of limb deficiency is 0.69 per 1,000 (McGuirk et al. 2001).

Synonyms and Related Disorders

Amelia; Ectromelia (ectrodactyly); Limb deficiency/reduction; Phocomelia

Genetics/Basic Defects

1. Causes: heterogeneous
   a. Known syndromes
      i. Holt-Oram syndrome
      ii. Fanconi syndrome
      iii. Split hand deformity
      iv. EEC syndrome
      v. Thrombocytopenia-absent radius (TAR) syndrome
   b. Chromosome abnormalities
   c. Teratogens
      i. Thalidomide (Tseng et al. 1996; Radomsky and Levine 2001)
         a) A hypnosedative drug, introduced and marketed as Contergan in Germany in the 1950s
         b) Promoted as a safe sedative and was found to be useful as an antiemetic during pregnancy, resulting in its widespread use throughout Europe in late 1960
         c) Has been used in the past few decades in a variety of dermatologic conditions (e.g.,erythema nodosum leprosum, prurigo nodularis, actinic prurigo, discoid lupus erythematosus, aphthous stomatitis, Behcet syndrome, and graft-versus-host disease)
         d) Side effects: teratogenicity and peripheral neuropathy
         e) Producing a symmetrical pattern of deficiency (or polydactyly) on the preaxial side of both arms and legs
      ii. Misoprostol (prostaglandin E1 analog)
         a) Asymmetrical digit loss
         b) Constriction rings
         c) Syndactyly
   d. Fetal constraint
      i. Ectopic tubal gestation
      ii. Uterine structural anomalies
      iii. Early amnion rupture
   e. Vascular disruption
      i. Early chorionic villous sampling
         a) Symmetrical digit loss
         b) Constriction rings
         c) Syndactyly
      ii. Dilation and curettage
      iii. Exposure to ergotamine
      iv. Trauma to the abdomen and placenta
   f. Unknown causes

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2. The pattern of malformation in dysmelia (Henkel and Willert 1969)
   a. A diminution of skeletal material
   b. Disturbance of maturation of remaining skeletal elements
   c. Relationship of the malformed extremities to each other
3. A diminution of skeletal material: common to all malformations of dysmelia
   a. Reduction tendencies of individual bones: The reduction of the skeletal material of the individual bone follows a certain direction and sequence:
      i. Thumb: The reduction tendency of the thumb directs from proximal to distal:
         a) Hypoplastic tubular bones of the thumb and the first metacarpal in the mildest cases
         b) Reduction of skeletal material beginning at the base of the first metacarpal in the more severe cases
         c) The shaft of the thumb becomes aplastic with increasing severity
         d) The last remnant of the first metacarpal is its head, followed by defective proximal phalanx.
         e) Preservation of the terminal phalanx until, in total aplasia, all bones of the thumb disappear
      ii. Big toe and first metatarsal: the reduction tendency same as the thumb
      iii. Radius and tibia: The reduction tendency directs from distal to proximal:
         a) Hypoplasia: the mildest degree of malformation of the radius or the tibia
         b) A defect seen in the distal part of the metaphysis with increasing severity, extending in a proximal direction with more severe deformities
         c) The head disappears last, before the radius or tibia becomes totally aplastic.
      iv. Humerus and femur: The reduction tendency directs from proximal to distal:
         a) Hypoplastic: the mildest cases of the axial form of ectromelia
         b) A defect of bone at the proximal end (just distal to the head of the humerus or in the region of the neck and the trochanter in the femur) in more pronounced cases
         c) Distal epiphysis represents the last part of the humerus or the femur until it disappears in total aplasia.
   b. Reduction tendency of the limb as a whole:
      i. Upper limb
         a) Mild manifestations of the deformity restricted to the radial ray of the hand
         b) With increasing severity, the radius becomes involved and only after the radius is either completely absent or its remnants have fused with ulna is the humerus affected.
      ii. Lower limb
         a) Impairment of the tibia and the tibial ray in mild cases
         b) The tibia need not be totally absent and its remnants need not be fused before the femur shows signs of reduction.
         c) The isolated malformations of the femur have been observed without impairment of the distal part of the limb.
      iii. Coincidental impairment of the shoulder and pelvic girdles with the reduction of the limb mass
         a) The degree of the impairment dependents on the severity of the humeral or femoral defect.
         b) Most pronounced in phocomelia and amelia
      iv. Reduction of the hand and fingers
         a) Strictly dependent on the severity of the defect of the skeleton of the arm
         b) A decrease in the number of remaining fingers as the defect of the skeleton of the arm increases
         c) Radial hypoplasia: All fingers may be present; their number is reduced to four or even three in the axial types and very often to one in phocomelia.
         d) The reduction of the hand starting at the thumb and progressing from the radial to the ulnar side, so that with increasing severity of the arm deficiency, the index, middle, and ring fingers are absent.
      v. Reduction of foot in dysmelia
         a) Reduction progresses from the tibial to the fibular rays.
         b) Isolated malformations of the tibial ray: extremely rare in dysmelia

c. The axis of malformation in dysmelia:
   i. Combination of the humerus, radius, and radial ray of the hand in an axis of malformation within the skeleton of the upper extremity, sparing the ulnar
   ii. Same combination seen in the lower extremity, where the axis is formed by the femur, the tibia, and the tibial ray of the foot, sparing the fibula
   iii. In the short axial types, the ulna or the fibula is the only long bone of the extremity that still exists.
d. Fusion of the adjacent bones:
   i. The skeletal elements undergoing fusion: always hypoplastic or partially aplastic
   ii. Fusion occurring in parallel bones (carpals, tarsals, metacarpals, metatarsals, radius, and ulna) or in bones arranged longitudinally (phalanges, humerus, and ulna)
   iii. Tendency toward synostosis in the lower extremity appears to be limited to the bones of the foot.

4. Disturbance of maturation of remaining skeletal elements
   a. Retardation of cartilage ossification in bones not directly involved in the defect
   b. Ossification centers far away from the part directly involved tend to ossify in a delayed manner.
5. Relationship of the malformed extremities to each other
   a. Bilateral and symmetrical in manifestation in most cases of amelia
   b. Presence of lower limbs is observed in most patients with dysmelia of the upper extremity, even if the arms are phocomelic or amelic.

Clinical Features

1. Classification of dysmelia (Henkel and Willert 1969)
   a. Ectromelia:
      i. Definition: used to include those dysmelia in which the radius and the tibia with their peripheral rays and the humerus or the femur are involved.
      ii. Classification (Henkel and Willert 1969): There is a need to subdivide into the distal, axial, and proximal forms of ectromelia because there are differences in manifestation and severity of skeletal abnormality and in some cases, synostosis occurs as well as reduction.
         a) Distal form of ectromelia
         b) Axial form of ectromelia
         c) Proximal form of ectromelia
   b. Phocomelia:
      i. Definitions
         a) Used to include those dysmelia in which no remnants of long bones are seen between the limb girdle and the peripheral part (hands and foot)
         b) Used to describe the congenital anomaly in which a limb is represented by a flipper-like appendage
      ii. Classification (Frantz and O'Rahilly 1961)
         a) Type I: complete phocomelia (hand or digits attached directly to trunk)
         b) Type II: proximal phocomelia (Forearm bones between hand and trunk)
         c) Type III: distal phocomelia (hand attached directly to humerus)
      iii. Unclassifiable limbs (Tytherleigh-Strong and Hooper 2003)
         a) Type A: an abnormal humerus with an abnormal single forearm bone
         b) Type B: an abnormal humerus with an abnormal radius and ulna
         c) Type C: an abnormal humerus fused to a forearm bone or bones
   c. Amelia: used to include the most severe degree of dysmelia in which there is total loss of an extremity
2. Distal form of ectromelia
   a. Confined to the distal part of the extremity
   b. Involving the radial ray of the hand and the radius only
      i. Thumb type: the mildest degree of dysmelia, affecting the first ray of the hand only with the following two different manifestations:
         a) Triphalangism of the thumb
         b) Hypoplasia of the thumb
      ii. Radial type: sparing the ulnar
         a) Hypoplasia of the radius
         b) Hypoplasia of the radius with radioulnar synostosis
         c) Partial aplasia of the radius
         d) Partial aplasia of the radius with radioulnar synostosis
         e) Total aplasia of the radius

c. Involving the tibial ray of the foot and the tibia only
   i. Big toe type
      a) Triphalangism of the big toe
      b) Duplication of the big toe
   ii. Tibial type: sparing the fibula
      a) Hypoplasia of the tibia
      b) Partial aplasia of the tibia
      c) Total aplasia of the tibia

3. Axial form of ectromelia
   a. Involvement of the distal as well as the proximal part of the limb
      i. Involving the radius, the radial ray of the hand, and the humerus
         a) Sparing the ulnar
         b) The malformed radius: hypoplastic, partly aplastic, or totally aplastic
         c) The remnants of the radius in partial aplasia: regularly fused with the ulna, presenting as radioulnar synostosis
      ii. Involving the tibia, the tibial ray of the foot, and the femur
         a) Sparing the fibula
         b) The remnant of the tibia not showing tendency toward synostosis
   b. The different degrees of reduction of the humerus or the femur leading to the upper and lower limb types:
      i. Upper limb type
         a) Long axial type of the arm: hypoplasia or partial aplasia of the humerus with partial aplasia of the radius and radioulnar synostosis or with total aplasia of the radius
         b) Intermediate axial type of the arm: subtotal aplasia of the humerus with partial aplasia of the radius and radioulnar synostosis or with total aplasia of the radius
         c) Short axial type of the arm: total aplasia of the humerus with partial aplasia of the radius and radioulnar synostosis or with total aplasia of the radius
      ii. Lower limb type
         a) Long axial type of the leg: hypoplasia or partial aplasia of the femur with partial or total aplasia of the tibia
         b) Intermediate axial type of the leg: subtotal aplasia of the femur with partial or total aplasia of the tibia
         c) Short axial type of the leg: total aplasia of the femur with partial or total aplasia of the tibia

4. Proximal form of ectromelia
   a. Can be found only in the lower limb
   b. No parallel defect in the upper limb
   c. Only involves the proximal part of the lower limb, the femur, which can display all different degrees of reduction, leading to the following subtypes:
      i. Long proximal type: hypoplasia of the femur, coxa vara or partial aplasia of the femur without impairment of the distal part of the limb
      ii. Intermediate proximal type: subtotal aplasia of the femur without impairment of the distal part of the limb
      iii. Short proximal type: total aplasia of the femur without impairment of the distal part of the limb

5. Phocomelia
   a. Absent humerus, radius, and ulna or femur, tibia, and fibula
   b. Remainder of the extremity
      i. Consisting of a malformed hand formed by one, two, or three ulnar finger rays and ulnar parts of the carpus or of a similarly affected foot
      ii. Directly attached to a hypoplastic shoulder girdle or to a misshapen pelvis

6. Amelia
   a. The most severe form of dysmelia
   b. Total absence of the arm or the leg
   c. Shoulder girdles: hypoplastic in the absence of the arms
   d. Pelvis: deformed in a box-like shape in the absence of the legs

7. Differential diagnosis (Tseng et al. 1996; Radomsky and Levine 2001)
   a. Transverse limb defects
      i. Adam-Oliver syndrome
      ii. Amniotic band sequence
      iii. Oromandibular limb hypogenesis syndrome
      iv. Poland anomaly
      v. Fetuses with homozygous α-thalassemia
   b. Preaxial limb defects
      i. Chromosome syndromes
      ii. Facio-radial syndromes (e.g., Nager syndrome)
      iii. Hemato-radial syndromes
         a) Aase syndrome
         b) Fanconi anemia
         c) TAR syndrome

iv. Holt-Oram syndrome
v. Poland anomaly
vi. Roberts syndrome
vii. VATER association

c. Central limb defects
i. EEC syndrome
ii. Poland anomaly

d. Postaxial limb defects
i. Cornelia de Lange syndrome
ii. Facio-ulnar syndromes (e.g., Miller syndrome)
iii. Femur-fibula-ulna complex
iv. Ulnar mammary syndrome

e. Amniotic band syndrome and other mechanical and constraint problems
i. Digital constrictions and amputations
ii. Transverse amputations of the distal and proximal limbs, with a normal limb above the amputation
iii. Amelia

f. Vascular compression, disruption thrombosis, embolization
i. Transverse amputations
ii. Postaxial and preaxial limb reduction defect
iii. Femoral hypoplasia
iv. Digital amputation or hypoplasia
v. Poland anomaly

g. Genetic diseases
i. Many dominant and recessive syndromes
a) Bilateral and unilateral limb reduction defect of preaxial or postaxial type
b) Ectrodactyly
c) Monodactyly
ii. Limb reduction defects as features of many different genetic disorders, such as absent radius with absence/hypoplasia of the thumb

h. Cytogenetic abnormalities (e.g., del(13q) syndrome and trisomy 18 syndrome)
i. Severe limb hypoplasia
ii. Polydactyly
iii. Absent thumb
iv. Absent radius
v. Other multiple congenital anomalies

i. Thalidomide embryopathy (Radomsky and Levine 2001)
i. Deformities of the upper and lower extremities: grossly symmetric, although opposite limbs are often unequally affected to some degree
a) Amelia
b) Phocomelia
c) Bone hypoplasia
d) Absence of bones
ii. Abnormalities of the external ears
a) Anotia
b) Micro pinna
c) Small or absent auditory canals
iii. Abnormalities of the eyes
a) Anophthalmia
b) Microphthalmos
c) Coloboma
d) Cataracts
iv. Face
a) Hypoplastic nasal bridge
b) Choanal atresia
v. CNS malformations
a) Facial nerve paralysis
b) Deafness
c) Marcus Gunn or jaw-winking phenomenon
d) Crocodile-tear syndrome
e) Seizure disorder
vi. Respiratory tract anomalies
a) Laryngeal and tracheal abnormalities
b) Abnormal lobulation of the lungs
vii. Cardiovascular anomalies
a) Capillary hemangioma, extending from dorsum of the nose to the philtrum in the midline
b) Congenital heart diseases (conotruncal defects)
viii. Gastrointestinal anomalies
a) Upper intestinal atresia
b) Congenital absence of the gall bladder and the appendix
c) Anal stenosis
d) Inguinal hernias
ix. Renal anomalies
a) Abnormal rotation of the kidney
b) Pelvic position of the kidneys
c) Horseshoe kidney
d) Hydronephrosis
e) Double ureter
x. Genital anomalies
a) Double vagina
b) Vaginal atresia

c) Rectovaginal fistula
d) Cryptorchidism
xi. Mortality: 40% at or shortly after birth
j. Warfarin and diphenylhydantoin
i. Digital hypoplasia
a) Usually mild
b) Can be severe
ii. Limb hypoplasia due to chronic exposure throughout gestation, usually very mild
k. Maternal diabetes
i. Femoral hypoplasia
ii. Sacral agenesis

Diagnostic Investigations

1. Radiography (Cobben et al. 1994)
   a. Evaluate limb defects
   b. Evaluate non-limb skeletal defects
2. Diagnostic protocol for preaxial defects
   a. Blood count including thrombocytes
   b. Hb F (electrophoresis)
   c. Urine sediment
   d. Renal sonography
   e. Echocardiography
   f. Chromosome analysis
   g. Audiologic evaluation
   h. Ophthalmologic evaluation

Genetic Counseling

1. Recurrence risk (Cobben et al. 1994)
   a. Patient's sib
      i. Genetic syndromes: depending on the inheritance pattern of the disorder
      ii. Chromosome abnormalities: about 1% unless the parent carries a translocation
      iii. Environmental factors: not increased unless the mother exposes to the teratogen during pregnancy
      iv. Non-syndromic nonfamilial reduction defects of one limb
         a) Transversal: <1%
         b) Postaxial: <1%
         c) Preaxial: Low
         d) Central: low
      v. Non-syndromic nonfamilial reduction defects of more than one limb
         a) Transversal: probably low
         b) Postaxial: probably low
         c) Preaxial: unknown
         d) Central: unknown
   b. Patient's offspring
      i. Genetic syndromes: depending on the inheritance pattern of the disorder
      ii. Chromosome abnormalities: patients usually not surviving to reproduction
      iii. Environmental factors: not increased unless patient exposes to the same teratogen during pregnancy
      iv. Non-syndromic nonfamilial reduction defects of one limb
         a) Transversal: <1%
         b) Postaxial: <1%
         c) Preaxial: probably low
         d) Central: probably low
      v. Non-syndromic nonfamilial reduction defects of more than one limb
         a) Transversal: possibly low
         b) Postaxial: possibly low
         c) Preaxial: unknown
         d) Central: autosomal dominant
2. Prenatal diagnosis
   a. Transvaginal sonography: an important element in the evaluation of any first trimester limb deficiencies
   b. Second trimester ultrasonography to detect limb deficiencies and other associated anomalies
   c. Chromosome analysis from amniocentesis or CVS to rule out chromosome anomaly
3. Management
   a. Avoid using teratogenic agents during pregnancy
   b. Management of malformation of the upper extremities
      i. Bilateral upper extremity: amelia and/or phocomelia
         a) Good prosthetic fitting of children based primarily on relating prosthetic function to the functional needs of the patient to be fitted
         b) Satisfactory foot function, a prerequisite to the prosthetic habilitation of the severe bilateral upper limb problem in children

c) Compensatory prehension patterns developed by the feet, helpful particularly in total toilet care and total dressing and undressing

ii. Upper extremity: paraxial hemimelica
   a) Passive stretching
   b) Application of splints to stabilize the wrists

iii. Bilateral transverse hemimelia: fit with standard prostheses with hooks as terminal devices

c. Management of malformation of the lower extremities
   i. Lower extremity phocomelia
      a) Fit with a special bucket on a pair of short skis to develop balance
      b) Prostheses to help walking
   ii. Bilateral transverse lower hemimelia: fit with conventional appliances

d. Occupational therapy: exercise and other treatment of the upper extremities to increase strength and dexterity to prepare to operate prostheses

e. Prosthetic training of the children

f. Parents' contribution
   i. Observation of the child's training session
   ii. Parent to learn to:
      a) Put on and remove prostheses
      b) Care and encourage use of the prostheses
      c) Cleanse the stump

g. Prosthetic devices
   i. Every effort to be made to develop a prosthesis that will compensate for the absence of functions and restore independence to the greatest possible degree
   ii. Main objectives
      a) To assist the child to develop a normal body image
      b) To construct a prosthesis based on sound anatomical principles which has an adequate range of motion
      c) To fit the prosthesis early so that, at a few months of age, the child unconsciously accepts it as a part of his body

h. Psychosocial counseling
   i. To assist parents to cope with the situation
   ii. To explain the plan of treatment to parents
   iii. Overall success of a given family in accepting and adjusting to a congenital deformity: related to its educational level and the usual pattern of behavior of its members under stress

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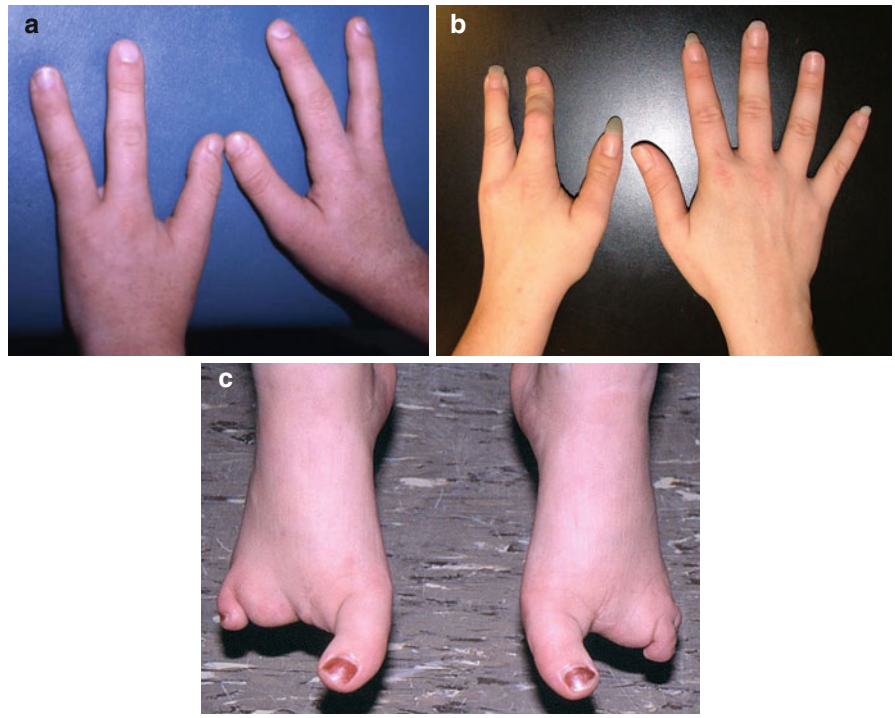

Fig. 1 (**a**–**c**) Ectrodactyly of hands and feet in three patients showing symmetric and asymmetric anomalies

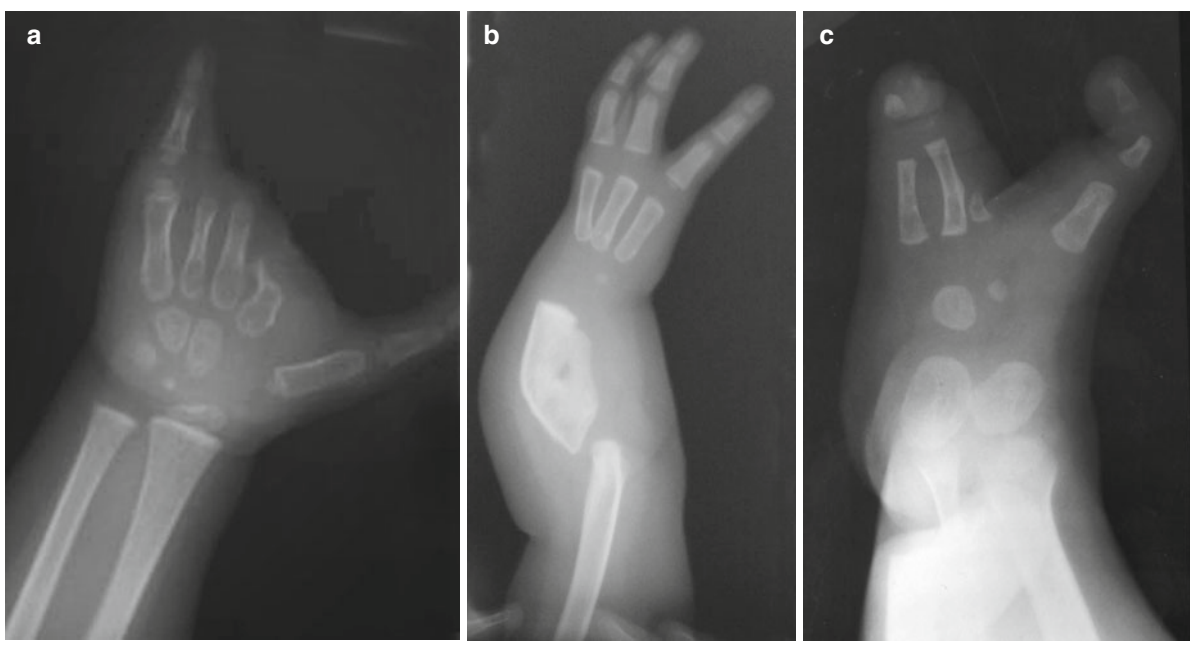

Fig. 2 (**a**–**c**) Radiographs of ectrodactyly (two hands and a foot) in three patients showing different types of ectrodactyly

Fig. 3 (**a**–**c**) An embryo with phocomelia showing deficient limbs, illustrated by radiograph

Fig. 4 (**a**, **b**) A neonate with amelia of the upper limbs and reduction malformations of the lower limbs

Fig. 5 A child with amelia showing complete absence of upper extremities

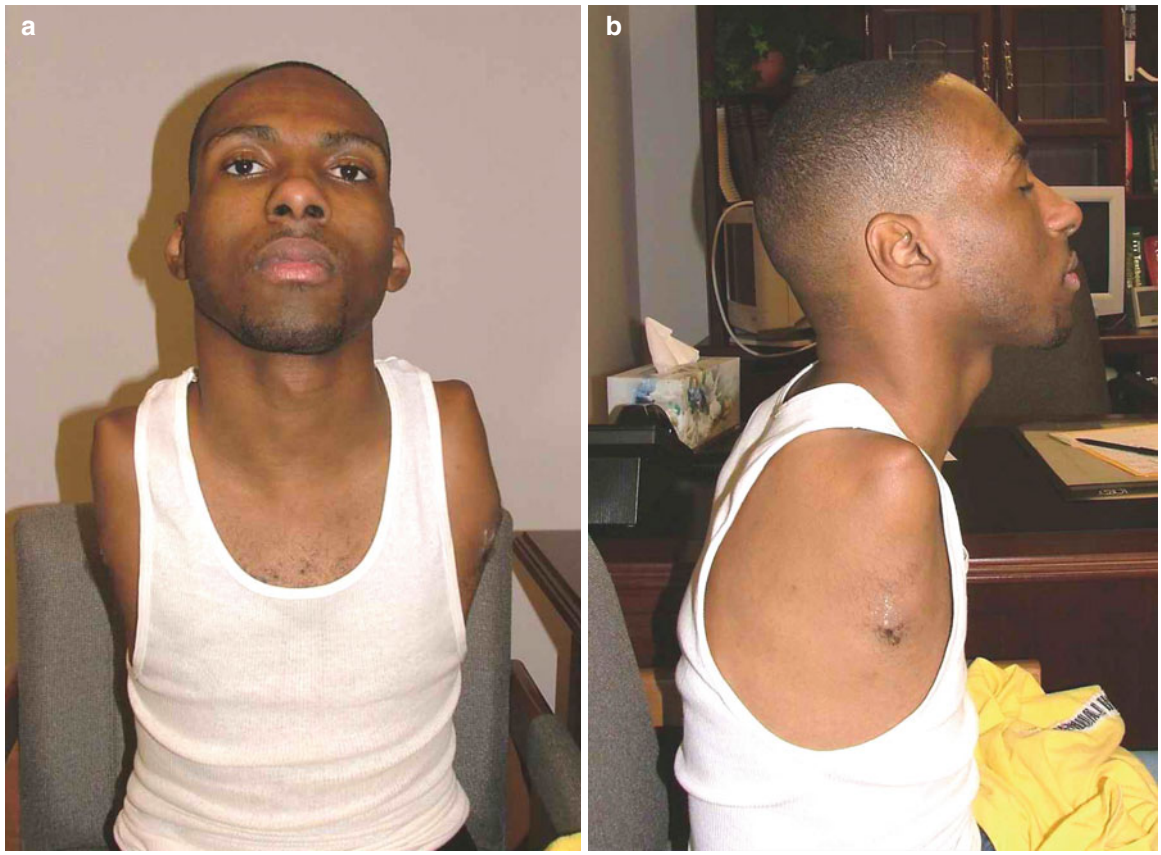

Fig. 6 (**a**, **b**) A patient with amelia of the upper extremities. He is intelligent, uses his chin and shoulder to write, and drives a car by using one foot to turn the driving wheel and one foot to pedal the accelerator and brake

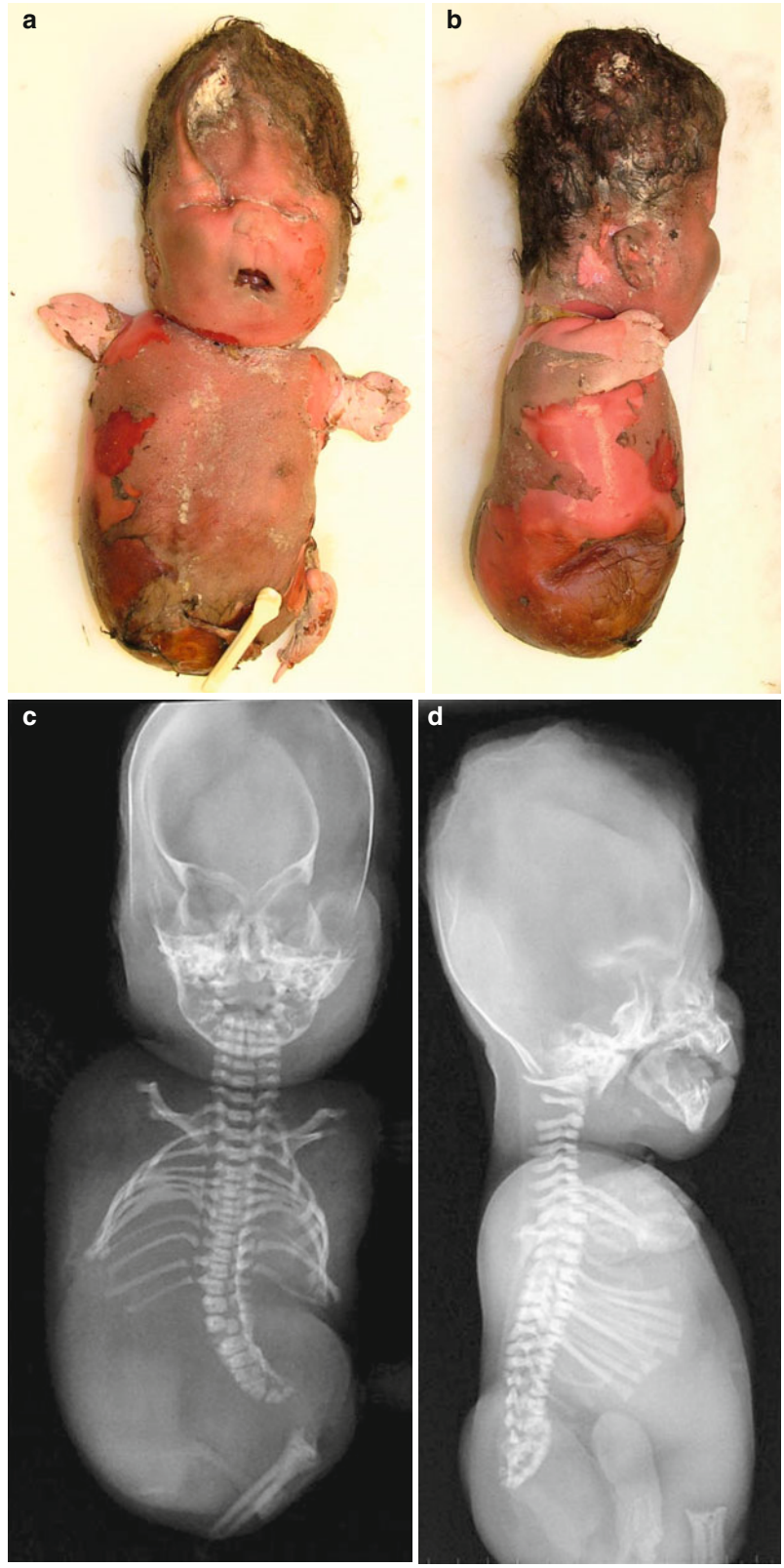

Fig. 7 (**a**–**d**) A macerated stillborn with phocomelia. Her upper extremities consist of hands attached to the shoulders with absence of the long bones. Her left lower extremity consists of a foot attached via thin twisted skin to the pelvic area with absence of the long bones. Right lower extremity was completely absent. There were severe dysplastic vertebrae, fusions of ribs, and absence of pelvic bones. In addition, the infant had blind vagina, absent right kidney, rudimentary left kidney, hypoplastic lungs, and microphthalmia

Fig. 8 (**a**–**g**) A girl and a lady with phocomelia showing flipper-like hands, illustrated by radiographs

Fig. 9 An infant with transverse reduction of the lower extremities

Fig. 10 An infant with unilateral transverse reduction of left upper extremities (intrauterine amputation), constriction ring of the left big toe, and syndactyly of the toes of both feet, secondary to amniotic band syndrome

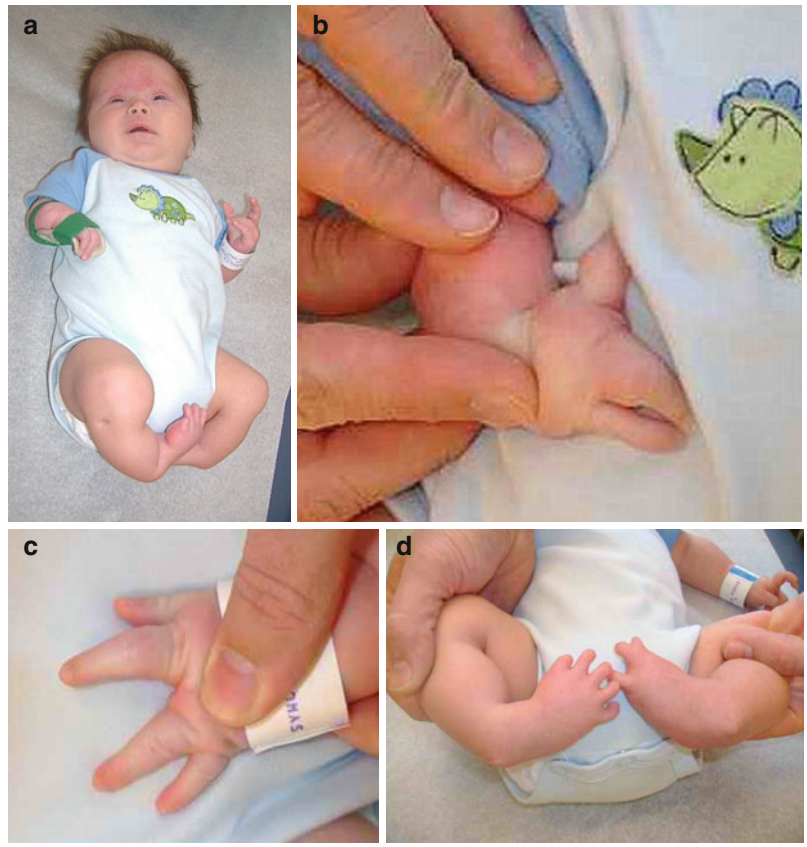

Fig. 11 (**a**–**d**) An infant with reduction malformations of both upper and lower extremities

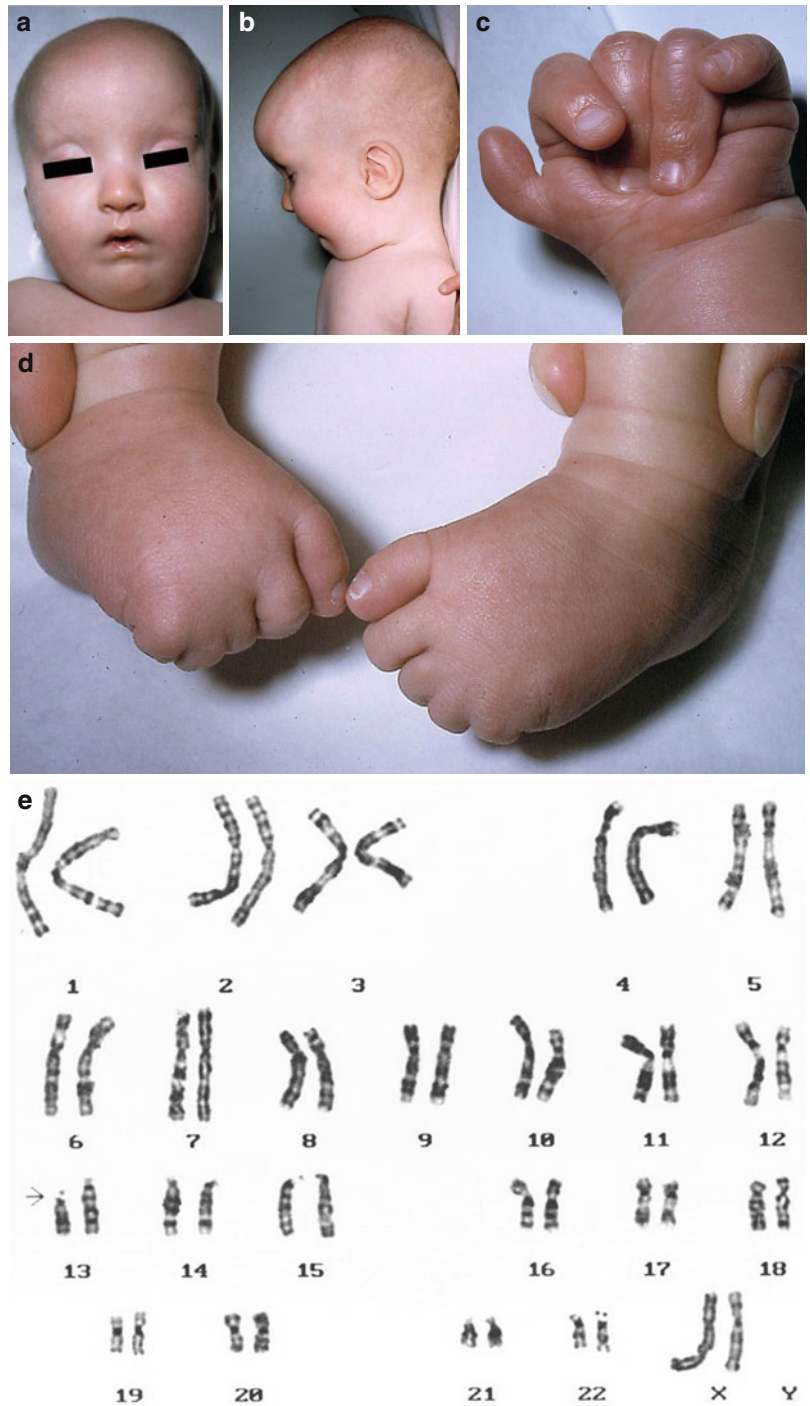

Fig. 12 (**a**–**e**) A neonate with del(13q) syndrome showing hypoplastic thumbs, syndactyly of toes, in addition to multiple congenital anomalies. The karyotype shows the deletion of 13q

Fig. 13 Radiograph of another neonate with del(13q) syndrome showing limb reduction anomalies of the upper extremities

Fig. 14 A neonate with trisomy 18 syndrome showing limb reduction defects of the upper extremities in addition to multiple congenital anomalies

Dysplasia Epiphysealis Hemimelica

Dysplasia epiphysealis hemimelica is a rare osteocartilaginous overgrowth involving one or multiple epiphyses or ossification centers, usually in the lower extremity on one side of the body. In 1926, Mouchet and Belot described a condition called tarsomegaly, which Trevor, later in 1950, called tarso-epiphyseal aclasis. As the tarsal bones are not the only bones involved, Fairbank in 1956 used the term dysplasia epiphysealis hemimelica. The term reflects the characteristic hemimelica involvement, typically affects either the medial or the lateral side of the epiphysis, with the medial side affected twice as frequently (Lang and Aztiuz 1997; Kuo et al. 1998; Araujo et al. 2006; Mann et al. 2010). The condition has been referred to as Trevor disease.

Synonyms and Related Disorders

Trevor disease

Genetics/Basic Defects

1. Inheritance:
   a. No known hereditary factor, except a report of a single family with seven members affected by different combinations of dysplasia epiphysealis hemimelica, intracapsular chondroma, extraskeletal osteochondroma, and typical osteochondroma (Hensinga et al. 1974)
   b. Male-to-female ratio: 3:1
2. Etiology and pathogenesis
   a. Etiology unknown
   b. A congenital disorder becoming clinically evident in the course of the development of the epiphyses
   c. Basic pathologic process: an abnormal proliferation of cartilage in an epiphysis, similar to osteochondroma

Clinical Features

1. Most frequent presentation: ages 2–14 years (birth to 63 years of age) (Gerscovich and Greenspan 1989)
2. Chief clinical signs
   a. Unilateral asymmetric bony hard swelling on the extremities
   b. Usually on the inner or outer aspect of the knee and/or ankle
   c. With or without pain
   d. With or without restriction of motion
   e. Slow progression
3. Apparent deformity
   a. Varus or valgus deformity depending on the site of involvement
   b. Genu valgum or varum depending on the site of involvement
   c. Flexion contracture
   d. Pes planus
   e. Pes equinus
4. Sites of involvement
   a. Lower extremities, more commonly affected than the upper extremities

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i. Four most common locations of involvement (Rosero et al. 2007)
a) Talus-calcaneus (22%)
b) Distal tibia-fibula (22%)
c) Proximal tibia (11%)
ii. Proximal tibial epiphysis
iii. Tarsal navicular
iv. First cuneiform
v. Middle and lateral cuneiforms
vi. Metatarsals
vii. Phalanges

b. Upper extremities: very uncommon involvement (Vanhoenacker et al. 1999; Takagi et al. 2000; Rosero et al. 2007)
i. Carpal bones
a) Scaphoid
b) Lunate
c) Capitate
d) Hamate
e) Trapezium
f) Trapezoid
ii. Metacarpals
iii. Phalanges
iv. Proximal radius
v. Proximal and distal ulna
vi. Proximal and distal humerus
vii. Glenoid cavity
viii. Coracoid process of the scapula

c. Pelvis
i. Acetabulum
ii. Pubic bone
iii. Iliac bone

5. Affected limb
a. May be longer than the unaffected one due to:
i. The enlargement of several ossification centers
ii. Increased diaphyseal length
b. May be shorter due to focal early closure of the epiphyseal plate
6. Quiescent following epiphyseal plate fusion
7. Prognosis
a. Relatively benign condition
b. Malignant degeneration has not been reported
8. Classification based on degrees of involvement (Azouz et al. 1985)
a. Localized form
i. Usually affecting the bones of the hindfoot or ankle
ii. Also may affect an epiphysis

b. Classical form
i. Characteristic hemimelic distribution seen in more than one area in a single lower extremity (two third of the reported cases), particularly:
a) Talus
b) Distal femoral epiphyses
c) Distal tibial epiphyses
ii. Lesion localized to the ankle and foot, called Mouchet and Belot type

c. Generalized or severe form
i. Involving a whole lower extremity from the pelvis to the foot or ankle
ii. Involving femoral head, symphysis pubis, or triradiate cartilage of the acetabulum

Diagnostic Investigations

1. Radiography (Gerscovich and Greenspan 1989)
a. Skeletal survey to look for sites of involvement
b. Earliest radiographic sign
i. Appearance of secondary centers of ossification adjacent to an epiphysis
ii. Slow enlargement of these centers eventually merging with each other and then with the epiphysis
c. Asymmetric hemimelic distribution of overgrowth of one side of epiphysis with irregular contour and ossification
i. Generally only half or part (either the medial or lateral half) of an epiphysis or ossification center affected
ii. Rarely involving the entire epiphysis
d. Overgrowth of adjacent bones
e. Adjacent (probably secondary) metaphyseal and growth plate involvement
i. Exhibiting widening and streak-like metaphysis (as in Ollier disease)
ii. Spur formation (as in osteochondroma)
f. Mature lesions showing enlargement of one side of an epiphysis, simulating as osteochondromatous mass or enlargement of one side of an ossification center
g. Epiphysis irregularly calcified and ossified
h. Joints usually deformed
i. Advanced bone age in unaffected epiphyses
j. Less common findings

   i. Loose bodies in affected joints
   ii. Osteochondral fractures
   k. Bilateral involvement extremely rare
2. CT of the lesions
   a. Improving diagnostic accuracy in the growing skeleton
   b. Demonstration of the anatomic relationship of the involved structures
   c. Visualization of the soft tissues, bones, and tumorous mass
   d. Evaluation of the condition of the articular surfaces
3. MRI imaging (Keret et al. 1992; Peduto et al. 1999)
   a. To identify a definite plane of separation between the pathologic osteochondromatous mass and the normal epiphysis
   b. To accurately identify bony and cartilaginous structural abnormalities in multiple planes noninvasively without ionizing radiation
   c. To identify secondary changes in menisci, tendons, ligaments, and muscles
4. Histopathology
   a. Osteocartilaginous exostosis (with cartilaginous cap) arising from an epiphysis, apophysis, or round bone (Oates)
   b. Nests of cartilage cells showing active proliferation during growth of the lesions
   c. Diminishing amount and activity of the cartilage as the lesions mature
   d. Increased size of lesions in adults showing areas of actively proliferating cartilage
   e. Infrequently with an area of necrosis, presumably caused by inadequate nutrition
   f. Histological findings (Bahk et al. 2010)
      i. Identical to those of osteochondromas
      ii. Presence of caps of disorganized hyaline cartilage
      iii. Endochondral ossification of varying degrees underlying the caps

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: not increased
2. Prenatal diagnosis: not been reported
3. Management
   a. Observation in asymptomatic cases; no cases of malignant transformation reported (Kuo et al. 1998)
   b. Surgical excision of the mass or corrective osteotomy generally recommended for the following lesions:
      i. Causing disabling pain
      ii. Interfering function
      iii. Increasing deformity of the involved joint
   c. Simple excision indicated if the cartilaginous overgrowth is not in the weight-bearing articular surface
   d. Extraarticular osteotomy indicated for correction of varus/valgus deformities if the arthrogram shows the smooth joint surface
   e. Anticipate recurrence of the angular deformity after the corrective osteotomy if the growth plate at the affected joint is open and active

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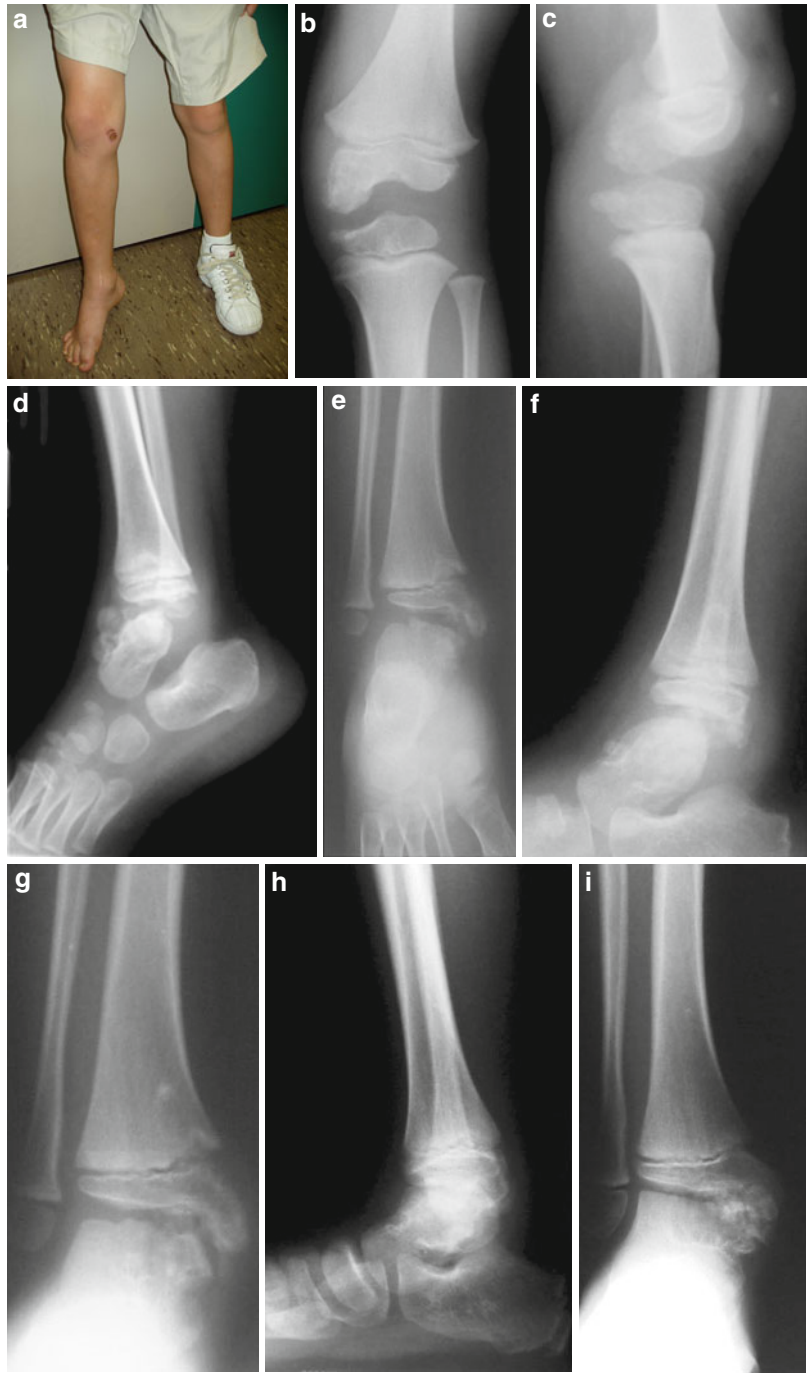

Fig. 1 (**a**–**i**) A 9-year-old boy with dysplasia epiphysealis hemimelica showing hard swellings on the inner sides of the knees and the ankle of the right lower extremities. The knee radiographs at 9 years of age show the secondary ossification center merged with the medial side of the epiphyses of the distal femur and that of the proximal tibia. The radiographs of ankles at 4, 5, and 9 years of age show irregularly calcified mass extending from medial malleolus of the distal tibia and involvement of the talus. The patient had bony protuberance of the right knee and right ankle without pain or restriction of motion. The age of onset was about 2 years of age

Fig. 2 A 5-year old boy was seen because of swollen right knee with complaint of knee pain and limping

Fig. 3 Note the swelling of the medial aspect of the right knee

Fig. 4 The knee radiograph shows second ossification center merged with the medial aspect of the epiphysis of the distal femur

Dystonia

Dystonia is characterized by sustained, nonsuppressible contractions of agonist and antagonist muscles, resulting in twisting and repetitive movements that typically lead to abnormal postures (Friedman and Standaert 2001; Brűggermann and Klein 2010).

Synonyms and Related Disorders

Dystonia (types 1–19); Primary (idiopathic) dystonia; Secondary dystonia

Genetics/Basic Defects

1. Genetically defined forms of the primary dystonias and dystonia-plus syndromes (Brűggermann and Klein 2010)
   a. Monogenic forms of dystonia have been assigned the acronym DYT according to the gene or gene locus involved
   b. This assortment of clinical rather than heterogeneous dystonias and dyskinesias is represented by a current list of 20 DYTs, in which monogenic forms of dystonia are included in chronological order based on first appearance in the literature
   c. Although this listing of DYTs can serve as an orientation, it does not represent a logical classification in the strict sense of the word. Rather, the monogenic forms can be pragmatically grouped as:
      i. Pure dystonias
         a) Part of the primary forms and thought to occur in the absence of neuropathologic changes
         b) Considered mainly to alter the function of neuronal basal ganglia circuits
      ii. Dystonia-plus syndromes: characterized by additional neurologic manifestations, such as parkinsonism and myoclonus (Albanese et al. 2006)
      iii. Paroxysmal dyskinesias: typically manifest episodically, dystonia usually is only one of several movement disorders present, and there are no interictal neurologic abnormalities
2. At least 19 different types of dystonia can be distinguished genetically as follows (Németh 2002; Brűggermann and Klein 2010):
   a. Dystonia type 1 (early-onset generalized primary torsion dystonia, Oppenheim dystonia)
      i. Autosomal dominant inheritance with reduced penetrance of about 30–40%
      ii. Locus: *DYT1* on chromosome 9q34
      iii. Mutations
         a) GAG deletion in the *DYT1* gene resulting in loss of Glutamic acid residues in the C-terminus of a novel ATP-binding protein, torsin A
         b) 18 base pair deletion resulting in loss of six amino acids (F323-Y328del) in a novel ATP-binding protein, torsin A

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b. Dystonia 2 (autosomal recessive torsion dystonia)
   i. Autosomal recessive inheritance
   ii. Locus: *DYT2* (chromosome map unknown)
c. Dystonia 3 (X-linked dystonia-parkinsonism, "lubag")
   i. X-linked recessive inheritance
   ii. Locus: *DYT3* on chromosome Xq13.1
d. Dystonia 4 (whispering dysphonia)
   i. Autosomal dominant inheritance
   ii. Locus: *DYT4* (chromosome map unknown)
e. Dystonia 5 (dopa-responsive dystonia-parkinsonism)
   i. Common autosomal dominant inheritance
      a) Locus: *GCH1* on chromosome 14q22.1–q22.2
      b) Caused by mutation in the *guanosine triphosphate cyclohydrolase I* gene, *GCH1*
   ii. Rare autosomal recessive form (Segawa syndrome)
      a) Associated with mutations in the tyrosine hydroxylase gene, *TH*
      b) Locus: *TH* on chromosome11p15.5
f. Dystonia 6 (adolescent-onset torsion dystonia of mixed type)
   i. Autosomal dominant inheritance
   ii. Locus: *DYT6* on chromosome 8p21-8q22
g. Dystonia 7 (adult-onset focal torsion dystonia)
   i. Autosomal dominant inheritance
   ii. Locus: DYT7 on chromosome 18p
h. Dystonia 8 (paroxysmal nonkinesigenic dyskinesia)
   i. Autosomal dominant inheritance
   ii. Locus: *DYT8* on chromosome 2q33-q25
i. Dystonia 9 (paroxysmal choreoathetosis with episodic ataxia and spasticity)
   i. Autosomal dominant inheritance
   ii. Locus: *DYT9* on chromosome 1p21-p13.3
j. Dystonia 10 (paroxysmal kinesigenic choreoathetosis)
   i. Locus: *DYT10* on chromosome 16p11.2-q12.1
   ii. Autosomal dominant inheritance
k. Dystonia 11 (myoclonus-dystonia)
   i. Autosomal dominant inheritance
   ii. Locus: *DYST11* on chromosome 7q21
   iii. Caused by mutations in the ϵ-sarcoglycan gene in most families
l. Dystonia 12 (rapid-onset dystonia-parkinsonism)
   i. Autosomal dominant inheritance
   ii. Locus: *DYT12* on chromosome 19q
m. Dystonia 13 (multifocal/segmental dystonia)
   i. Autosomal dominant inheritance
   ii. Locus: *DYT13* on chromosome 1p36
n. Dystonia 14: recently redefined as *DYT5*
o. Dystonia 15 (myoclonus-dystonia)
   i. Autosomal dominant inheritance
   ii. Locus: *DYT15* on chromosome 18p
p. Dystonia 16 (young-onset dystonia-parkinsonism)
   i. Autosomal recessive inheritance
   ii. Locus: *DYT16* on chromosome 2p
q. Dystonia 17 (autosomal recessive primary torsion dystonia)
   i. Autosomal recessive inheritance
   ii. Locus: *DYT17* on chromosome 20pq
r. Dystonia 18 (paroxysmal exertion-induced dyskinesia 2)
   i. Autosomal dominant inheritance
   ii. Locus: *DYT18* on chromosome 1p
s. Dystonia 19 (episodic kinesigenic dyskinesia 2)
   i. Autosomal dominant inheritance
   ii. Locus: *DYT19* on chromosome 16q
t. Dystonia 20 (paroxysmal nonkinesigenic dyskinesia 2)
   i. Autosomal dominant inheritance
   ii. Locus: *DYT20* on chromosome 2q

3. Secondary dystonia (Schlaggar and Mink 2003)
   a. Association with a number of disorders
      i. Hepatolenticular degeneration (Wilson disease)
         a) Dystonia in over a third of the patients
         b) Associated with lesions in the putamen in 80% of cases
      ii. Hallervorden–Spatz disease (pantothenate kinase-associated neurodegeneration)
      iii. Huntington chorea
      iv. Lesch–Nyhan disease
      v. Metachromatic leukodystrophy
      vi. Methylmalonic acidemia
      vii. Mitochondrial disorders
      viii. Ceroid lipofuscinosis
      ix. Gangliosidoses
      x. Glutaric aciduria
      xi. Ataxia telangiectasia
      xii. Niemann-Pick disease type C
      xiii. Early-onset parkinsonism

xiv. Corticobasal degeneration
xv. Certain forms of spinocerebellar ataxia
a) Spinocerebellar ataxia 3 (Machado–Joseph disease): The severity of the dystonic symptoms is related to the length of the trinucleotide repeat
b) Spinocerebellar ataxia 17 (caused by mutations in the thymine-adenine-thymine-adenine binding protein: Dystonia may be the presenting sign of the disorder
xvi. Other inherited disorders (Cloud and Jinnah 2010)

b. Other causes
i. Psychogenic
ii. Vascular lesions such as carotid occlusive disease and hemorrhagic stroke
iii. Anoxic brain injury (cerebral anoxia/hypoxia): a well-known cause of secondary dystonia
iv. Acute disseminated encephalomyelitis
v. Trauma
a) Head trauma: Dystonia is among the most common movement disorders following severe head injury
b) Peripheral trauma causing segmental dystonia
vi. Both acute and chronic use of dopamine blocking medications and other medications
a) Haloperidol
b) Resperidol
c) Fluphenazine
d) Thioridazine
e) Chlorpromazine
f) Metoclopramide
g) Phenytoin
h) Stonatrioran
vii. Other acquired and sporadic causes (Cloud and Jinnah 2010)

4. Pathophysiology: a new interpretive hypothesis involving multiple levels of the nervous system
a. Spinal cord: increased spinal motor neuron excitability in patients with generalized dystonia due to reduced presynaptic inhibition and compromised supraspinal inhibition systems
b. Basal ganglia: disturbed pattern of basal ganglia output neurons
c. Thalamus: disorganization of input–output properties and hyperactivity in thalamic neurons in two dystonic cynomolgus monkeys
d. Somato-sensory system: increased temporal discrimination thresholds for tactile stimuli
e. Sensorimotor integration and motor cortical function
i. Abnormal somatotopic arrangement of sensorimotor interaction
ii. Abnormal functioning of cortico-subcortical loops causing abnormalities of both intracortical inhibition and cortical excitability
5. Dystonia with unknown etiology

Clinical Features

1. Dystonia describes a symptom that may be part of many disorders with a variety of causes
a. An abnormal sustained posture that is often writhing or twisting in quality
b. Can be rapid or slow
c. Often painful
2. Classifications of dystonia
a. Classification based on distribution of dystonia
i. Primary/generalized dystonia
a) Occurs in childhood
b) Often begins focally in the legs and progresses to a generalized symptom involving the entire body
ii. Focal dystonia
a) May occur at any age
b) Typically starts in adulthood
c) Affects an isolated body area, such as hand and arm (writer's cramp), neck (cervical dystonia, previously known as spasmodic torticollis), vocal/laryngeal apparatus (dystonic adductor dysphonia or whispering dysphonia), mouth (oromandibular dystonia, musician's cramp), or eyelids (blepharospasm)
d) Multifocal dystonia (two or more noncontiguous parts affected)
iii. Segmental dystonia
a) May occur at any age
b) Typically starts in adulthood
c) Involves only the right or left side of the body

d) Cranial (two or more parts of cranial and neck musculature affected)
e) Axial (neck and trunk affected)
f) Brachial (one arm and axial; both arms, with or without neck, with or without trunk)
g) Crural (one leg and trunk; both legs, with or without trunk)

iv. Hemidystonia: affects ipsilateral arm and leg
v. Secondary dystonia
a) Can be generalized, focal, or segmental
b) Induced by a disease or ingested substance
c) Can occur at any time
d) Treated by identifying the underlying medical disorder or substance

b. Classification based on age of onset of dystonia
i. Early-onset dystonia
a) Often starts in a limb
b) Tends to generalize and frequently has a genetic origin
ii. Adult-onset dystonia
a) Usually spares the lower extremities
b) Frequently involves cervical or cranial muscles
c) A tendency to remain focal
d) Sporadic in most cases

3. Clinical characteristic in genetically defined forms of dystonia and dystonia-plus syndromes (Klein et al. 1999; Brűggermann and Klein 2010)
a. Dystonia type 1 (early-onset generalized primary torsion dystonia)
i. Early-onset torsion dystonia (onset usually childhood)
ii. May present as focal, usually in the limbs
iii. Often generalizes to other body parts as the disease progresses
b. Dystonia type 2 (autosomal recessive torsion dystonia)
i. Early onset
ii. Generalized or segmental torsion dystonia
c. Dystonia type 3 (X-linked dystonia-parkinsonism, "lubag") meaning "twist," a local dialect in the Island of Panay in Philippines)
i. Only described in individuals from the Philippines
ii. Usually males
iii. Onset usually adulthood
iv. Usually generalized dystonia
v. Parkinsonism (50% of cases) unresponsive to L-dopa
vi. Progressive neurodegenerative syndrome
d. Dystonia type 4 (whispering dysphonia)
i. Described in a single large Australian family
ii. Laryngeal and cervical dystonia
iii. Age of onset: 13–37 years
e. Dystonia type 5 (dopa-responsive dystonia-parkinsonism)
i. Childhood onset of dystonia
ii. Onset of dystonia in a limb, typically a leg, resulting in gait disturbance
iii. Gradual progression to generalized dystonia (usually more pronounced in the legs)
iv. Dystonia with concurrent or subsequent parkinsonism
v. Diurnal worsening of symptoms
a) Aggravation of symptoms toward the evening
b) Alleviation of symptoms in the morning after sleep
vi. A variety of atypical presentations
a) Generalized hypotonia
b) Proximal weakness
c) Gait disturbance
d) "Atypical cerebral palsy"
vii. A dramatic response to L-dopa
f. Dystonia type 6 (adolescent-onset torsion dystonia of mixed type)
i. Described in two Mennonite families
ii. Adolescent onset
iii. Mostly segmental torsion dystonia
iv. Focal or generalized (rare)
v. Cranial, cervical, or limb dystonia
g. Dystonia type 7 (adult-onset focal torsion dystonia)
i. Described in a single German family
ii. Adult-onset focal dystonia
iii. Torticollis
iv. Writer's cramp
v. Spasmodic dysphonia
vi. Blepharospasm

h. Dystonia type 8 (paroxysmal dystonic choreoathetosis)
   i. Variable age of onset (early childhood, adolescence or early adulthood)
   ii. Attacks of dystonia/choreoathetosis
   iii. Precipitated by stress, hunger, fatigue, alcohol, caffeine, nicotine, and chocolate
i. Dystonia type 9 (paroxysmal choreoathetosis with episodic ataxia and spasticity)
   i. Age of onset: 2–15 years
   ii. Attacks of dystonia, paresthesias, and double vision
   iii. Precipitated by exercise, fatigue, stress, alcohol
   iv. Spastic paraplegia between attacks
j. Dystonia type 10 (paroxysmal kinesigenic choreoathetosis)
   i. Attacks of dystonia/choreoathetosis
   ii. Precipitated by sudden unexpected movements
   iii. Respond to anticonvulsant therapy
k. Dystonia type 11 (myoclonus-dystonia)
   i. Onset usually in the first or second decade of life
   ii. Rapid, jerk-like movements
   iii. Responsive to alcohol
   iv. Combined with variable degrees of dystonia
l. Dystonia type 12 (rapid-onset dystonia-parkinsonism)
   i. Acute or subacute onset (develop over hours or weeks) of generalized dystonia
   ii. In combination with parkinsonism
m. Dystonia type 13 (multifocal/segmental dystonia)
   i. Described in a single Italian family
   ii. Juvenile or early adult onset of segmental dystonia
   iii. With prominent cranial-cervical and upper limb involvement
   iv. Some focal dystonia, some generalized dystonia
n. Dystonia type 15 (myoclonus-dystonia)
   i. Described in a single Canadian family
   ii. Characterized by jerky movements of the upper limbs, hands, and axial muscles
   iii. Myoclonus dystonia and limb dystonia: alcohol responsive
o. Dystonia type 16 (dystonia-Parkinsonism)
   i. Recessively inherited form of early-onset generalized dystonia associated with a homozygous missense mutation in the *PRKRA* gene (Camargos et al. 2008)
   ii. Described in three Brazilian families, sharing the same P222L mutation, inherited from a common founder
   iii. Clinical features
      a) Prominent bulbar involvement with dysphonia, dysarthria, and even dysphagia
      b) Parkinsonism: a less prominent feature (Klein 2008)
p. Dystonia type 17 (recessive torsion dystonia)
   i. Three sisters from Lebanese family suffering from recessively inherited primary focal torsion dystonia with onset in adolescence
   ii. Site of onset: cervical with progression to segmental in two sisters and generalized dystonia in one
   iii. Prominent features
      a) Dystonia: not levodopa responsive in this family
      b) Dysarthria
q. Dystonia type 18 (paroxysmal exertion-induced dyskinesia 2)
   i. The attacks: combination of chorea, athetosis, and dystonia in excessively exercised body regions
   ii. Legs: most frequently affected
   iii. Other features
      a) Epilepsy
      b) Hemolytic anemia
      c) Migraine
   iv. A ketogenic diet: an effective therapeutic regimen
   v. Closely resembles DYT type 9 (paroxysmal choreoathetosis with episodic ataxia and spasticity): remains to be seen whether DYT type 18 and DYT type 9 are the same condition
r. Dystonia type 19 (episodic kinesigenic dyskinesia 2): A second form of paroxysmal kinesigenic dyskinesia was designated DYT type 19

   s. Dystonia type 20 (paroxysmal nonkinesigenic dyskinesia 2)
      i. A second form of paroxysmal nonkinesigenic dyskinesia was described in a single Canadian family
      ii. Clinical features similar to those of DYT8 dystonia/dyskinesia
4. Important clinical "red flags" leading to correct diagnosis of a specific genetic form before molecular testing (Brűggermann and Klein 2010)
   a. Diurnal variation of symptoms and response to levodopa in DRD (DYT5)
   b. Prominent orobulbar and speech involvement (DYT6)
   c. A combination of dystonia with myoclonus, ameliorated by alcohol intake in myoclonus-dystonia (DYT11); and abrupt onset of severe dystonia and parkinsonism in RDP (DYT12)
   d. An inherited dystonia also should be considered in the case of an early onset and when a certain ethnic background and positive family history are present (e.g., a high prevalence of DYT1 dystonia in Ashkenazi Jews and of DYT3 X-linked dystonia-parkinsonism [XDP, "lubag"] in Filipinos)
   e. Notably, the presence of a heritable condition may be masked by a small number of family members, nonpaternity, or adoption
   f. Similarly, reduced penetrance, variable expressivity, and de novo mutations are potential reasons for a "pseudo"-negative family history
   g. With the exception of five rare forms (DYT2, DYT3, DYT5b, DYT16, and DYT17), all monogenic dystonias follow an autosomal dominant pattern of transmission with reduced penetrance

Diagnostic Investigations

1. Electromyography shows a simultaneous contraction of both agonist and antagonist muscles
2. MRI of the brain (Cloud and Jinnah 2010)
   a. Warranted for all ages
   b. Can identify a causal structural defect
   c. Can provide clues to some degenerative disorders in adults and specific treatable developmental or metabolic disorders in younger individuals, such as Wilson disease, glutaric aciduria, biotin-responsive basal ganglia disease
3. Dopa-responsive dystonia
   a. GTPCH1-deficient dopa-responsive dystonia
      i. Decreased concentration of both total biopterin (BP) and neopterin (NP) in cerebrospinal fluid in patients with GTPCH1 deficiencies
      ii. Phenylalanine loading test to detect a subclinical defect in phenylalanine metabolism
      iii. DNA mutation analysis to detect *GCH1* mutation
   b. TH-deficient dopa-responsive dystonia
      i. Normal BP and NP, and reduced-3-methoxy-4-hydroxy-phenylethyleneglycol in CSF
      ii. DNA mutation analysis to detect *TH* mutation
4. Mutational screening has become available on a commercial basis for most of the known dystonia-causing genes (www.genetests.org)
   a. For 10 of the 20 DYT loci (DYT1, DYT3, DYT5a, DYT5b, DYT6, DYT8, DYT11, DYT12, DYT16, and DYT18), genes have been identified (Brűggermann and Klein 2010)
   b. Current guidelines for genetic testing and counseling are based on criteria established by the European Federation of Neurological Societies that were revised in 2009
      i. Molecular testing for the GAG deletion in the *DYT1* gene is recommended in patients with limb-onset generalized dystonia and symptom onset before the age of 26 years, regardless of family history
      ii. Comprehensive mutational analysis for GCH1 mutations, including gene dosage studies, is recommended in patients with early-onset generalized dystonia and clear symptom relief following levodopa therapy, irrespective of family history
      iii. Mutational screening for *SGCE* mutations is recommended only in cases with the typical combination of dystonia and myoclonus and a suggestive family history
      iv. RDP and tyrosine hydroxylase (TH)–associated DRD (DYT5b) are exceedingly rare. XDP (DYT3) is restricted to a specific population. Therefore, no general recommendations have been proposed for these forms (Harbo et al. 2009)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal recessive inheritance: 25%
      ii. Autosomal dominant inheritance: not increased unless one of the parent carries a mutant allele in which case, there is a 50% risk of having an affected sib
      iii. X-linked recessive inheritance; 50% of male sib will be affected given the mother is a carrier
      iv. Secondary dystonias: risk depending on the etiology
   b. Patient's offspring
      i. Autosomal recessive inheritance: not increased (all offspring are carriers) unless the spouse is also a carrier in which case, there is a 50% risk of having an affected offspring
      ii. Autosomal dominant inheritance: 50%
      iii. X-linked recessive inheritance: None of the sons will be affected; all of the daughters will be carriers
      iv. Secondary dystonias: risk depending on the etiology
2. Prenatal diagnosis is possible for some forms of dystonia by DNA analysis of the fetal blood obtained from amniocentesis of CVS provided the disease-causing allele(s) of an affected family member have been identified
3. Management (Goetz and Horn 2001; Klein and Ozelius 2002; Cloud and Jinnah 2010)
   a. Treatment of dystonia
      i. Begins with proper diagnosis and classification
      ii. An appropriate search for underlying etiology
      iii. An assessment of the associated functional impairment
      iv. Must be tailored to the individual needs of the patient
      v. Physical therapy and occupational therapy can be useful in many patients
      vi. Botulinum toxin: currently the mainstay of treatment for focal and segmental dystonia
      vii. Oral medications and deep brain stimulation: the mainstays of therapy for generalized dystonia
   b. Generalized idiopathic dystonia
      i. Medical therapy
         a) Anticholinergic agents (trihexyphenidyl): first choice (a moderate response in about 40–50% of dystonia patients)
         b) Benzodiazepines (diazepam, clonazepam)
         c) Dopamine depletors (tetrabenazine)
         d) γ-aminobutyric acidergics (baclofen)
         e) Atypical neuroleptics (clozapine, olanzapine)
      ii. Intrathecal baclofen infusion
      iii. Ablative therapies, reserved for patients in whom medical therapies fail
         a) Pallidotomy
         b) Thalamotomy
   c. Dopa-responsive dystonia
      i. A dramatic response to small dosages of levodopa (100 mg a day) (confirms the diagnosis)
      ii. Maintenance with low-dose levodopa for life may improve from severe inability to completely normal function
   d. Focal dystonias
      i. Unresponsive to systemic drug treatment in most case
      ii. Frequently well controlled by periodic botulinum toxin (BTX) injections into the muscles directly involved in the dystonia
      iii. Try with intrathecal baclofen and surgery if oral medications fail
   e. Cervical dystonias resistant to BTX: selective peripheral denervation

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Fig. 1 A 7-year-old girl with progressive dystonia showing dystonic posturing with gait locking of the knees and swiveling of the hips to propel the legs forward. She developed normally until age 6 when she started to have loss of balance, falling, unable to get the foot off the ground, stiffing of lower and upper extremities, and slurring of speech. Plasma amino acids, urine organic acids, blood chemistry, lactate/pyruvate, ceruloplasmin, copper, arsenic, lead, 5-methyltetrahydrofolate, neurotransmitter metabolites/amines, tetrahydrobiopterin/neopterin, and various lysosomal enzymes were all normal. No mutations were detected on mitochondrial myopathy mtDNA, *DYT1*, and *PANK2*. MRI of the brain showed bilateral hyperdense basal ganglia lesions. Use of levodopa/dopamine agonists has at best, been minimally beneficial

Dystrophinopathies

The dystrophinopathies include a spectrum of muscle disease caused by mutations in the *DMD* gene that encodes the protein dystrophin. They are characterized by a spectrum of muscle disease that ranges from mild to severe. The mild end of the spectrum includes the phenotypes of asymptomatic increase in serum concentration of creatine phosphokinase (CK) and muscle cramps with myoglobinuria and isolated quadriceps myopathy. The severe end of the spectrum includes progressive muscle diseases that are classified as Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) when skeletal muscle is primarily affected and as X-linked dilated cardiomyopathy (XLDCM) when the heart is primarily affected. In this chapter, I will limit my discussion on DMD and BMD.

DMD is one of the most common types of muscular dystrophy in childhood, primarily affecting skeletal and cardiac muscle. It is one of the most common of all clinical genetic disorders. Its incidence is estimated to be approximately 1 in 3,500 live male births. BMD is a milder allelic form of dystrophin deficiency, affecting 1 in 30,000 male births.

Synonyms and Related Disorders

Becker and Duchenne muscular dystrophy

Genetics/Basic Defects

1. DMD
   a. Inheritance
      i. X-linked recessive
      ii. Exceptionally high mutation rate of 10^{-4} in both sperm and eggs
      iii. Approximately 1/3 of cases are due to new genetic mutations
      iv. Approximately, 2/3 of cases occurring by inheritance of the disease-causing gene from the carrier mother
      v. Only males affected (as a rule)
   b. *DMD* gene
      i. Observation of a series of young females affected clinically as Duchenne muscular dystrophy with an X-autosome translocation
         a) Breakpoint in the X chromosome in the same place (Xp21.1)
         b) Different autosomes involved for each affected female
         c) Mapping of dystrophin gene to chromosome Xp21
      ii. The largest human gene, covering 2.5 megabases and including 79 exons
      iii. The enormity of the DMD gene along with the spontaneous mutation rate of each base pair allows a high frequency of novel mutations.
   c. Dystrophin, the product (protein) of the human dystrophin gene (*dys*)
      i. Loss of dystrophin at the muscle membrane clearly related to mutations in the gene encoding dystrophin at band Xp21
      ii. Cloning of the dystrophin gene by positional cloning in the late 1980s constituted the initial proof that deletions in the Xp21 region were associated with the disease
      iii. The dystrophin gene (Muntoni et al. 2003)
         a) The largest gene of the 30,000 genes that encode proteins in the human genome

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b) Consisting of 79 exons spanning more than 2.6 million bp of genomic sequence
c) Correspond to about 0.1% of the total human genome
d) Correspond to about 1.5% of the entire X chromosome

iv. Southern blot analysis of affected boys with a complete set of cDNA probes
a) Over 60% with detectable deletions
b) Six percent with duplications
c) A number of point mutations described recently

v. Consequences of absent dystrophin in skeletal and cardiac muscles in affected patients
a) Muscle contraction leading to membrane damage and activation of the inflammatory cascade
b) Progressing to muscle necrosis, fibrosis, and loss of function

d. The DMD phenotype most frequently due to mutations that cause a disruption in the reading frame (Wagner 2002)

2. BMD
a. Inheritance: X-linked recessive (same as DMD).
b. Also caused by mutations in the gene for dystrophin at Xp21.1.
c. The BMD phenotype most often due to mutations that preserve the open reading frame but in which portions of the protein are deleted. Frame deletions of the long rod segment of the gene are particularly forgiving and produce a mild phenotype (Wagner 2002).

3. Mechanism for female DMD and BMD
a. Turner syndrome with a *dystrophin* mutation on the remaining X chromosome (Chelly et al. 1986)
b. Skewed X inactivation either in the female DMD mutation carriers (Yoshioka et al. 1998)
c. Balanced X-autosome translocation patients (Verellen-Dumoulin et al. 1984)
d. Uniparental disomy of the entire X chromosome with mutations (Quan et al. 1997)
e. Co-occurrence of mutations in both dystrophin and androgen receptor genes (Katayama et al. 2006)
f. Double dystrophin mutations on both X chromosomes (Fujii et al. 2009)

Clinical Features

1. DMD (Roland 2000)
a. During early infancy
i. Asymptomatic
ii. Normal motor milestones
iii. Rare global developmental delay or delayed achievement of early motor milestones

b. Four to five years of age: onset of symptoms
i. A waddling gait
ii. Difficulty in climbing stairs due to pelvic weakness
iii. Difficulty in running
iv. Toe walking resulting from tight Achilles tendon
v. Inability to jump
vi. Frequent falling
vii. Neck flexor weakness with marked head lag when pulling to sit from the supine position

c. Progressive difficulty in rising from the floor secondary to weakness of proximal pelvic girdle and proximal leg muscle, resulting in the Gower's maneuver requiring the use of the hands to "climb up the legs"
d. Pseudohypertrophy of muscles, especially calf muscles: unusually firm and rubbery consistency on palpation
e. Compensatory lumbar lordosis to maintain an upright posture secondary to weakness of hip extensors
f. Weakness of the arms (proximal more severely affected than distal) apparent as the disease progresses
g. Marked laxity of the shoulder girdle musculature with prominent spontaneous winging of the scapulae
h. Inability to walk usually before 13 years of age
i. Rapid development of fixed skeletal deformities following loss of ambulation
i. Equinovarus deformities of the feet
ii. Scoliosis
iii. Wheelchair confinement by adolescence
j. Unexplained cardiac arrest and/or myoglobinuria: features of malignant hyperthermia during general anesthesia in rare instances

k. Progressive and restrictive respiratory deficit with nocturnal hypoventilation in the latter teens to early 20s secondary to weak intercostal muscles
l. Eventual respiratory failure requiring assisted ventilation
m. Some degree of mental impairment is usually present. Approximately 25% of patients have IQ below 75, presumably due to the lack of dystrophin in the brain.
n. Natural history
   i. Progressive and predictable deterioration of muscle function
   ii. Cause of death: cardiopulmonary insufficiency in the late second or third decade
o. Female carriers
   i. Usually asymptomatic
   ii. Manifesting female carriers (rare): Occasional, slow progressive myopathy of moderate severity with elevated CPK (>1,000) and associated symptoms in about 8% of carriers. Following conditions induce expression of the disease phenotype:
      a) Random X-inactivation: The extent of clinical involvement is dependent in part upon the degree of skewed X-chromosome inactivation in somatic cells.
      b) Turner syndrome having a single X chromosome
      c) X-autosome translocation that disrupts the dystrophin gene and causes nonrandom inactivation of the normal allele on the other X chromosome

2. BMD
   a. A more benign and variable presentation with later onset and slower progression
   b. Onset of symptoms after age 6–12
   c. Progressive symmetrical muscle weakness and atrophy
      i. Proximal greater than distal
      ii. Often with calf hypertrophy
      iii. Weakness of quadriceps femoris may be the only sign.
   d. Activity induced cramping in some patients
   e. Flexion contractures of the elbows may occur late in the course
   f. Wheelchair dependency, if present, after 16 years of age
   g. Preservation of the neck flexor muscle strength in BMD, differentiating it from DMD
   h. Rare BMD patients not diagnosed until adulthood and never lose ambulation
   i. A proportion of cases have some degree of mental impairment
   j. Heart failure from dilated cardiomyopathy, a common cause of morbidity and the most common cause of death, despite the milder skeletal muscle involvement
   k. Death usually in the fourth or fifth decade
   l. Female carriers
      i. Clinical features similar to DMD female carriers.
      ii. About 5–10% of female carriers show some degree of muscle weakness.
      iii. Often with calf hypertrophy.
      iv. May develop dilated cardiomyopathy.

Diagnostic Investigations

1. Determination of serum creatine kinase (CK-MM)
   a. Fifty-fold elevation (BMD) to 100-fold elevation (DMD) in affected boys, resulting from leakage of the muscle isoform
   b. Serum creatine kinase levels: range of values overlapping with the normal range in carrier females, making the test less than definitive
2. Determination of other enzymes: grossly elevated aldolase, SGOT, lactic dehydrogenase, and pyruvate kinase
3. Electrocardiography and echocardiography to detect cardiac involvement
   a. Electrocardiography
      i. Abnormalities in the early stage of the disease
         a) Tall R-wave
         b) Deep Q-wave
      ii. Arrhythmias
      iii. Progressive cardiomyopathy in the mid-teens
         a) Myocardial dilatation
         b) Myocardial thickening
   b. Echocardiography
      i. Left ventricular dilatation and dysfunction
      ii. Mitral regurgitation secondary to dilated cardiomyopathy or associated mitral valve prolapse

4. Radiography for scoliosis
5. Pulmonary function testing with negative inspiratory force and forced vital capacity as disease progresses
6. Cytogenetic analysis
   a. Males affected with DMD and other X-linked disorders such as retinitis pigmentosa, chronic granulomatous disease, McLeod red cell phenotype, glycerol kinase deficiency, and adrenal hypoplasia as part of contiguous gene deletion syndrome
      i. High resolution chromosome studies
         a) To detect visible deletions
         b) To detect chromosome rearrangements involving Xp21.1
      ii. FISH analysis with probes covering the *GK* and *NRDB1* genes in addition to exons in the *DMD* gene
   b. Females with classic DMD
      i. May have X chromosome rearrangement
      ii. May have deletion involving Xp21.1
      iii. May have complete absence of an X chromosome (45,X)
      iv. May have complete uniparental disomy of the X chromosome
      v. Warrant high-resolution chromosome studies
7. Electromyography (EMG) to distinguish a myopathic process from a neurogenic disorder
   a. Not diagnostic
   b. Demonstrating characteristic myopathy
   c. Reduction in the duration and amplitude of motor unit action potentials
   d. An enhanced frequency of polyphasic potentials
8. DNA analyses for diagnostic confirmation
   a. Deletion of the dystrophin gene in 60% of patients: 98% of all deletions which occur in hotspots within the dystrophin gene can be recognized by multiplex PCR which amplifies 18–25 of the gene's 79 exons from genomic DNA obtained from blood samples
   b. Duplications (6% of cases): the next most common mutation of the dystrophin gene, also detectable by multiplex PCR amplification
   c. Point mutations (1/3 of patients) difficult to identify due to the large size of the gene
   d. Enhanced single-strand conformation polymorphism (SSCP) and heteroduplex analysis: highly sensitive and possible to detect approximately 90% of patients with DMD
   e. RNA-based methods, such as reverse-transcriptase PCR (RT-PCR)
   f. Protein truncation test: to rapidly screen the DMD gene for translation terminating mutations
9. Muscle biopsy (needle biopsy vs. open biopsy under general anesthesia), frequently performed when a clinically suspected DMD patient does not have a large deletion or duplication by genomic DNA testing
   a. Histology
      i. Rounding of muscle fibers
      ii. Marked variability in muscle fiber size
      iii. Increased central nucleation
      iv. Fiber splitting
      v. Presence of necrotic and regenerating fibers along with large, round hyaline fibers
      vi. Virtual replacement of muscle fibers by fatty and fibrous tissue in late stage
   b. Dystrophin determination by Western blot analysis or immunostaining
      i. Usually little or no detectable dystrophin in patients with DMD
      ii. Dystrophin reduced in amount or abnormal in size in patients with BMD
10. Carrier testing (Mathews 2003)
   a. Carrier testing of young girls or genetic testing of siblings of patients with DMD should be delayed until they are old enough to participate in the decision-making process.
   b. Appropriate to test the mother who has an affected boy with deletion or duplication identified by standard DNA screening, especially if there are other female relatives of childbearing age who are at risk for being carriers.
   c. Possibility of gonadal mosaicism (up to 15%) exists when the mother does not carry the boy's mutation
      i. Her sisters could not have inherited the mutation.
      ii. Her daughter may have inherited the mutations.
   d. Offer linkage analysis to modify risk of carrier status if no mutation is known or if tissue for DNA analysis is not available
      i. Knowledge of a childhood CPK level in the at risk girl helpful
      ii. Elevated CPK in an at-risk female is presumptive evidence of her being a carrier
   e. Muscle biopsy: not a helpful test in determining carrier status.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib given that the mother is a carrier (has a disease-causing mutation) (the carrier mother with one defective gene and one normal gene is usually not affected)
      i. Fifty percent risk to her son to receive the disease gene and express the disease.
      ii. Fifty percent risk to her daughter to receive the disease gene and become a carrier.
      iii. Mother, regardless of proven carrier status or does not have a *DMD* mutation detectable in her DNA, has an empiric risk of 15–20% of having an affected male fetus due to presence of maternal germinal mosaicism.
      iv. Mother with concomitant somatic and germline mosaicism: The risk to sibs of inheriting a DMD mutation may be higher than if the mother has germline mosaicism only (van Essen et al. 2003).
   b. Patient's offspring
      i. Males with DMD: Patient usually succumb or too debilitated to reproduce
      ii. Males with BMD
         a) May reproduce.
         b) None of the sons will inherit the mutation.
         c) All the daughters are carriers.
   c. Germline mosaicism (den Helderman-van Enden et al. 2009)
      i. Causes the presence of multiple affected offspring from apparently noncarrier parents.
      ii. In X-linked DMD/BMD, the recurrence risk for noncarrier females due to germ line mosaicism has been estimated to be between 14% and 20% (95% confidence interval) (Darras and Francke 1987; Bakker et al. 1987, 1989 van Essen et al. 1992) if the risk haplotype is transmitted.
      iii. A recurrence risk of 8.6% (4.8–12.2) if the risk haplotype is transmitted with a remarkable difference between proximal (15.6%) (4.1–27.0) and distal (6.4%) (2.1–10.6) deletions (den Helderman-van Enden et al. 2009). Overall, most mutations originated in the female. Deletions occur more often on the X chromosome of the maternal grandmother, whereas point mutations occur on the X chromosome of the maternal grandfather. In unhaplotyped de novo DMD/BMD families, the risk of recurrence of the mutation is 4.3%.
2. Prenatal diagnosis
   a. In case of a known and readily detectable gene defect
      i. Amniocentesis and mutation analysis of amniocytes, usually by multiplex PCR
      ii. Preimplantation diagnosis by single-cell PCR of blastomere or polar body
      iii. Fetal nucleated erythrocytes from maternal blood analyzed by multiplex PCR
   b. In case of unknown gene defect
      i. Fetal sexing, allowing females to proceed to term
      ii. Linkage analysis
      iii. Fetal muscle biopsy for quantitative dystrophin analysis may serve as a diagnostic option (Nevo et al. 1999)
   c. Comparative genomic hybridization (CGH) (Bovolenta et al. 2010)
      i. Molecular diagnosis of DMD: requires a great deal of effort due to enormous size of the gene and to allele heterogeneity.
      ii. While multiplex ligation-dependent probe amplification (MLPA) represents the standard molecular technique for detecting exonic DMD gene rearrangements (Kesari et al 2008), several comparative genomic hybridization (CGH) platforms have recently been reported to rapidly screen the entire DMD gene, as well as neighboring sequences, for deletions and duplications (Hegde et al 2008; del Gaudio et al 2008; Bovolenta et al 2008).
3. Management (Kapsa et al. 2003; Mathews 2003)
   a. Largely supportive
      i. Physical therapy to eliminate the need for surgical release of contractures
         a) Night splints with ankle foot orthoses (AFOs)
         b) Daily stretching
         c) Crucial to maintain ambulation as long as possible because its loss is associated with contractures and scoliosis, and, in turn, associated with restrictive lung disease

ii. Regular use of an incentive spirometer at home to prolong pulmonary function
iii. Continuous positive airway pressure (CPAP)
iv. Bilevel positive airway pressure BiPAP: more physiologic
v. Psychological support

b. American College of Chest Physician Statement on the respiratory and management of patients with Duchenne dystrophy undergoing anesthesia (Birnkrant 2009)
c. Treatment of dystrophic cardiomyopathy
i. An angiotensin-converting enzyme inhibitor
ii. With or without a β-blocker
iii. A diuretic
d. Pharmaceutical agents (steroids) shown great promise in delaying the progression of DMD
i. Prednisone
ii. Deflazacort (not FDA approved but used widely in Europe and Canada)
e. Orthopedic surgery
i. Release of joint contractures
ii. Spine fusion to minimize painful spinal deformity and secondary pulmonary complications
f. Prescribe wheelchair when dependency becomes inevitable
g. Careful monitoring of pulmonary function
h. Ventilation for respiratory failure
i. Genetic therapies in DMD: Use of viral and plasmid vectors to deliver dystrophin to dystrophin–deficient muscle in vivo (Kapsa et al. 2003)
i. Truncated dystrophin genes (minidystrophin and microdystrophin transgenes): improve force output and other features of the dystrophic *mdx* phenotype
ii. Tissue-specific promoters: Targeted transgene expression via muscle-specific promoters, a good platform for vector-mediated therapeutic delivery of *dys* to dystrophic muscle
iii. Plasmid vectors
iv. Viral vectors
a) Adenoviral vectors
b) Adenoassociated vectors
c) Retroviral vectors
d) Lentiviral vectors
e) Other viral vectors including herpes simplex virus, Epstein-Barr virus, and chimeric adeno-retrovirus

j. Corrective gene therapy (Kapsa et al. 2003; Nelson et al. 2009)
i. Targeted corrective gene conversion therapies
a) Introduction of construct of homologous DNA containing a nonhomologous sequence into mammalian cells in vitro induces specific genetic transformations in the host chromosomal DNA.
b) An attractive therapeutic strategy for DMD if the DNA can be delivered to the muscles efficiently.
ii. Small fragment homologous replacement (SFHR): involves the application of PCR amplicons to correct mutant loci in vitro or in vivo
iii. Chimeraplasty with hybrid RNA-DNA molecules (chimeraplasts) that promote gene conversion via intranuclear DNA mismatch repair mechanisms
iv. Gentamicin
a) An aminoglycoside antibiotics targeting functional complexes (typically ribosomes)
b) Causes a relaxation in codon recognition
c) Enables stop-codon read-through of the *mdx* nonsense mutation (a mutation that produces a stop codon in the transcribed mRNA) in exon 23 of the dystrophin gene in the *mdx* mouse
v. Cell-mediated delivery of *dys*
a) Use cell transplantation to deliver normal (non-dystrophic) *dys* to dystrophic muscle
b) Use donor myogenic precursor cells to remodel the dystrophic muscle of the recipient
c) Systemic applications of stem-cell subpopulations
d) Use autologous cells (as an alternative to donor cells) which can be isolated, genetically engineered, and used to deliver functional dystrophin to the dystrophic muscle

vi. Muscle derived precursor cells
   a) Delivery of normal dystrophin by the transplantation of non-dystrophic muscle derived precursor cells
   b) Resulting in some recovery of normal function in dystrophic muscle
   c) Greatly compromised by host immune response
vii. Non-muscle stem cells
   a) Induction of a few systemically injected bone-marrow cells to enter muscle after regeneration induced by injury.
   b) These cells with neuronal, osteogenic, myogenic, and haemopoietic expression profiles may provide alternatives for cell-based delivery of non-dystrophic loci to dystrophic muscle.
viii. Utrophin
   a) A 395 kDa ubiquitous protein homologue of dystrophin.
   b) Utrophin expression has a widespread sarcolemmal distribution in human dystrophic muscle.
ix. Other alternative approaches that may be useful in the support of functional improvement in dystrophic muscle include:
   a) $\alpha 7\beta 1$ integrin
   b) Myoprotective or myoproliferative cytokine factors such as leukemia inhibitory factor and insulin-like growth factor-1
   c) Inhibition of myostatin
x. Emerging genetic therapies to treat DMD
   a) A drug, PTC124, was identified that suppresses nonsense codon translation termination. PTC124 can lead to restoration of some dystrophin expression in human Duchenne muscular dystrophy muscles with mutations resulting in premature stops.
   b) Two drugs developed for exon skipping, PRO051 and AVI-4658, result in the exclusion of exon 51 from mature mRNA. They can restore the translational reading frame to dystrophin transcripts from patients with a particular subset of dystrophin gene deletions and lead to some restoration of dystrophin expression in affected boys' muscle in vivo.
   c) Both approaches have concluded phase I trials with no serious adverse events.

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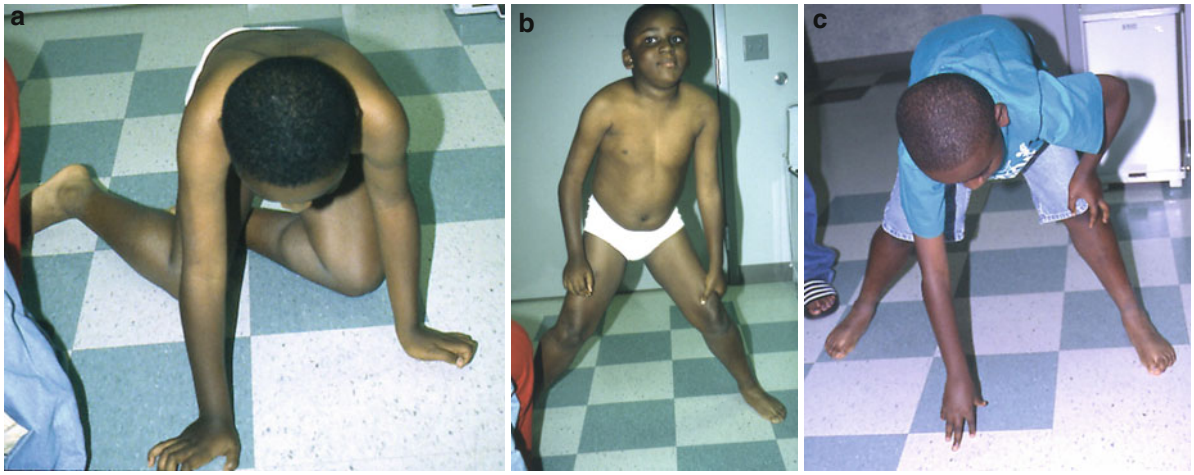

Fig. 1 (**a**–**c**) A 10-year-old boy with DMD showing Gower sign maneuver. He walked before 16 months of age and had trouble getting up. Radiography showed mild cardiomegaly. Muscle biopsy showed absence of dystrophin. Molecular genetic analysis revealed exons 45–50 deletion of the dystrophin gene

Fig. 2 A 12-year-old boy with DMD showing moderate calf hypertrophy. He began to fall frequently at school, could not get up from sitting position and had waddling gait, proximal muscle weakness, prominent lordosis, decreased deep tendon reflexes, and mild mental retardation. Muscle biopsy revealed absence of dystrophin

Fig. 3 A 10-year-old boy with DMD starting to use wheelchair for ambulation. He had tip toe walking at age of 6 and markedly elevated CPK at 24,000–26,000. Muscle biopsy of quadriceps femoris muscle showed marked variation in fiber size, moderate number of necrotic fibers, occasional regeneration fibers and hyalinized fibers, mild increase in internal nuclei, a few split fibers, and moderate increase in perimysial and endomysial connective tissue. Molecular genetic analysis revealed deletion of exon 45 of the dystrophin gene

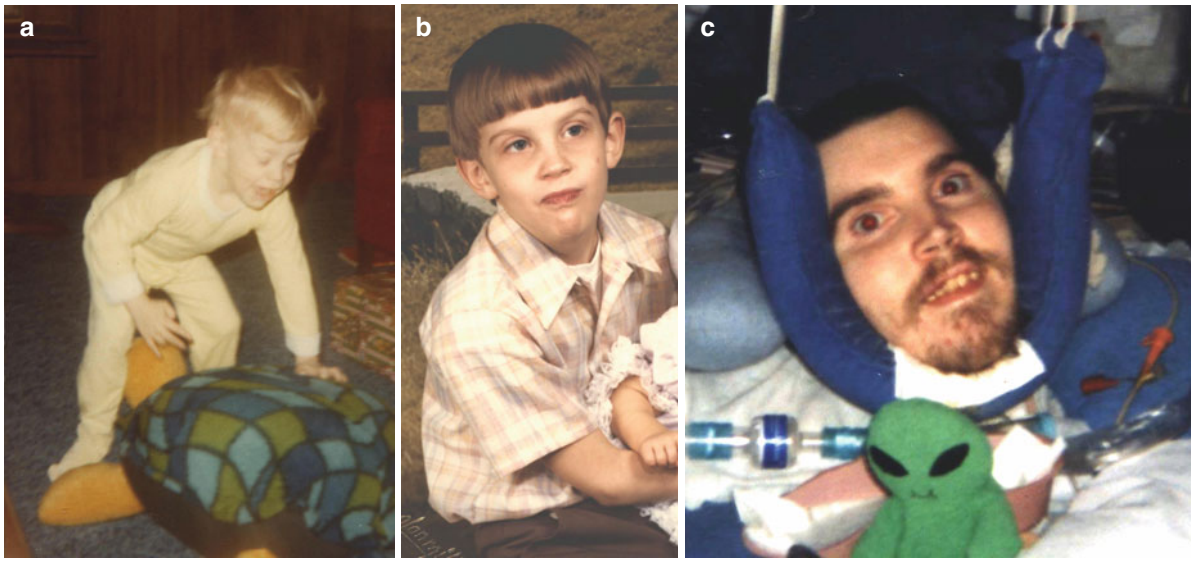

Fig. 4 (**a**–**c**) A male with DMD at 4-, 10-, and 29-year-old showing the progression of the disease. He has deletion of exons 49–54 of the dystrophin gene

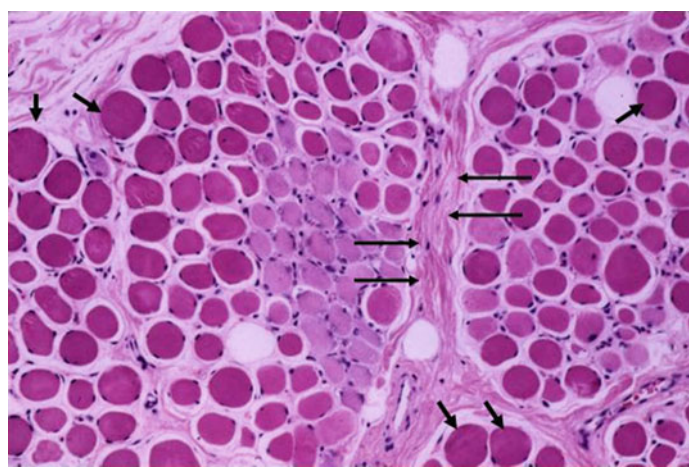

Fig. 5 Biopsy of left calf muscle of another patient at age 4 showed widening of perimysium (*large arrows*) and endomysium with fibrosis; variation of fiber size with presence of large rounded fibers (*small arrows*). Degenerative fibers were often seen (H & E, x400)

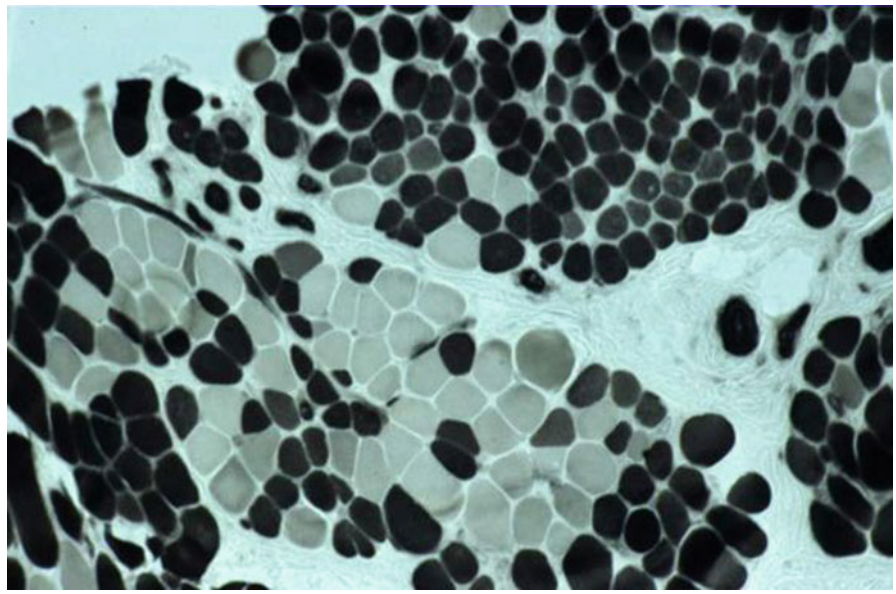

Fig. 6 Enzyme histochemical stain showed both type I (*dark stained*) and type II (*light stained*) fibers are randomly affected and there is a remarkable variation of fiber size even at the early stage (myosin ATPase at 4.6, x400)

Ectrodactyly-Ectodermal Dysplasia-Clefting (EEC) Syndrome

EEC syndrome is an ectodermal dysplasia syndrome associated with ectrodactyly and cleft lip/palate.

Genetics/Basic Defects

1. Inheritance (Akahoshi et al. 2003; Barrow et al. 2002; Clements et al. 2010)
   a. Familial cases (50%)
      i. Autosomal dominant inheritance
      ii. Variable clinical expression and incomplete penetrance (93–98%)
   b. Sporadic cases (50%): more severe phenotype than the familial cases
2. At least three distinctive EEC loci identified
   a. EEC1 (7q11.2-q21.3)
   b. EEC2 (chromosome 19 pericentromeric region)
   c. EEC3 (3q27)
3. Molecular basis of EEC
   a. Causative mutations for EEC syndrome have only been identified in *p63* with identification of heterozygous mutations in the DNA-binding domain of the *p63* gene at 3q27
   b. The p63 protein
      i. A member of the *p53* family
      ii. Implicated in apoptosis rather than tumor suppression. Increased susceptibility for cancer development has not been shown in patients with EEC syndrome.
   c. Pathogenic mutations in the *TP63* transcription factor have been identified as the molecular basis of EEC syndrome and to date 34 mutations have been reported (Clements et al. 2010). The majority of mutations involve heterozygous missense mutations in the DNA-binding domain of TP63, a region critical for direct interactions with DNA target sequences
4. Genotype–phenotype correlation
   a. A genotype–phenotype correlation described for *p63* mutations in EEC syndrome, limb-mammary syndrome, and isolated split hand/split foot malformation: a specific pattern of missense mutations exists in EEC syndrome that are not generally found in split hand/foot malformation or limb-mammary syndrome (Van Bokhoven et al. 2001)
   b. Emerging paradigm for genotype–phenotype correlation (Clements et al. 2010)
      i. EEC syndrome, the prototype of all TP63 ectodermal dysplasia disorders, is the most prevalent syndrome resulting from mutations in the *TP63* gene (Brunner et al. 2002; Bougeard et al. 2003) with more than 200 cases reported in the literature
5. EEC syndrome as a model of apoptosis disturbance
   a. Split hands and feet are caused by a failure of cell death between fingers and between toes
   b. Urogenital anomalies are due to abnormal regression of Wolffian or Mullerian duct
   c. Facial clefts are attributed to the abnormal elimination of excess cells during fusion of the archetypal plate

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Clinical Features

1. Significant intra/interfamilial variability (Bigatà et al. 2003)
2. Cardinal signs (triad)
   a. Ectrodactyly
   b. Ectodermal dysplasia
   c. Orofacial clefts
3. Distal limb malformations: highly variable
   a. Ectrodactyly (84%)
      i. Also called split hand/foot malformation
      ii. A central reduction of the hands and feet that is often associated with syndactyly
   b. Present in all four or any combination of extremities involved or not present at all
4. Ectodermal dysplasia (77%): may exhibit the following signs:
   a. Sparse scalp hair
   b. Sparse eyebrows and eyelashes
   c. Thin and brittle nails
   d. Hypohidrosis
   e. Thin and dry skin with an increased susceptibility to eczema
   f. Dental anomalies
      i. Hypodontia
      ii. Coniform-shaped teeth
      iii. Enamel dysplasia
5. Characteristic face
   a. Bilateral cleft lip and/or palate (68%)
   b. Maxillary hypoplasia
   c. Short philtrum
   d. Broad nasal tip
   e. Choanal atresia
   f. Anomalies of the lacrimal ducts resulting in blepharitis, keratitis, and dacryocystitis (59%)
6. Urogenital defects (23%)
   a. Hydronephrosis
   b. Hydroureter
   c. Renal agenesis
7. Conductive hearing loss (14%)
8. Developmental delay
9. Occasional CNS malformations
   a. Rare growth hormone deficiency secondary to hypothalamic-pituitary insufficiency
   b. Holoprosencephaly associated with hypogonadotropic hypogonadism and central diabetes insipidus
   c. Isolated absent septum pellucidum
10. Phenotype overlapping with split hand/foot malformations
11. TP63-associated disorders (Clements et al. 2010): Clinical features overlap with EEC syndrome, although several distinct characteristics may help distinguish them
    a. AEC (ankyloblepharon, ectodermal dysplasia, clefting) (Hay–Wells) syndrome (McGrath et al. 2001): Typical features include:
       i. Ankyloblepharon filiforme (partial eyelid fusion)
       ii. Skin erosions are typical features
    b. ADULT (acro, dermato, ungula, lacrimal, tooth) syndrome (Chan et al. 2004): Common features include:
       i. Mammary gland/nipple hypoplasia
       ii. An absence of clefting
       iii. Increased skin freckling
    c. Rapp–Hodgkin syndrome (Bougeard et al. 2003; Chan et al. 2005): Typical features include:
       i. Similar to AEC syndrome
       ii. Usually an absence of ankyloblepharon
       iii. Characteristic facies with midfacial hypoplasia and microstomia
    d. Limb-mammary syndrome (Van Bolhoven et al. 1999)
       i. Similar limb defects to those seen in EEC syndrome, including absence or severe hypoplasia of digits and fusion/separation defects such as syndactyly
       ii. Additional clinical features
          a) Mammary gland/nipple hypoplasia
          b) Cleft palate only and limited
          c) No skin or hair abnormalities

Diagnostic Investigations

1. Ophthalmologic evaluation for tear duct obstruction
2. Early audiological assessment
3. Renal ultrasound for associate renal anomalies
4. Radiographic evaluation for ectrodactyly
5. Starch-iodine test (the skin is painted with tincture of iodine, air-dried, and sprayed with starch) after sweat stimulation with intradermal injections of pilocarpine to demonstrate hypohidrosis (Bigatà et al. 2003)
6. Direct molecular analysis is possible for EEC (TP63-related disorders) (www.genetests.org)

Genetic Counseling

1. Counseling according to autosomal dominant inheritance
   a. Patient's sib:
      i. Recurrence risk of 50% if a parent is affected
      ii. Recurrence risk not increased if both parents are normal
   b. Patient's offspring: recurrence risk of 50%
   c. Dilemmas in counseling due to highly variable clinical expression
   d. Consider the possibility of nonpenetrance due to gonadal mosaicism
2. Prenatal diagnosis
   a. Prenatal ultrasonography
      i. Cleft lip/palate
      ii. Ectrodactyly
      iii. Associated anomalies
   b. Molecular genetic analysis of p63 gene mutation (South et al. 2002)
      i. On fetal DNA extracted from CVS and amniocytes by direct sequencing and restriction endonucleases digestion (loss of *AciI* site on mutant allele)
      ii. Using a preimplantation genetic diagnostic approach
3. Management (Bigatà et al. 2003)
   a. Supportive (multidisciplinary team approach)
      i. Artificial tear for tear duct blockage
      ii. Anticipate recurrent ophthalmologic infections
      iii. Periodic odontologic management to prevent dental malocclusion and caries
      iv. Simple emollients for dry skin
   b. Surgery
      i. Early surgery for tear duct blockage
      ii. Surgery for all defects causing functional impairment
         a) Cleft lip/palate
         b) Ectrodactyly
         c) Associated anomalies

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Fig. 1 A stillborn with severe EEC syndrome

Fig. 2 An infant with EEC syndrome

Fig. 3 (**a**–**c**) An infant with EEC syndrome

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a group of clinically and genetically heterogeneous heritable connective tissue disorders affecting skin, ligaments, joints, blood vessels, and internal organs. EDS is characterized by skin extensibility, joint hpermobility, and tissue fragility. EDS result from mutations in genes involved in extracellular matrix formation and organization, leading to a predisposition for loss of structural integrity in tissues within multiple organ systems (Barabas 1967). The prevalence of EDS is estimated to be about 1 in 5,000 births.

Synonyms and Related Disorders

EDS I (Gravis type); EDS II (mitis type); EDS III (hypermobile type); EDS IV (arterial-ecchymotic type); EDS VI (kyphoscoliotic type); EDS VIIA, VIIB (arthrochalasis type); EDS VIIC (Dermatospraxis type); EDS VIII; EDS IX (occipital horn syndrome/X-linke cutis laxa); EDS IX (occipital horn syndrome/X-linke cutis laxa); EDS X; EDS XI

Genetics/Basic Defects

1. Classic type (includes EDS type I, gravis type and EDS type II, mitis type)
   a. Autosomal dominant inheritance
   b. Mutations in the *COL5A1* gene (mapped at 9q34.2-q34.3), *COL5A2* (mapped at 2q31), and *COL1A1* (mapped at 17q21.31-q22) genes result in EDS I. Mutations in the *COL1A1* is not a major cause of classic EDS
   c. Mutations in the *COL5A1* and *COL5A2* genes result in EDS II.
2. Hypermobile type (EDS type III)
   a. Autosomal dominant inheritance in the classic form of type III EDS.
   b. Mutations in *COL3A1*, typically cause EDS IV, also cause EDS III.
   c. Mutations in the *TNXB* gene that encodes tenascin-X (neither a collagen nor a collagen-modifying protein) result in a variation of the classic form of the Ehlers-Danlos syndrome.
      i. Autosomal recessive disorder
      ii. Clinical findings (joint hypermobility, soft hyperextensible skin, and easy bruising without skin scars) are compatible with Beighton's description of Ehlers-Danlos syndrome type III or "benign familial hypermobility."
3. Vascular type (EDS type IV, arterial-ecchymotic type)
   a. Autosomal dominant inheritance
   b. *COL3A1 l*ocus: 2q31
   c. Caused by mutations in the gene that encodes type III procollagen (*COL3A1*), which is the major component of blood vessels, viscera, and the uterus. Consequently, individuals with this type often experience life-threatening vascular and gastrointestinal complications.

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4. Kyphoscoliosis type (EDS type VI, ocular-scoliotic type)
   a. Autosomal recessive inheritance
   b. *PLOD* gene mapped to 1p36.3-p36.2
   c. Caused by mutations in the *PLOD* gene encoding lysyl hydroxylase
   d. Caused by deficient activity of the enzyme procollagen lysyl hydroxylase
   e. EDS VIA: reduced activity of lysyl hydroxylase
   f. EDS VIB: normal enzyme level
5. Arthrochalasis type (EDS types VIIA and VIIB, arthrochalasis multiplex congenita)
   a. Autosomal dominant inheritance.
   b. EDS VIIA caused by mutations in the genes for type I collagen (*COL1A1*)
   c. EDS VIIB caused by mutations in the genes for type I collagen (*COL1A2*), mapped at 7q22.1.
6. Dermatospraxis type (EDS type VIIC)
   a. Autosomal recessive inheritance
   b. Caused by homozygous mutations in the *ADAMTS2* gene (5q23) encoding procollagen I N-terminal peptidase resulting in procollagen peptidase deficiency
7. Other types
   a. EDS type V
      i. X-linked recessive inheritance
      ii. Described in only two families with clinical features similar to EDS II
      iii. Molecular basis unknown
   b. EDS type VIII
      i. A rare type
      ii. Autosomal dominant inheritance
      iii. Similar to classic type except the presence of periodontal friability
   c. EDS type IX
      i. Previously redefined as occipital horn syndrome (X-linked cutis laxa)
      ii. An X-linked recessive condition allelic to Menkes syndrome
      iii. Abnormal copper utilization secondary to defective copper transport resulting in decreased activity of lysyl oxidase, an important copper-dependent enzyme required for cross-linking in collagen biosynthesis and elastin fibers
   d. EDS type X
      i. Autosomal recessive inheritance
      ii. Described only in a single family
      iii. Associated platelet aggregation due to a defect in fibronectin
   e. EDS type XI
      i. Termed familial joint hypermobility syndrome
      ii. Autosomal dominant inheritance
      iii. Previously removed from the EDS classification

Clinical Features

1. Classic type (EDS I and II) (Beighton et al. 1998; Malfait et al. 2011)
   a. Major diagnostic criteria: The presence of scars with joint hypermobility suggests the classical type.
      i. Skin hyperextensibility
      ii. Widened atrophic scars (the hallmark "cigarette-paper" scars, a manifestation of tissue fragility)
      iii. Joint hypermobility
      iv. Positive family history
   b. Minor diagnostic criteria
      i. Smooth, velvety skin
      ii. Molluscoid pseudotumors
         a) Fresh lesions associated with scars
         b) Frequently found over pressure points such as elbow and knees
      iii. Subcutaneous spheroids
         a) Small subcutaneous spherical hard bodies
         b) Frequently mobile and palpable on the forearms and shins
         c) May be calcified and detectable radiologically
      iv. Complications of joint hypermobility
         a) Sprains
         b) Dislocations
         c) Recurrent joint subluxations in the shoulder, patella, and temporomandibular joints
         d) Pes planus
      v. Muscle hypotonia
      vi. Delayed gross motor development
      vii. Easy bruising
      viii. Manifestations of tissue extensibility and fragility
         a) Hiatal hernia
         b) Anal prolapse in childhood
         c) Cervical insufficiency
      ix. Surgical complications (postoperative hernias)
      x. Positive family history

c. Other features
   i. Families with variable severity (mild, moderate, and severe) of the skin manifestations
   ii. Dyspareunia and sexual dysfunction: occasional complaints
   iii. Fatigue: a frequent complaint
2. Hypermobile type (EDS III)
   a. Major diagnostic criteria
      i. Skin involvement (variable hyperextensibility and/or smooth, velvety skin)
      ii. Generalized joint hypermobility (dominant clinical feature)
   b. Minor diagnostic criteria
      i. Recurrent joint dislocations (particularly shoulder, patella, and temporomandibular joints)
      ii. Chronic joint/limb pain (early onset, chronic, and possibly debilitating)
      iii. Positive family history
   c. Other features
      i. Early-onset, chronic, and possibly debilitating musculoskeletal pain
      ii. Aggravation of joint symptoms during pregnancy but a complete return to the former status is possible
   d. Natural history and manifestations (Castori et al. 2010)
      i. The most difficult form to diagnose
      ii. A diagnosis of exclusion for the following disorders:
         a) Underlying bone dysplasia
         b) Neuromuscular disorder (such as Bethlem myopathy)
         c) Various similar connective tissue disorders, including other types of EDS and the fibrillinopathies
      iii. Lack of a major clinical trait except for joint hypermobility
      iv. Lack of specific diagnostic laboratory tests, although tenascin-X monoallelic or biallelic inactivation can be documented in no more than 10% of the patients (Schalkwijk et al. 2001; Zweers et al. 2003).
      v. Clinical presentations
         a) Recurrent articular dislocations (also after surgical repair)
         b) Chronic/recurrent articular pain in adults or young adults with joint hypermobility and/or a history of infancy/childhood joint hypermobility
         c) Soft/velvety skin and/or easy bruising with joint hypermobility or a history of infancy/childhood joint hypermobility
         d) Chronic asthenia with recurrent articular pain and negative screening for inflammatory arthritis
         e) Acute thoracic pain due to spontaneous rib luxation/subluxation (rare)
         f) Early-onset uterine/vescical/rectal prolapse (19%)
         g) Chronic gastrointestinal discomfort including chronic recurrent dyspepsia/gastritis, gastro-esophageal reflux, irritable bowel disease, recurrent unexplained abdominal pain, and constipation/diarrhea
3. Vascular type (EDS IV)
   a. Major diagnostic criteria: The presence of any two or more major criteria is highly indicative of diagnosis of EDS IV; biochemical testing is strongly recommended to confirm the diagnosis.
      i. Thin translucent skin (especially noticeable on the chest or abdomen)
      ii. Arterial/intestinal/uterine fragility or rupture (presenting signs in 70% of adults with vascular type of EDS)
         a) Spontaneous arterial rupture peaks in the 3rd or 4th decade but may occur earlier, most commonly involves midsized arteries, and is the most common cause of sudden death. The sites of arterial rupture are the thorax and abdomen (50%), head and neck (25%), and extremities (25%).
         b) Intrapartum uterine rupture and pre-/postpartum arterial rupture result in 15% mortality. Vaginal and perineal tears may complicate pregnancies during delivery.
         c) Gastrointestinal ruptures occur in about 25% of patients, most common in the sigmoid colon.
         d) Ruptures of the small bowel and stomach are rare. The rupture may present as an acute abdomen.
      iii. Easy bruising
         a) Lifelong history
         b) Spontaneous or with minimal trauma

iv. Characteristic facial appearance in some affected patients due to a decrease in the subcutaneous adipose tissue
  a) Thin lips and philtrum
  b) Small chin
  c) Thin nose
  d) Large eyes
v. Family history of the vascular type of EDS

b. Minor diagnostic criteria: The presence of one or more minor criteria contribute to the diagnosis of the vascular type of EDS, but are not sufficient to establish the diagnosis
i. Acrogeria (an aged appearance of the extremities, particularly the hands)
ii. Hypermobility of small joints (usually limited to the digits)
iii. Tendon and muscle rupture (knee)
iv. Talipes equinovarus (clubfoot) (12%)
v. Early-onset varicose veins
vi. Arteriovenous, carotid-cavernous sinus fistula
vii. Pneumothorax/pneumohemothorax (common in childhood)
viii. Chronic joint subluxations/dislocations
  a) TMJ
  b) Patella
  c) Ankles
ix. Congenital dislocation of the hips
x. Gingival recession
xi. A positive family history consistent with autosomal dominant inheritance with sudden death in close relatives

c. Other features
i. An uncommon subtype: diagnosis often made only after a catastrophic complication or at postmortem examination
ii. Acute abdominal and flank pain (diffuse or localized): a common manifestation of arterial or intestinal rupture
iii. Subcutaneous venous pattern particularly apparent over the chest and abdomen
iv. Hypermobility of large joints and hyperextensibility of the skin: unusual in the vascular type
v. The teenage boys: at higher risk for arterial rupture possibly due to further weakening of the defective collagen during the prepubertal growth spurt
vi. Patients undergoing surgery: prone to have arterial rupture in the postoperative period, possibly due to increased collagenase activity after surgical trauma
vii. Aneurysms (if present) resulting from arterial tears with walled-in hematomas or pseudoaneurysms
viii. Danger of varicose-vein surgery in unrecognized cases since the extreme fragility of all blood vessels can lead to a loss of a limb or even loss of life

4. EDS V
a. An extremely rare X-linked, recessively inherited disorder
b. Clinically similar to EDS II
i. Joint hyperextensibility
ii. Slightly hyperelastic skin
iii. Skin subject to mildly abnormal scarring
c. Normal life span
d. Asymptomatic female carriers

5. Kyphoscoliosis type (EDS VI)
a. Major diagnostic criteria: Presence of 3 major criteria is suggestive of diagnosis of EDS, kyphoscoliosis type.
i. Generalized joint laxity (recurrent joint dislocations common in adults)
ii. Severe muscle hypotonia at birth
iii. Kyphoscoliosis, present at birth or within the first year of life, progressive (adults with severe kyphoscoliosis are at risk for restrictive lung disease and pneumonia)
iv. Scleral fragility and rupture of the ocular globe
b. Minor diagnostic criteria
i. Tissue fragility, including atrophic scars
ii. Easy bruising
iii. Marfanoid habitus
iv. Microcornea (most patients)
v. Radiologically considerable osteopenia (osteoporosis)
vi. Family history (e.g., affected sibs)
c. Other features
i. Pronounced muscular hypotonia leading to delayed gross motor development.

ii. Severe phenotype often results in loss of ambulation in the second or third decade.
iii. Scleral fragility leading to rupture of the ocular globe after minor trauma.
iv. Cardiovascular complications
a) Vascular rupture: the major life-threatening complication.
b) Both aortic dilatation/dissection and rupture of medium-sized arteries may occur.
c) Mitral valve prolapse common.
v. Differential diagnosis: severe neonatal form of Marfan syndrome.

6. Arthrochalasia type (EDS VIIA and VIIB)
a. Major diagnostic criteria:
i. Severe generalized joint hypermobility, with recurrent subluxations
ii. Congenital bilateral hip dislocation (present in all biochemically proven individuals, may lead to short stature)
b. Minor diagnostic criteria:
i. Skin hyperextensibility
ii. Tissue fragility, including atrophic scars
iii. Easy bruising
iv. Muscle hypotonia
v. Kyphoscoliosis (may lead to short stature)
vi. Radiologically mild osteopenia
c. Other features
i. Short stature resulting from complication of severe kyphoscoliosis and/or hip dislocation
ii. Differential diagnosis: Larsen syndrome

7. Dermatosparaxis type (EDS VIIC)
a. Major diagnostic criteria:
i. Severe skin fragility (wound healing not impaired, scars not atrophic)
ii. Sagging, redundant skin (redundancy of the facial skin resulting in an appearance resembling cutis laxa) analogous to the animal disease dermatosparaxia
b. Minor diagnostic criteria:
i. Soft, doughy skin texture
ii. Easy bruising (substantial)
iii. Premature rupture of fetal membranes
iv. Large hernias (umbilical, inguinal)
c. Other features
i. Blue sclera
ii. Palmar creases
iii. Micrognathia
iv. Joint laxity without subluxations

8. EDS VIII
a. Chronically inflamed, heavily pigmented, discrete, and pretibial plaques (granulomatous collagen degeneration)
b. Premature periodontal disease
c. Premature loss of teeth
d. Hypermobile joints
e. Thin, soft, and hyperextensible skin
f. Easy bruising skin
g. Skin prone to abnormal scarring
h. No consistent biochemical or structural changes detectable

9. Occipital horn syndrome (EDS IX)
a. Also called X-linked cutis laxa
b. Skeletal dysplasia
i. Occipital horns
ii. Broad clavicles
iii. Deformed radii, ulnae, and humeri
iv. Narrow rib cage
v. Undercalcified long bones
vi. Coxa valga
c. Unusual facial appearance
d. Hypermobility of finger joints
e. Limitation of extension of elbows
f. Chronic diarrhea
g. Genitourinary abnormalities
i. Bladder diverticulae
ii. Susceptible to rupture of the bladder
h. Vascular complications
i. Splenic artery aneurysm
ii. Hepatic artery aneurysm
i. Neuropathologic findings
i. Neovascularization and extreme reduplication of the cerebral arteries with cystic medial degeneration
ii. Cerebellar hypoplasia
iii. Focal cortical dysplasia
iv. Cerebellar heterotopias
j. Abnormal copper utilization
i. Depleted serum copper level
ii. Depleted serum ceruloplasmin level

10. Ehlers-Danlos syndrome with fibronectin deficiency (EDS X)
a. A mild, recessively inherited variant of Ehlers-Danlos syndrome

b. Resembling EDS types II and III
c. Thin, fragile, and easily scarred skin
d. Joint hypermobility
e. Excessive bruising
f. Abnormal platelet aggregation but correctable with normal fibronectin

Diagnostic Investigations

1. Classic type
   a. Ultrastructural studies
      i. Disturbed collagen fibrillogenesis
      ii. A characteristic "cauliflower" deformity of collagen fibrils
   b. Abnormal electrophoretic mobility of the proα1(V) and proα2(V) chains of collagen type V in some patients
   c. Demonstration of a mutation in *COL5A1* and/or *COL5A2* genes
   d. Echocardiogram to measure aortic root size
2. Hypermobile type: *TNXB* sequencing by research only
3. Vascular type
   a. Demonstration of structurally abnormal collagen type III produced by cultured skin fibroblasts
   b. Demonstration of a mutation in the *COL3A1* gene
   c. Surveillance of aneurysm by MRI or CT scan without contrast material or venous subtraction angiography
4. Kyphoscoliosis type
   a. Demonstration of deficient activity of the enzyme procollagen lysine hydroxylase in affected individuals, diagnosed by biochemical testing of the urine and enzyme assay of cultured fibroblasts
   b. Demonstration of an increased ratio of deoxypyridinoline to pyridinoline crosslinks in the urine measured by HPLC, a highly sensitive and specific test (Malfait et al. 2011)
   c. Demonstration of mutations of the *PLOD* gene that encodes the enzyme procollagen lysyl hydroxylase (Malfait et al. 2011)
   d. Echocardiogram to measure aortic root size
5. Arthrochalasis type
   a. Electrophoretic demonstration of pNα1(I) or pNα2(I) chains extracted from dermal collagen or harvested from cultured skin fibroblasts
   b. Mutation analysis (complete or partial exon 6 skipping in cDNAs of *COL1A1* or *COL1A2* respectively)
6. Dermatospraxis type: electrophoretic demonstration of pNα1(I) or pNα2(I) chains from collagen type I extracted from dermis in the presence of protease inhibitors, or obtained from cultured skin fibroblasts

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal recessive: 25% risk of having an affected sib
      ii. Autosomal dominant: risk low (1–5%) unless the parent is affected or having somatic mosaicism or germline mosaicism
      iii. X-linked recessive: 50% risk of having an affected brother if the mother is a carrier
   b. Patient's offspring
      i. Autosomal recessive: risk not increased unless the spouse is a carrier.
      ii. Autosomal dominant: 50% risk of having an affected offspring.
      iii. X-linked recessive: None of the sons will be affected; all daughters will be carriers.
2. Prenatal diagnosis
   a. Possible by demonstrating the disease causing mutation in the fetal cells from CVS or amniocentesis or by linkage analysis for families in which linkage has been established
   b. Possible by biochemical assay on cultured fetal cells for demonstrating biochemical defect in the specific type of collagen
3. Management
   a. General approach: conservative and preventive management of most skin and joint problems
      i. Avoid tension when sutures are applied
      ii. Leave removable sutures in place for twice the usual time
      iii. Physical therapy to strengthen the muscles that need to provide support for the loose ligaments
   b. Classic type (Malfait et al. 2011)
      i. Medical intervention limited to symptomatic therapy and prophylactic measures
      ii. Wear protection pads or stocking
      iii. Avoid contact sports
      iv. Physiotherapy for children with hypotonia and delayed motor development

v. Antimicrobial prophylaxis for patients with mitral valve prolapse
vi. Ascorbic acid helps avoid easy bruising but does not change the basic clinical picture

c. Hypermobile type (Levy 2010)
i. Physical therapy tailored to the individual
ii. Assisted devices
a) Braces to improve joint stability
b) Wheelchair or scooter to offload stress on lower-extremity joints
c) Suitable mattress to improve sleep quality
iii. Pain medication tailored to symptoms: severe pain may need pain specialist's help
iv. Appropriate therapy for gastritis/reflux/delayed gastric emptying/irritable bowel syndrome
v. Possible beta-blockade or rarely surgical approach for progressive aortic enlargement
vi. Psychological and/or pain-oriented counseling

d. Kyphoscoliotic type
i. Orthopedic management of kyphoscoliosis
ii. Physical therapy for older children, adolescents, and adults
iii. Antimicrobial prophylaxis for patients with mitral valve prolapse
iv. Aggressive control of blood pressure
v. Improve with large doses of ascorbic acid because vitamin C is a cofactor for the enzyme that is deficient (Pyeritz 2000)
a) Improve urinary excretion of hydroxylysine
b) Improve muscle strength and wound healing

e. Vascular type (Pyeritz 2000; Pepin and Byers 2011)
i. The most severe form of EDS
ii. Prompt recognition of the major complications
iii. Difficult to repair ruptured arteries because of the pronounced vascular fragility
iv. Rupture of the bowel, a surgical emergency
v. Avoid pregnancy because the risk of vascular rupture is especially high during pregnancy
vi. Minimize risk of trauma by avoiding contact sport, heavy lifting, and weight training
vii. Treat high blood pressure aggressively
viii. Elective surgical management of vascular disorders in EDS patients using open and endovascular procedure (Brooke et al. 2010)
a) Associated with good outcomes
b) Can be safely performed and should not be withheld until rupture or acute symptoms arise
ix. Patient education
a) Possible complications
b) Need for close monitoring
c) Attention to sudden unexplained pain

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Fig. 1 (**a**, **b**) Hyperextensible joints enable a girl and two sisters with EDS to exhibit difficult hyperextensible joint maneuvers

Fig. 2 Familial Ehlers-Danlos syndrome in the son (**a**–**d**), the daughter (**e**), and the father (**f**–**h**) exhibiting hyperextensible joints and hyperelastic skin. The son also has fascia weakness presenting as a hernia on the lower chin

Fig. 3 (**a**–**f**) A male and a female with EDS showing hyperextensible joints and hyperelastic skin

Fig. 4 (**a**–**c**) Three siblings (12-year-old boy, 10-year-old girl, and 7-year-old girl) with Ehlers-Danlos syndrome showing markedly stretchable abdominal walls. Their mother is also affected with a history of hyperextensible joints with subluxations of sternum-collar bone junction, TMJ, hip, and knees

Fig. 5 (**a**, **b**) A 40-year-old female with hypermobile type of Ehlers-Danlos syndrome showing hyperextensible joints and stretch marks of the skin. She suffers from rectal, bladder, and uterine prolapses. She had four placental abruptions and had ventral hernias repaired twice. She had shoulder dislocations three times and patella dislocations more than ten times. She had a history of recurrent articular and abdominal pain and episodic constipations and diarrheas

Fig. 6 Typical EDS showing easy bruises and scars of the skin

Fig. 7 (**a**, **b**) An 8-year-old girl with Ehlers-Danlos syndrome showing marked scarring of the skin

Ellis-van Creveld Syndrome

In 1940, Ellis and van Creveld described a syndrome, characterized by ectodermal dysplasia, polydactyly, chondrodysplasia, and congenital heart disease. Ellis-van Creveld syndrome, also called chondroectodermal dysplasia, is relatively common in inbred communities, such as the Amish of Lancaster County where it occurs in 1/5,000 births compared to 1/60,000 births in the general population.

Synonyms and Related Disorders

Chondroectodermal dysplasia

Genetics/Basic defects

1. Inheritance
   a. Autosomal recessive inheritance
   b. Parental consanguinity in 30% of cases
2. Basic defect (Arya et al. 2001)
   a. Generalized dysplasia of endochondral ossification
      i. Delayed in the primary centers
      ii. Premature in the secondary centers
      iii. Leads to short stature with progressive distal shortening of the extremities
   b. Caused by mutations in a novel gene, *EVC1*, which is mapped to chromosome 4p16.1 (Ruiz-Perez et al. 2000)
   c. Caused by mutations in a second gene, called *EVC2*, that gives rise to the same phenotype of the syndrome (Galdzicka et al. 2002)
   d. Molecular heterogeneity and possibility of involvement of other genes) suggested by more mutations in both *EVC1* and *EVC2* in two thirds of the patients (Tompson et al. 2007)
   e. May be allelic to Weyers acrodental dysostosis

Clinical Features

1. A clinical tetrad (Al-Khenaizan et al. 2001; Arya et al. 2001)
   a. Chondrodystrophy
      i. The most common feature affecting the tubular bones
      ii. Disproportionate dwarfism
      iii. Progressive distal limb shortening
         a) Symmetrical
         b) Affects the forearms and lower legs
   b. Polydactyly
      i. A constant finding
         a) Bilateral
         b) Post-axial
      ii. Polydactyly of the hands observed in most cases
      iii. Polydactyly of the feet observed only in 10% of cases
   c. Hidrotic ectodermal dysplasia (up to 93%)
      i. Nails
         a) Hypoplastic
         b) Dystrophic
         c) Friable
         d) Completely absent in some cases
      ii. Teeth
         a) Neonatal teeth
         b) Partial anodontia
         c) Small teeth
         d) Delayed eruption

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e) Enamel hypoplasia commonly resulting in abnormally shaped teeth with frequent malocclusion
iii. Occasional sparse hair
d. Cardiac anomalies (50–60%)
i. A single atrium
ii. AV canal
iii. Ventricular septal defect
iv. Atrial septal defect
v. Patent ductus arteriosus
vi. The major cause of shortened life expectancy
2. Other clinical findings
a. Other oral lesions (Cahuana et al. 2004)
i. A fusion of the anterior portion of the upper lip to the maxillary gingival margin
a) Resulting in absence of mucobuccal fold
b) Causing the upper lip to present a slight V-notch in the middle
ii. Multiple labiogingival frenula frequent
iii. Lower alveolar ridge often serrated
b. Musculoskeletal anomalies
i. Low-set shoulders
ii. A narrow thorax
iii. Frequently lead to respiratory difficulties
iv. Knock knees (genu valgum)
v. Lumbar lordosis
vi. Broad hands and feet
vii. Sausage-shaped fingers
c. Genitourinary anomalies (22%)
i. Hypospadias
ii. Epispadias
iii. Hypoplastic penis
iv. Cryptorchidism
v. Vulvar atresia
vi. Focal renal tubular dilation in medullary region
vii. Nephrocalcinosis
viii. Renal agenesis
ix. Megaureters
d. CNS
i. Normal intelligence in most patients
ii. Occasional CNS anomalies or mental retardation

Diagnostic Investigations

1. Radiography (Arya et al. 2001)
a. Essential features
i. Postaxial polydactyly
ii. Progressively distal shortening of segments (acromesomelia with relative shortening of the distal and middle segment of the limbs and phalanges)
iii. Generalized thickness and coarseness of bones
b. Other features depending on disease severity and age
i. Curvature of the humerus
ii. Enlargement of distal ends of the radii and ulnae
iii. Hypoplastic distal phalanges
iv. Short, broad middle phalanges
v. Fusion of metacarpals
vi. Fusion of the hamate and capitate bones of the wrists
vii. Supernumerary carpal bone centers
viii. Clinodactyly
ix. Synostosis
x. Wedge-shaped tibial epiphyses
xi. Genu valgum with hypoplasia of the upper lateral tibia
xii. Fibula disproportionately smaller than the tibia
xiii. Pelvic dysplasia with low iliac wings and spur-like downward projections at the medial and lateral aspects of the acetabula
xiv. Narrow thorax with short ribs
2. Echocardiography for cardiac malformations
3. Histopathology: disorganization of chondrocytes in the physeal growth zone of the long bones and vertebrae in the prenatal period and retardation of physeal growth zones in the childhood
4. Mutation analysis

Genetic Counseling

1. Recurrence risk
a. Patient's sib: 25%
b. Patient's offspring: not increased unless the spouse is a carrier
2. Prenatal diagnosis
a. Fetoscopy
b. Ultrasonography (Arya et al. 2001)
i. A narrow chest
ii. Postaxial polydactyly
iii. Short limbs, especially middle and distal segments
iv. A single atrium

c. Molecular genetic testing
   i. Using linked microsatellite markers flanking the *EVC* locus (Arya et al. 2001)
   ii. Mutation analysis of *EVC1* and *EVC2* genes (www.genetests.org)

3. Management
   a. Dental cares (Cahuana et al. 2004)
      i. Childhood
         a) To prevent caries by dietary counseling, plaque control, and oral hygiene instruction
         b) Crown or composite buildups for microdonts
         c) Partial dentures to maintain space and improve mastication, esthetics, and speech because of congenitally missing teeth
         d) Orthodontic treatment
      ii. Adulthood: require implants and prosthetic rehabilitation to replace congenitally missing teeth
   b. Cardiac surgery to correct cardiac anomalies
   c. Urologic management for genitourinary anomalies
   d. Orthopedic cares
      i. Polydactyly excision
      ii. Surgery for genu valgum

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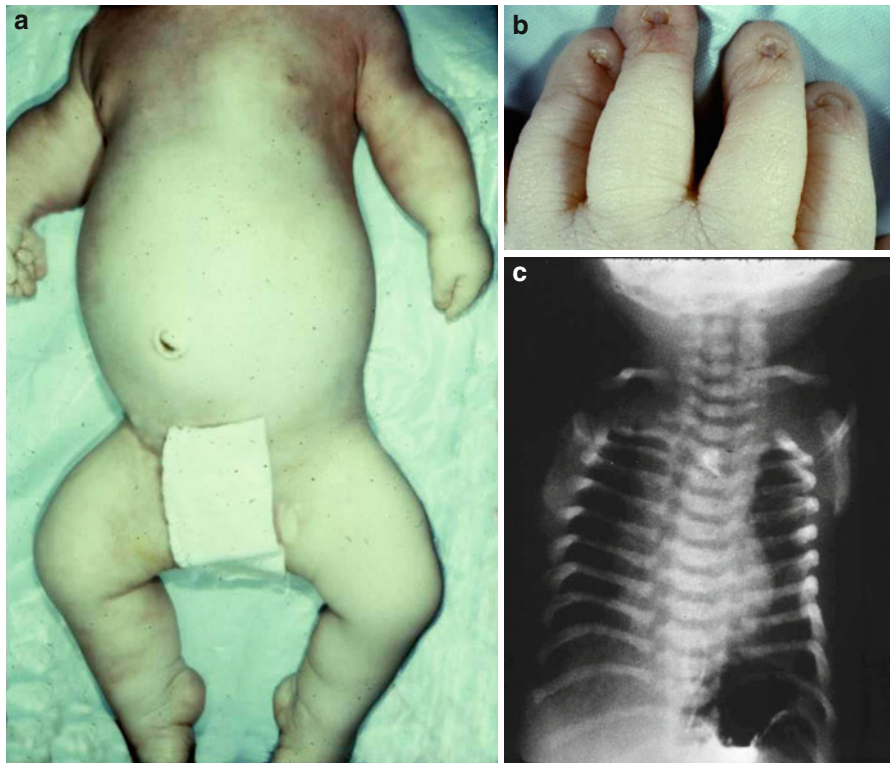

Fig. 1 (**a**–**c**) A neonate with small chest and short extremities. The fingernails are small and deformed. The baby had six fingers on each hand. Radiograph of the chest shows short ribs but the vertebral bodies are normal

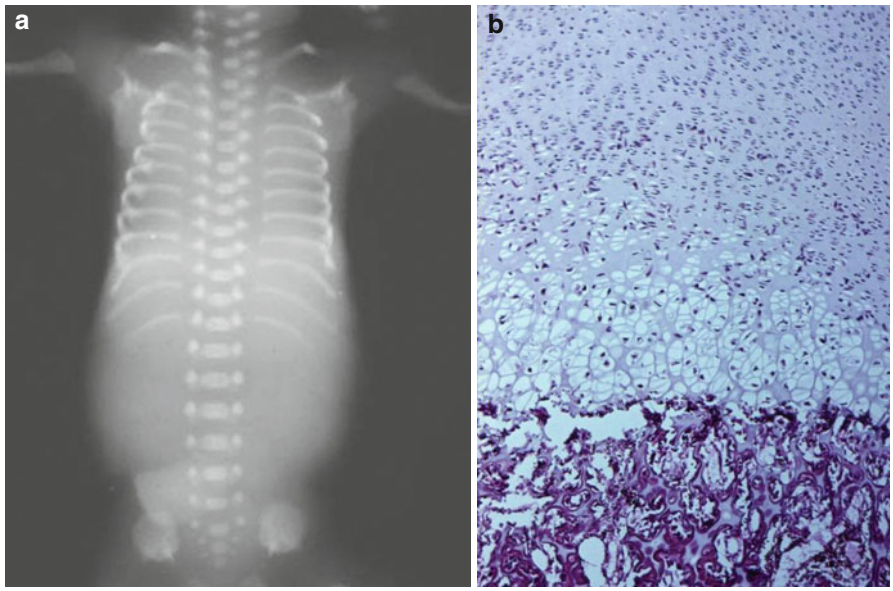

Fig. 2 (**a**, **b**) Radiograph of a fetus with Ellis-van Creveld syndrome showing short ribs and vertically shortened ilia. The vertebral bodies are unremarkable. Photomicrograph of femoral physeal growth zone shows disorganization of chondrocytes. The physeal growth zone of vertebrae showed better columnization

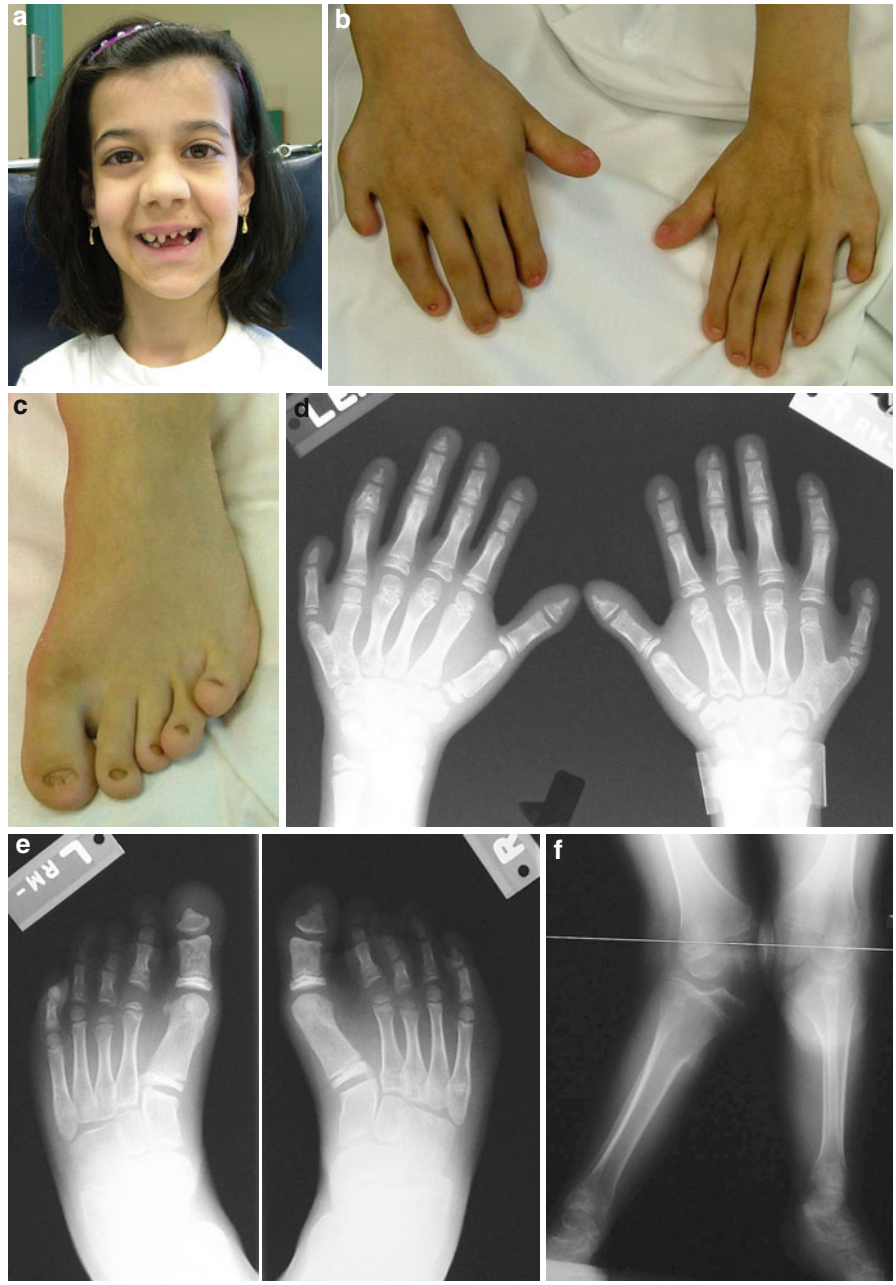

Fig. 3 (**a**-**f**) A 10-year-old Lebanese girl, a product of a consanguineous parents, with Ellis-van Creveld syndrome showing oligodontia and malformed teeth, severe nail hypoplasia of the hands and feet, and broad hands with bilateral post-axial polydactyly. Radiographs show polydactyly, fusion of metacarpals and carpal centers, cone epiphyses of the middle and distal phalanges, and genu valgum

Enchondromatosis

Enchondromas are benign cartilaginous growth in the intramedullary region of the bones, predominantly affecting the metaphyses of long bones (Silve and Jüppner 2006). When two or more bones are affected with enchondromas, the condition is called multiple enchondromatosis. Maffucci first described the syndrome of multiple enchondromas and subcutaneous hemangiomas in 1881, 18 years before Ollier described multiple enchondromatosis.

Synonyms and Related Disorders

Maffucci syndrome; Ollier syndrome

Genetics/Basic Defects

1. Inheritance
   a. Maffucci syndrome
      i. Not hereditary
      ii. A congenital disorder
   b. Ollier syndrome
      i. Not hereditary
      ii. A congenital disorder
   c. Obvious inheritance of enchondromatosis: unusual
   d. No candidate loci identified
   e. Ollier syndrome and Maffucci syndrome: possibly a spectrum of the same disease process (Mellon et al. 1988). The latter condition is complicated by vascular anomalies and hemangiomas.
2. Basic Defect and Pathogenesis
   a. Enchondromas believed to be a part of a generalized mesodermal dysplasia
   b. Appearance of enchondromata close to the epiphysis can severely affect the progressive development of a bone, resulting in distortion in the shape and length of the bone
3. Proposed origin of enchondroma formation
   a. Endochondral bone ossification: a highly regulated process, requiring the progression of undifferentiated mesenchymal cells into hypertrophic chondrocytes and the subsequent replacement of a cartilaginous matrix by mineralized bone
   b. Development of enchondromas in the metaphysis of long tubular bones in close proximity to the growth plate
   c. Consequently, enchondromas resulted from abnormalities in signaling pathways controlling the proliferation and differentiation of chondrocytes, leading to the development of intraosseous cartilaginous foci
   d. Osteochondromatosis possibly results from abnormal regulation of proliferation and terminal differentiation of chondrocytes in the adjoining growth plate, since enchondromas are usually present in close proximity to, or in continuity with, growth-plate cartilage (Hopyan et al. 2002)
      i. Parathyroid hormone related protein (PTHRP) delays the hypertrophic differentiation of proliferating chondrocytes.
      ii. Indian hedgehog (IHH) promotes chondrocytes proliferation.
      iii. Identification of a mutant PTH/PTHRP type I receptor (PTHR1) in human enchondromatosis that signals abnormally

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in vitro and causes enchondroma-like lesions in transgenic mice
   a) The mutant receptor constitutively activates Hedgehog signaling.
   b) Excessive Hedgehog signaling is sufficient to cause formation of enchondroma-like lesions.
4. Hereditary nature of the disorder reported
   a. Generalized enchondromatosis observed in a son of the father who presented with mild skeletal dysplasia but without evidence of enchondromas
   b. A heterozygous mutation (R150C) in the PTH/PTHrP receptor (*PTHR1* gene) was inherited from the father in one of these cases (Hopyan et al. 2002)
   c. Heterozygous mutations in PTHR1 that impair receptor function participate in the pathogenesis of Ollier disease in some patients (Couvineau et al. 2008)

Clinical Features

1. Maffucci syndrome (Lewis and Ketcham 1973; Kaplan et al. 1993)
   a. Age of onset
      i. Bony or soft tissue abnormalities at birth in 27% of cases
      ii. Average age of onset: 4 years (ranging from birth to 30 years of age)
   b. Skeletal lesions: multiple enchondromas
      i. Can occur anywhere in the body
      ii. Most commonly in the hands, followed by tibia/fibula, foot, femur, humerus, radius/ulna, ribs, pelvis, scapula, and head
      iii. Common long bone involvement
      iv. Kyphoscoliosis caused by direct involvement of the spine
      v. Progressive skeletal deformities
         a. Enlarged fingers
         b. Bowed legs
         c. Asymmetric limb shortening
         d. Pathological fractures
      vi. High incidence (23%) of malignancies, especially chondrosarcomas (15%) which lead to greater tissue destruction
      vii. Vascular malignancies may occur occasionally
   c. Vascular lesions: subcutaneous and sometimes visceral hemangiomas
      i. Occur anywhere in the body
      ii. Most commonly in the hands, followed by foot, arm, leg, trunk, and head/neck
      iii. Hemangiomas also reported in the leptomeninges, eyes, pharynx, tongue, trachea, and intestines
      iv. Appear as blue subcutaneous nodules that sometimes can be emptied by pressure or by elevating the lesions above the level of the heart
      v. Unilateral or bilateral lesions
      vi. Phlebitis often results from thrombi forming within the hemangiomatous vessels
      vii. Characteristic calcified thrombi
      viii. Histologic types of hemangiomas
         a) Venous: most often
         b) Capillary
         c) Mixed venous/capillary type
      ix. Lymphangioma, a rare aspect of the mesodermal dysplasia in Maffucci syndrome
      x. Spindle cell hamangiomatosis as a component of Maffucci syndrome
   d. Neoplastic changes
      i. Overall malignancy rate: 37% (Kaplan et al. 1993)
      ii. Chondrosarcoma (15%) (Albregts and Rapini 1995; Abdelmalek and Stanko 2008)
         a) The neoplasm most commonly associated with Maffucci syndrome.
         b) Average age of onset is 40 years (ranging from 13 to 69 years of age).
         c) The most common sites: pelvis, shoulder girdle, distal femur, and proximal tibia (Goto et al. 2003).
      iii. Malignant astrocytoma
      iv. Ovarian tumors
      v. Pancreatic tumors
      vi. Hemangiosarcoma
      vii. Lymphangiosarcoma
      viii. Other neoplasms
   e. Normal intelligence
   f. Short stature
   g. Minimally affected individuals
      i. No major functional impairment
      ii. Unrestricted employment

iii. Moderate cosmetic deformity only
iv. Reconstructive or corrective surgery, limited to one or two major procedures with acceptable final results
v. Ablative surgery, restricted to amputation of a finger or a toe

h. Moderately affected individuals
i. Significant functional impairment
ii. Self supporting and able to work most of the time
iii. Ambulatory
iv. Reconstructive surgery or amputation and prosthesis helpful
v. Ablative surgery restricted to potentially functional (transfemoral or transhumeral) amputation

i. Severely affected individuals
i. Severe functional impairment
ii. Inability to work
iii. Chronic invalidism
iv. No surgical rehabilitation possible
v. Forequarter or hindquarter amputation required

2. Ollier syndrome
a. Nonhereditary cartilage dysplasia of bone
i. A form characterized by enchondromas located mainly at the extremities (hand)
ii. Consisting of multiple, asymmetrically distributed, intraosseous cartilaginous foci and subperiosteal deposition of cartilage, either exclusively or predominantly involving one side of the body
iii. Can be symmetric lesions as in our case 2 and cases presented by Khoo et al. 2008; Choh and Choh 2009)
iv. Multiple enchondromas as described in Maffucci syndrome
v. Enchondromata in infancy and early childhood:
a. Quite innocuous
b. Appearing as small radiolucent defects
vi. Characteristic lesions develop as the skeletal growth progresses:
a. Localized asymmetric impairment of growth
b. Asymmetric shortening & bowing of extremity parts (especially forearm and/or lower leg)
vii. No increase in size of the lesions after the cessation of the normal growth

b. Taut-elastic skin over hyaline cartilage distensions
c. Marked asymmetry of swellings with local growth deficiency
d. Firm, indolent, rounded distensions continuous with bone on one or more fingers or toes
e. Kyphoscoliosis
f. Joint impairment
g. Spontaneous fractures in affected area
h. Rare malignant (chondrosarcoma) transformation
i. Major orthopedic manifestations (Fang et al. 2009)
i. Asymmetrical limb shortening and deformity
ii. Swelling and deformity of the hands or feet
iii. Pathological fracture
j. Prognosis: difficult to assess
i. In general, cases with early onset have more severe prognosis.
ii. Localized cartilaginous changes, especially in a very young child, may induce major shortening of a lower extremity leading to limb asymmetry; in contrast, patient with numerous lesions may have a better prognosis.
iii. Early development of enchondromas in phalanges may lead to major finger deformities.
iv. Neural compressions: less frequently observed than in hereditary multiple exostosis.
v. Malignant transformation of enchondromas into chondrosarcomas usually occurs in young adults. The estimated incidence of malignant transformation is 5–50% of the cases.
vi. Association of Ollier disease with other tumors, such as ovarian juvenile granulosa tumor, has been reported.

3. Differential diagnosis: Other types of enchondromatosis (Kozlowski and Masel 2002; Bovée 2008)
a. Metachondromatosis
i. An autosomal dominant disorder
ii. A rare disorder exhibiting, synchronous, both multiple osteochondromas and enchondromas in children, involving the bones of the hands and feet

iii. Painless swelling of the hands and feet
iv. Normal intelligence
v. Short stature
vi. Radiographic features intermediate between exostosis and enchondromatosis

b. Spondyloenchondromatosis: characterized by platyspondyly
c. Spondyloenchondromatosis with basal ganglia calcification
d. Dysspondyloenchondromatosis: characterized by malsegmentation of the spine
e. Genochondromatosis I
   i. Enchondromatosis with celery type of metaphyseal lesions
   ii. Characteristic thickening of the clavicles
   iii. Regressive without any complications
f. Genochondromatosis II
   i. Enchondromatosis with celery type of metaphyseal lesions
   ii. Moderately severe hand involvement with long dense streaks and more irregular radiolucent channels
   iii. Regress without any complications
g. Dysplasia epiphysealis hemimelica (tarso-epiphysial aclasis) (Trevor disease) (Oestreich et al. 2002)
   i. A developmental disorder with cartilaginous overgrowth of a portion of one or more epiphyses.
   ii. Exostosis of epiphyseal growth centers and their equivalents that grow solely by enchondral ossification with no membranous ossification in the lesions.
      a) Apophyses
      b) Carpal bones
      c) Tarsal bones
      d) Sesamoids including the patella
   iii. Predominantly affects the lower extremity on one side of the body, usually restricted to either the medial (most frequent) or lateral side of the limb (hemimelica).
h. Hereditary multiple exostoses: see chapter on Hereditary multiple exostoses
   i. An autosomal-dominant disorder
   ii. A genetically heterogeneous disorder associated with mutations in *EXT1* or *EXT2* genes, which are both tumor suppressor genes
   iii. Clinically characterized by the development of benign tumors, multiple osteochondromas (exostoses), growing outward from the metaphyses of long bones
   iv. The most important criterion to distinguish enchondromas from osteochondromas seen in hereditary multiple exostoses (radiographic distinction) (Silve and Jüppner 2006)
      a) Osteochondromas are located at the bone surface
      b) Enchondromas are located in the center of bones

Diagnostic Investigations

1. Diagnosis of Ollier disease (Silve and Jüppner 2006)
   a. Based on clinical and conventional radiological evaluations
   b. Histological analysis
      i. Limited role
      ii. Mainly used if malignancy is suspected
   c. Additional studies such as scintigraphy, ultrasound, MRI
      i. Not useful for establishing the diagnosis
      ii. Indicated for the evaluation and surveillance of lesions that become symptomatic, such as pain and increase in size
2. Radiography (Kaufman 1973)
   a. Enchondromas
      i. Lesions usually arise within the medullary cavity, replacing the normal cancellous bone with the abnormal cartilage.
      ii. Lytic lesions initially contain calcifications in a punctate pattern.
      iii. Advanced lesions assume a ground glass appearance.
      iv. Predilection for the metaphysis or diaphysis.
      v. Bone often expands but with intact cortex.
      vi. Often with a scalloped border.
      vii. Pathologic fractures not uncommon.
      viii. Multiple asymmetric enchondromas of long and flat bones(characteristic ovoid or pyramid-shaped, linear translucent defects in metaphyses).
   b. Massive metaphyseal enlargement in any bones, particularly metacarpals and fingers

   c. Enchondromatosis with destruction and calcification
   d. Streaks of unossified cartilage in the metaphyses, sometimes extending into the diaphyses
   e. Madelung deformity
   f. Shortening of extremities
   g. Spinal deformity
   h. Occasional malignant degeneration
3. Major radiographic features (Fang et al. 2009)
   a. Oval/elongated radiolucent lesions, often with longitudinal striations
   b. Erosion of the cortices and subsequent calcification of the lesion producing a diffusely speckled appearance typical of enchondromata
   c. Long bones and small bones of hands and feet typically the most commonly affected sites
   d. Enchondromata almost exclusively in the metaphyseal region in long bones, possibly extending to the diaphysis
   e. Epiphysis affected at later age after closure of the growth plate
   f. Affected areas substantially enlarged and shortened cortical thinning associated with pathological fracture
4. Bone scan
   a. Exhibiting intense and increased uptake
   b. To locate polyostotic lesions
5. CT scan
   a. To delineate the extent of bone involvement
   b. A good diagnostic tool to demonstrate the high attenuation coefficient (classic in bone affected by fibrous dysplasia)
6. MRI
   a. To delineate the extent of bone involvement
   b. Enchondromas
      i. Low signal intensity on T1-weighted images
      ii. High signal intensity on T2-weighted images
      iii. High signal intensity on gradient recalled echo images similar to articular cartilage
7. F-18 FDG PET-CT imaging may prove to be useful in detecting malignant transformation of enchondromas in Maffucci syndrome. (Makis et al. 2010)
8. Histopathology
   a. Gross view of enchondromas: usually shows multiple oval-shaped or round cartilaginous nodules in osseous portions of bone.
   b. Individual nodules
      i. Limited at their periphery by woven or lamellar bone
      ii. Separated from each other by intertrabecular marrow spaces
   c. Cartilaginous tumor matrix: usually solid with myxoid changes, manifesting as frayings of the matrix
   d. Characteristics of enchondromas and chondrosarcomas
      i. Presence of a striking heterogeneity and diversity in the degree of cellularity and chondrocyte phenotype.
      ii. Because of the increased cellularity, the distinction between enchondroma and grade *I* chondrosarcoma in the context of enchondromatosis is extremely difficult or even impossible, the diagnosis therefore relies on the combination of radiographical (cortical destruction, soft tissue extension), clinical, and histological criteria.
9. Fine needle aspiration cytology
   a. Workup of soft tissue tumors
      i. An outpatient procedure
      ii. Minimal risk of complications
      iii. Can easily be performed from different parts of a large tumor
   b. Workup of bone tumors: comparable to cutting needle biopsy

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: not increased unless in rare familial cases
2. Prenatal diagnosis: bone lesions unlikely to manifest in the prenatal period
3. Management (Flach et al. 2001)
   a. Requires no treatment in the absence of clinical problems.
   b. Relief of symptoms.
   c. Early detection of malignancies.
      i. Suspect malignancy change if skeletal or soft-tissue lesions enlarge or become painful without antecedent trauma
      ii. Biopsy

d. Surgery indicated in case of complications.
   i. Pathologic fractures
   ii. Growth defect
   iii. Malignant transformation
e. Operative procedures.
   i. Corrective osteotomy
   ii. Epiphysiodesis
   iii. Hemiepiphysiodesis
   iv. Physeal stapling
   v. Lengthening of an arm or leg
   vi. Curettage and packing with bone graft material
   vii. Sclerotherapy, irradiation, and surgery for the vascular lesions
f. Serial surgery for distortion of knees and unequal leg length.
g. Limb lengthening, either gradual bone grafting or callus distraction: the most common method of correcting deformities in the lower limb.
h. Amputation in suspected malignancy with severe deformity of the limb due to intraosseous cartilaginous foci.
i. Radiotherapy: provide palliative benefit in patients with inoperable chondrosarcoma.
j. Annual surveillance of the enchondromas recommended for children and adults.
k. Periodic surveillance of the brain and abdomen for occult lesions indicated in patients who have enchondromatosis.
l. Long-term consideration to address the potential for malignant changes.
m. Interdisciplinary efforts of health care professionals from medicine, nursing, physical and occupational therapy, recreational therapy, and social services. Long-term consideration must address the potential for malignant changes.

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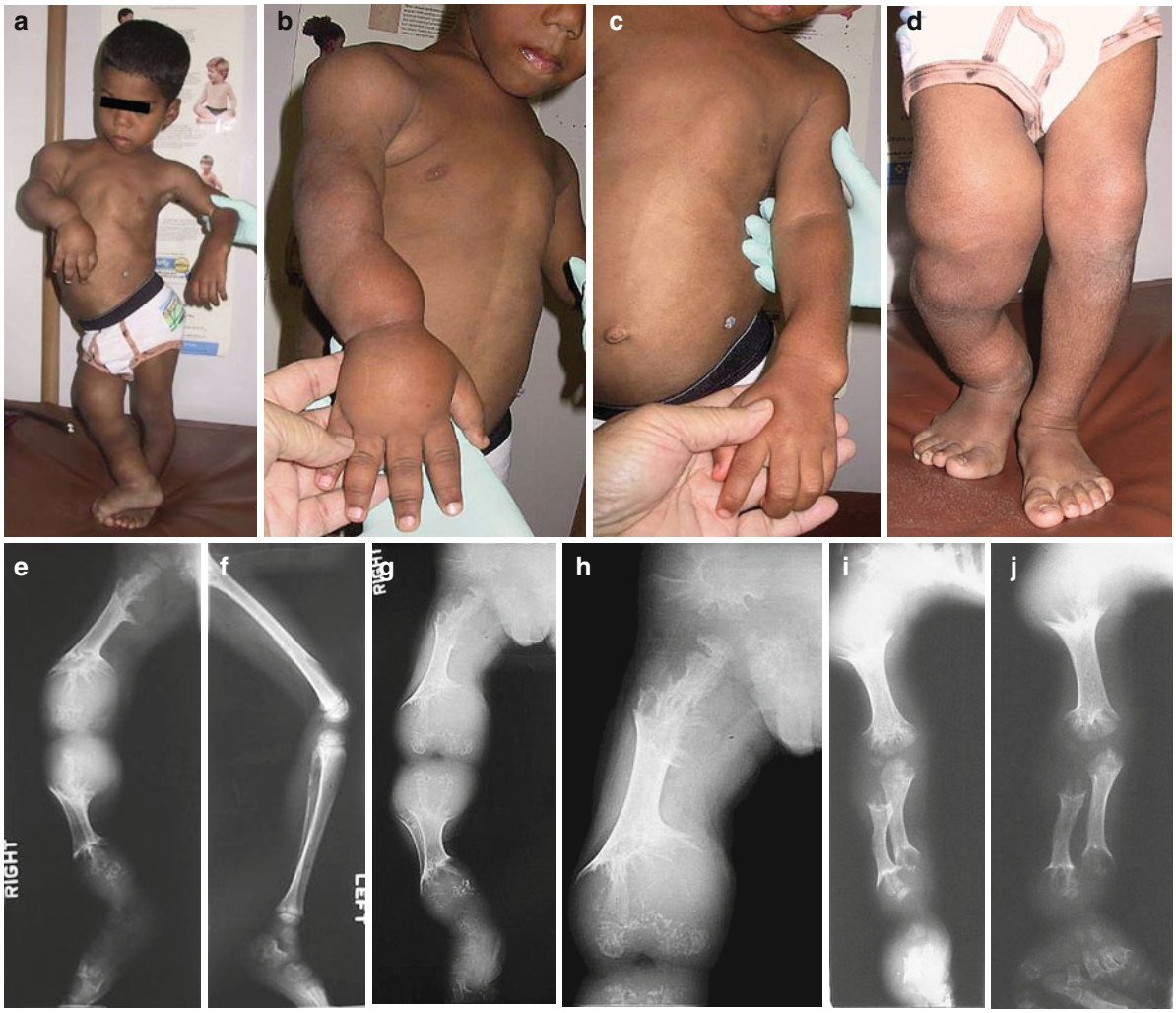
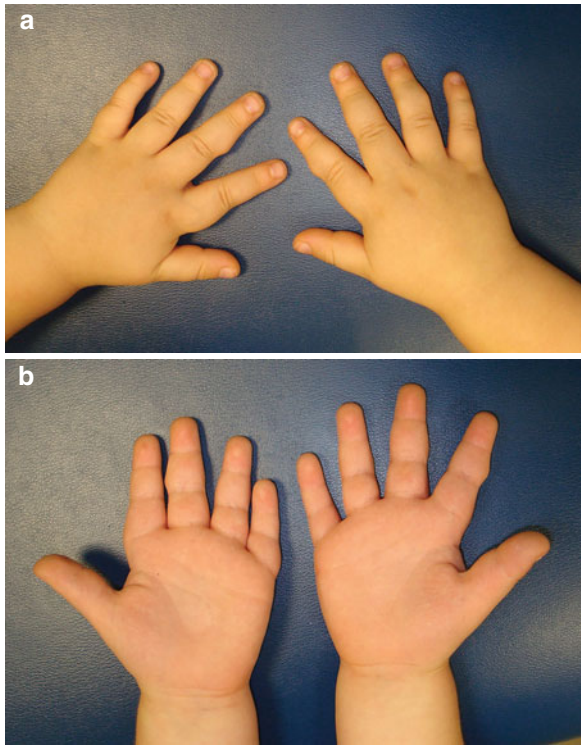
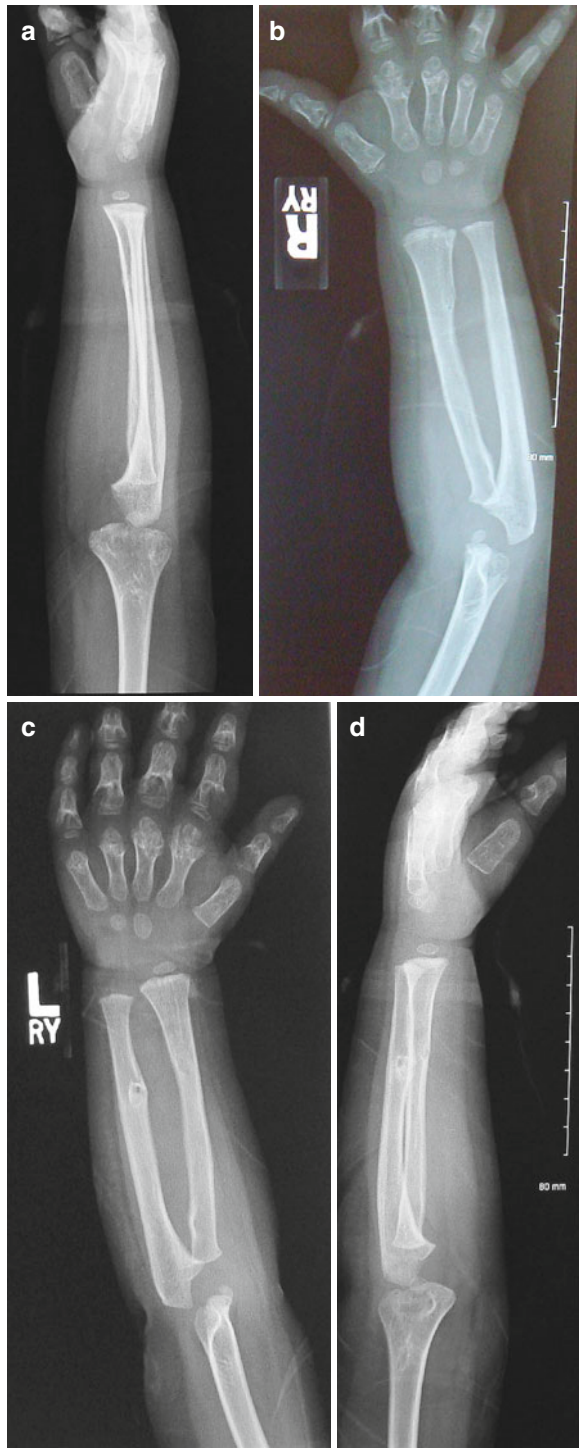


Figs. 1 (**a**–**j**) A 4-year-old boy with Ollier syndrome showing short stature, scoliosis, and severe limb deformities. The *right* limbs were affected by larger lesions with more prominent limb shortening. Marked swellings were evident on the right wrist and fingers. The left hand showed Madelung deformity. The radiographs showed massive metaphyseal enchondromatous lesions in the right upper and lower extremities. Streaks of radiolucency due to the abnormal cartilage extended into the diaphyses. The left femur, tibia, and fibula also showed lytic lesions

Fig. 2 A 4-year-old boy was seen because of swelling of phalangeal joints of multiple fingers on both hands with occasional joint pain. No vascular malformation was detected. Clinical and radiographic findings are consistent with Ollier disease



Figs. 3 (**a**, **b**) Close-up view of both hands showing multiple joint swelling on multiple fingers



Figs. 4 (**a**–**d**) Radiographs of both forearms and hands show multiple enchondromas involving phalanges and metacarpals of both hands and an enchondroma involving the midshaft of the left ulna

Fig. 5 Right hand radiograph shows multiple enchondromas (multiple well-defined osteolytic lesions with endosteal scalloping, cortical thinning, and bony expansion) involving proximal metaphyses of the second to fourth middle and proximal phalanges and the distal metaphyses of the second to third metacarpals

Fig. 6 Left hand radiograph shows multiple enchondromas involving proximal metaphyses of the second to fourth middle phalanges and the second to fifth proximal phalanges

Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a rare group of inherited disorders of skin fragility, characterized by a reduced resistance of the skin and mucous membranes to trauma, manifesting as blistering or erosion of the skin and the epithelial lining of other organs. Epidermolysis bullosa can be classified into three major types, namely, the simplex, the junctional, and the dystrophic types, based on the level of the epidermis or basement membrane zone in which blister is formed.

All types and subtypes of EB are rare. The overall incidence and prevalence of the disease within the USA is approximately 19 per 1 million live births and 8 per 1 million population, respectively (Fine 2010)

Synonyms and Related Disorders

Dystrophic epidermolysis bullosa; Epidermolysis bullos simplex; Junctional epidermolysis bullosa; Kindler syndrome

Genetics/Basic Defects

1. Epidermolysis bullosa simplex (EBS) (Eady 2001; Fine 2010)
   a. Autosomal dominant simplex type EB (most common type)
      i. Caused by mutations in the cytoskeleton structural proteins, keratin 5 (*KRT5*) and keratin 14 (*KRT14*) genes, leading to disruption of basal cells and the formation of bullae in the basal and parabasal cell zone
      ii. Keratins 5 and 14: expressed exclusively in basal cell layer of epidermis keratinocytes and essential for the maintenance of normal structural integrity
      iii. Disease severity correlates with the location within the keratin gene mutation
         a) Mutations in highly conserved genetic sequences leading to severe disease
         b) Mutations in less critical keratin gene regions manifesting as milder, more localized symptoms: Koebner variant (generalized blistering but no mucosal or nail changes) and Weber-Cockayne form (blistering is confined primarily to the easily traumatized palms and soles)
   b. Autosomal recessive simplex types (rare type)
      i. EBS with muscular dystrophy due to abnormal plectin, a protein involved in hemidesmosome formation (currently also classified as a subtype of hemidesmosomal epidermolysis bullosa)
      ii. EB without muscular dystrophy in patients homozygous for *KRT14* gene abnormalities
      iii. Skin fragility syndrome (a form of ectodermal dysplasia but can also be classified as acantholytic EB simplex variant) with formation of acantholytic vesicles within the epidermis due to plakophilin 1 (*PKP1*) gene mutations
      iv. Lethal acantholytic epidermolysis bullosa
         a) The first case report (Jonkman et al. 2005): Recessive mutations in *DSP* leading to truncation of the complete desmoplakin C-terminus (intermediate filament binding); loss of the intermediate filament

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binding domain of desmoplakin in both isoforms caused loss of keratin insertion of desmosomes which still had an inner and an outer dense plaque
   b) A novel homozygous deletion in *DSP* gene, encoding desmoplakin, in two infants born to same consanguineous parents (Bolling et al. 2010): Novel recessive *DSP* mutation predicted to result in truncation as well
2. Junctional epidermolysis bullosa
   a. Inheritance: autosomal recessive in most cases
   b. Herlitz type (epidermolysis bullosa letalis)
      i. Cause by mutations in laminin 5 gene
      ii. Associated with premature death
   c. Non-Herlitz type
      i. Caused by mutation in laminin 5 and type XVII collagen (*COL17A1*) genes
      ii. Generally associated with a good prognosis
   d. Junctional epidermolysis associated with pyloric atresia (Chung and Uitto 2010)
      i. Caused by mutations in a hemidesmosomal component, $\alpha_6\beta_4$ integrin (*ITGA6*, *ITGB4*)
      ii. Currently also classified as a subtype of hemidesmosomal epidermolysis bullosa
3. Dystrophic epidermolysis bullosa
   a. Inheritance: either autosomal dominant or autosomal recessive
   b. Molecular basis: abnormalities of collagen VII
      i. Caused by mutations in type VII collagen gene. *COL7A1* gene mutations have been identified in most cases in both recessive and dominant forms
      ii. Type VII collagen is a major component of the anchoring fibrils that tether the basement membrane structure and overlying epidermis to its dermal foundation
      iii. Severity of the phenotype dictated by missense mutation that alters a glycine residue in dominant dystrophic epidermolysis bullosa versus a nonsense or frameshift mutations in recessive dystrophic epidermolysis bullosa
4. Kindler syndrome
   a. Inherited in an autosomal recessive manner
   b. Pathogenesis of Kindler syndrome involves loss-of-function mutations in a newly recognized actin cytoskeleton-associated protein, now known as fermitin family homolog 1 and encoded by the gene *FERMT1* (Jobard et al. 2003)

Clinical Features

1. Epidermolysis bullosa simplex (Pai and Marinkovich 2002)
   a. General characteristics
      i. The most common heritable blistering process
      ii. Intraepidermal blistering at the level of the basal cell
      iii. Typical healing of blisters without scarring
      iv. Little involvement of other organ systems
      v. Extent and severity of disease improves with age
   b. EBS Koebner type
      i. Commonly involves hands, feet, and extremities
      ii. Onset at birth to early infancy
      iii. Often present with palmar-plantar hyperkeratosis and erosions
      iv. Mildly involves nails, teeth, and oral mucosa
   c. EBS Weber-Cockayne type
      i. Relatively mild variant of EBS
      ii. Commonly involves palms and soles only after a clearly identifiable traumatic event
      iii. May not present until adulthood
      iv. Hyperhidrosis of the palms and soles
      v. Most common complications involve secondary infections of blistering lesions on the feet
   d. EBS Dowling-Meara type
      i. A more severe subtype of EBS
      ii. Involves a more generalized distribution of blisters occurring at, or shortly after, birth
      iii. Pronounced inflammation with milia formation in infancy
      iv. Spontaneous blisters occurring in-groups on the trunk and proximal extremities
      v. Usually healing without scarring later in life
      vi. Hyperkeratosis may develop at age 6 or 7 years
      vii. Unlike the previous two subtypes, heat does not appear to exacerbate blistering
   e. Lethal acantholytic epidermolysis bullosa (Jonkman et al. 2005; Bolling et al. 2010)
      i. Striking phenotypic findings
         a) Extensive nonbullous epidermal dislodgment
         b) Universal alopecia
         c) Anonychia
         d) Rapid postnatal demise

ii. Malformed ears
iii. Cardiac enlargement and dysfunction in utero

2. Junctional epidermolysis bullosa
   a. General characteristics
      i. Blistering at the level of the lamina lucida
      ii. More severe blistering process
      iii. Presenting spontaneously or at sites of trauma with generalized blistering
   b. Herlitz or junctional epidermolysis letalis
      i. The commonest form of JEB formerly known as "lethal JEB"
      ii. Characterized by generalized blistering at birth
      iii. Extensive dental enamel hypoplasia
      iv. Tracheolaryngeal involvement leading to a hoarse cry, cough, and/or other respiratory difficulties
      v. Gastrointestinal involvement and genitourinary involvement leading to infection and obstructive sequelae
      vi. Rarely survives beyond 6 months secondary to chronic anemia, failure to thrive, and sepsis
      vii. Rare survivors: develop exuberant granulation tissue at sites of erosion, especially at the perioral region
   c. Non-Herlitz junctional epidermolysis bullosa
      i. Early clinical course similar to that found in Herlitz type JEB
      ii. Often survives infancy
      iii. May improve clinically with age
      iv. Rare and mild pulmonary involvement
      v. Scalp, nail, and tooth abnormalities common
      vi. Prominent non-healing periorificial lesions
      vii. Erosions in the mucous membranes resulting in strictures
   d. Generalized atrophic benign epidermolysis bullosa
      i. Generalized cutaneous blistering at birth
      ii. Blisters heal with a distinctive atrophic appearance
      iii. Blisters confined to sites of trauma
      iv. Alopecia
      v. Dental anomalies
      vi. Rare severe nail and mucosal involvement
   e. Junctional epidermolysis associated with pyloric stenosis
      i. A syndromic association of skin fragility and congenital gastrointestinal atresia, most frequently pyloric, although duodenal atresia with skin fragility has also been reported
      ii. Often with severe skin blistering and extensive multisystem mucosal blistering
      iii. Presence of pyloric and/or duodenal atresia
      iv. Often with urologic abnormalities
         a) Hydronephrosis
         b) Nephritis
      v. Many patients die during infancy
3. Dystrophic epidermolysis bullosa
   a. General characteristics
      i. Clinical hallmarks (Bruckner-Tuderman 2010)
         a) Trauma-induced blisters
         b) Healing with scarring
      ii. Sub-lamina densa blistering
      iii. Characterized by dermolytic blisters resulting in scarring and milia formations
      iv. Dystrophic scarring follows cutaneous blistering
   b. Dominantly inherited dystrophic epidermolysis bullosa
      i. Mild phenotype
      ii. Present with generalized blistering at birth or during infancy
      iii. Blistering at sites of maximal trauma
      iv. Healing with scarring and small keratinaceous cysts (milia)
   c. Transient bullous dermolysis of the newborn
      i. An uncommon variant
      ii. Blistering at sites of trauma that heals after several months without scarring
      iii. Variable mucous membrane and nail involvement
   d. Recessively inherited dystrophic epidermolysis bullosa: Hallopeau-Siemens type (the most severe form)
      i. Excessive fragile skin leading to blisters with minimal trauma
      ii. Extensive scarring leading to contractures and fusion of digital web spaces (pseudosyndactyly, "mitten deformities") that require surgical correction
      iii. Extremely itching and painful skin
      iv. Regular mucosal blistering leading to eating and swallowing disorders and ocular abnormalities
      v. Tendency to growth retardation and anemia

vi. Devastating complications unique to recessively inherited dystrophic epidermolysis bullosa
a) Increased propensity for cutaneous malignancy at sites of scarring (>40% of patients develop malignancy by age 30 years)
b) Aggressive nature of malignancy (squamous cell carcinoma)

4. Kindler syndrome
a. Trauma-induced blistering
b. Poikiloderma
c. Skin atrophy
d. Mucosal inflammation
e. Varying degrees of photosensitivity

Diagnostic Investigations

1. EM of skin biopsy (Pai and Marinkovich 2002)
a. A gold standard of laboratory diagnosis
i. To determine the level at which blistering occurs
ii. To obtain additional information on the morphology of various basement membrane zone components
b. Epidermolysis bullosa simplex
i. Cytolysis of the basal cells
ii. Distinctive clumping of the keratin tonofilaments
c. Junctional epidermolysis bullosa: rudimentary hemidesmosomes
d. Dystrophic epidermolysis bullosa: absent or altered anchoring fibrils
e. Hemidesmosomal epidermolysis bullosa: separation at the level of hemidesmosome just inside the basal keratinocytes
2. Transmission electron microscopy findings among selected EB subtypes (Fine 2010)
a. EB simplex (suprabasal) (EBS)
i. EB simplex superficialis: subcorneal cleavage
ii. Lethal acantholytic EB:
a) Suprabasal cleavage
b) Acantholysis
c) Perinuclear retraction of keratin filaments
iii. EBS, plakophilin deficiency:
a) Mid-epidermis cleavage
b) Perinuclear retraction of keratin filaments
c) Small suprabasal desmosomes
b. EBS (basal)
i. EBS, localized: basal keratinocyte cleavage
ii. EBS, Dowling-Meara
a) Basal keratinocyte cleavage
b) Clumped keratin filaments
iii. EBS, generalized other: basal keratinocyte cleavage
iv. EBS, autosomal recessive
a) Basal keratinocyte cleavage
b) Absent or reduced keratin filaments within basal keratinocytes
c. Junctional EB (JEB)
i. JEB, Herlitz
a) Intra-lamina lucida cleavage
b) Markedly reduced or absent hemidesmosomes
c) Absent subbasal dense plates
d) Absent anchoring filaments
ii. JEB, non-Herlitz
a) Intra-lamina lucida cleavage
b) Hemidesmosomes may be normal or reduced in size and number
iii. JEB with pyloric atresia
a) Intra-lamina lucida cleavage
b) Small hemidesmosome plaques with attenuated subbasal dense plates
d. Dominant dystrophic EB (DDEB)
i. DDEB, generalized
a) Sub-lamina densa cleavage
b) Normal or reduced numbers of anchoring fibrils
ii. DDEB, bullous dermolysis of the newborn
a) Sub-lamina densa cleavage
b) Electron-sense stellate shaped bodies within basal keratinocytes
c) Reduced numbers of anchoring fibrils
e. Recessive dystrophic EB (RDEB)
i. RDEB, severe generalized
a) Sub-lamina densa cleavage
b) Absent or rudimentary appearing anchoring fibrils
ii. RDEB, generalized other (generalized mitis)
a) Sub-lamina densa cleavage
b) Reduced or rudimentary appearing anchoring fibrils
3. Immunofluorescent microscopy (Pai and Marinkovich 2002)
a. Provide additional information on the level of blistering
b. Provide important clue to the underlying molecular defects

c. Antibodies against intracellular hemidesmosomal component such as BP230 and a lamina densa protein such as type IV collagen
   i. Samples from EBS: both antibodies localized to the floor of the blister
   ii. Samples from JEB
      a) Antibodies against BP230 localized to the roof of the blister
      b) Antibodies against type IV collagen localized to the floor
   iii. Samples from DEB: both antibodies localized to the roof of the blister
d. Samples lacking staining with antibodies specific to laminin 5 support a JEB diagnosis
e. Samples lacking staining with antibodies specific to type VII collagen support a DEB diagnosis
f. Absence of staining for BP180 supports a diagnosis of generalized atrophic benign epidermolysis bullosa

4. Laboratory approach to epidermolysis bullosa (Castiglia and Zambruno 2010)
   a. At first use of immunofluorescence epitope mapping (IFM) and transmission electron microscopy (TEM) examination of a skin biopsy to determine the level of skin cleavage and the presence of morphologic alterations of epithelial adhesion structures and the defective expression of specific protein components
   b. IFM and TEM enable definition of the major EB type and, in most cases, the subtype and identification of the protein component targeted by the mutations
   c. These analyses define the candidate genes for mutation screening and they must precede molecular testing, which should be primarily considered when:
      i. Prenatal or preimplantation diagnosis is being planned
      ii. The mode of genetic transmission cannot be delineated from the family pedigree in combination with IFM and TEM findings
      iii. Gene-replacement therapy protocol is foreseen
5. Linkage analysis of linked markers within or flanking the particular EB gene in families in which the inheritance pattern is known
6. Mutation detection for all forms of epidermolysis bullosa
   a. Mutation analysis
   b. Sequence analysis
7. Lethal acantholytic epidermolysis bullosa (Bolling et al. 2010)
   a. Electron microscopy
      i. Loss of keratin filament insertion and
      ii. Loss of the inner dense plaque
   b. A panel of antibodies directed against the desmoplakin C-terminus and the N-terminus/rod domain for immunofluorescence microscopy on a representative fresh frozen skin sample can provide an early diagnosis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal dominant
         a) 50% if a parent is affected
         b) Low recurrent risk when the parents are clinically unaffected
         c) Low recurrent risk but greater than that of the general population because of the possibility of germline mosaicism when the disease-causing mutation cannot be detected in the DNA of either parent
         d) Parental germline mosaicism have been reported in both EBS (Nagao-Watanabe et al. 2004) and DEB (Rouan et al. 1998; Cserhalmi-Friedman et al. 1999, 2001)
      ii. Autosomal recessive
         a) Carrier status of parents needs to be confirmed by molecular genetic testing because germline mosaicism and uniparental isodisomy have been reported (Takizawa et al. 2000; Cserhalmi-Friedman et al. 2002; Fassihi et al. 2005)
         b) Recurrence risk: 25%
   b. Patient's offspring
      i. Autosomal dominant
         a) A 50% risk of inheriting the mutation
         b) A 75% risk of having at least one mutation in the rare instance in which both parents have an autosomal dominant mutation such as in consanguineous union
      ii. Autosomal recessive: recurrence risk not increased unless the spouse is a carrier or affected

2. Prenatal diagnosis (Eady 2001; Fassihi and McGrath 2010)
   a. Fetal skin biopsy with EM analysis and/or immunohistochemistry with following drawbacks
      i. Drawbacks
         a) Fetal biopsy can only be obtained fairly late in gestation ($\geq$17 weeks)
         b) A relatively high rate of miscarriage
         c) Fetal status can only be determined by an expert in the ultrastructure of fetal skin who is qualified to make the diagnosis
      ii. An alternative option for rare families in which mutations cannot be identified and linked markers are not available to be used for prenatal diagnosis
   b. Villous trophoblasts, sampled during the first trimester, display immunoreactivity to $\alpha_6\beta_4$ integrin and plectin, thereby permitting diagnosis/exclusion of EB associated with pyloric atresia through tissue diagnosis (D'Alessio et al. 2008)
   c. DNA-based diagnosis on fetal DNA obtained by amniocentesis or CVS for all forms of epidermolysis bullosa
      i. Before any prenatal test, samples from both parents and any previous affected siblings are analyzed for pathogenic mutations
      ii. In autosomal recessive EB, ideally both parents must be shown to be heterozygous carriers of the pathogenic mutation(s)
      iii. The possibility of de novo mutations, nonpaternity, and uniparental disomy (the inheritance of both copies of a chromosome pair from just one parent) should be excluded before considering the suitability of the prenatal test
   d. Linkage analysis by linked markers within or flanking the *COL7A1* gene in several DEB families in which the inheritance pattern was known
   e. Preimplantation genetic diagnosis, an alternative to first-trimester prenatal diagnosis
      i. Involves in vitro fertilization, usually by intracytoplasmic sperm injection
      ii. Followed by the biopsy of a single cell from the eight-cell blastocysts (embryo)
      iii. Using complex polymerase chain reaction analysis to determine whether DNA from the single cell caries the parental mutations

3. Management (Herod et al. 2002; Bello et al. 2003)
   a. A multidisciplinary team approach, tailored to the severity and extent of skin involvement
   b. Blister management and dressing technique
      i. Avoidance of trauma as a primary goal
      ii. Puncture fresh blisters with a sterile needle and drain blister fluid with the blister roof left in situ so that the blister fluid cannot extend
      iii. Use white petrolatum-impregnated gauzes, hydrogels, fenestrated silicone dressings or absorbent foam silicone dressings for open wounds
      iv. Keep intravenous lines in place by using soft roller-gauze bandages
      v. Avoid dressing with adhesive tapes
      vi. Prevention and treatment of infections
   c. Prevention and treatment of complications (Pai and Marinkovich 2002)
      i. Change dressing regularly
         a) To control blistering and infection
         b) To prevent the debilitating contractures secondary to bullae formation in dystrophic EB
      ii. Physiotherapy
         a) To maintain mobility
         b) To decrease contracture formation
      iii. Corrective surgery recommended for digital fusion (mitten pseudosyndactyly) and contractures
      iv. Nutritional support
      v. Gastrointestinal management
         a) Dilatation of esophageal strictures
         b) Colonic interposition for advanced cases of strictures
         c) Gastrostomy tube insertion to provide nutrition
         d) Laxatives and increased dietary fiber for constipation, anal fissures, and perianal ulceration
      vi. Care for eye lesions
         a) Moisture chambers and ocular lubricants
         b) Treat corneal erosions with antibacterial ointments and use of cycloplegic agents to reduce ciliary spasms and provide comfort
      vii. Oral care
         a) Good oral hygiene
         b) Gentle cleaning of the mucosal surfaces with normal saline rinses
         c) Softest brush for regular cleansing

d. Pain management (Herod et al. 2002)
   i. Acute phase: experience considerable pain and discomfort caused by the expanding and often tense bulla
   ii. Chronic wounds: experience considerable pain caused by chronic wounds with denuded areas of skin and by therapeutic procedures
   iii. Analgesics
      a) Combination of paracetamol and ibuprofen or diclofenac for dressing changes associated with small wounds
      b) Potent analgesia and sedation required for large dressing changes (oral morphine solution and midazolam)
e. Management of anesthesia and surgery: should be undertaken in specialized centers familiar with the many complex aspects of EB care
f. Tumor detection in recessively inherited DEB
g. Advanced therapy to treat hard to heal wounds
   i. Cultured keratinocytes
   ii. Acellular dermal allograft plus ultrathin autografts
   iii. Living dermal skin substitute
   iv. Living bilayered skin equivalents
      a) Composite cultured skin (CCS)
      b) Graftskin
      c) Dermagraft

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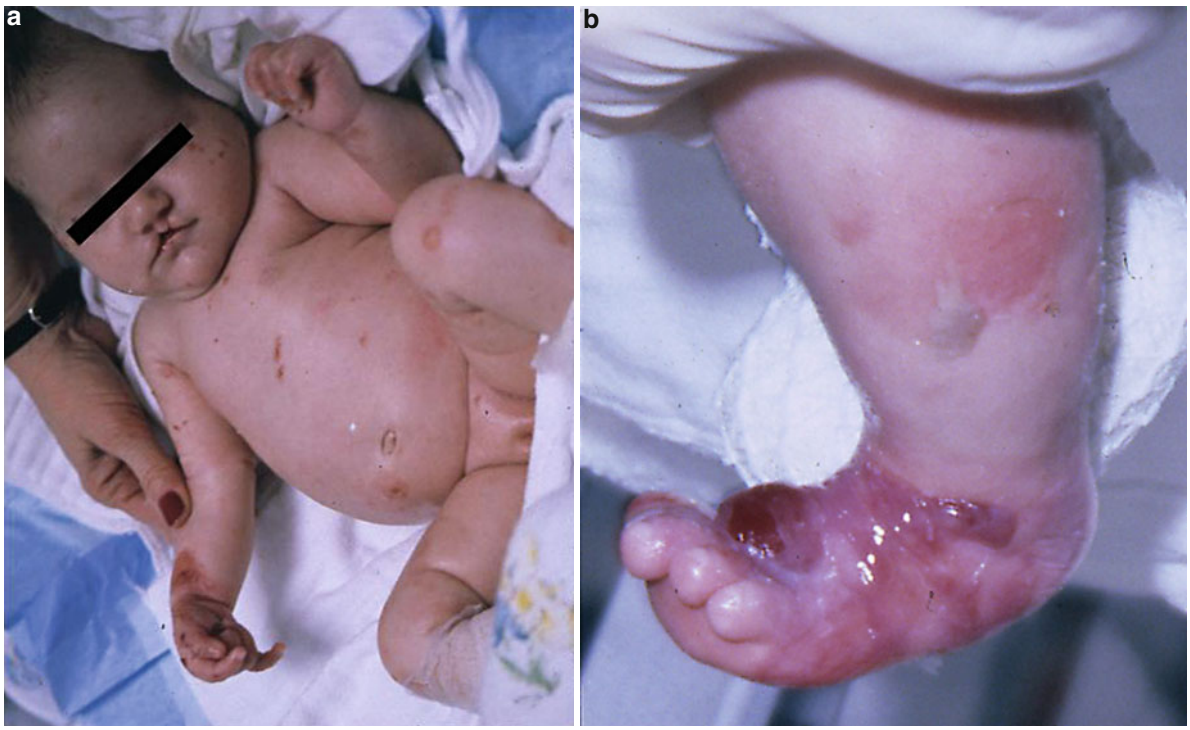

Fig. 1 (**a**, **b**) An infant with epidermolysis bullosa showing large blisters on the foot and smaller blisters on other part of the body

Fig. 2 (**a–d**) A 19-year-old female with recessively inherited dystrophic epidermolysis bullosa (Hallopeau-Siemens type) who was born with generalized blisters involving skin and mucosa, especially blisters and skin sloughing on the fingers and legs (**a**). She showed excessive fragile skin leading to blisters with minimal trauma, excessive scarring leading to contractures of the right foot and fusion of first and second toe on the right foot requiring surgical separation. She also had syndactyly of the second, third, and fourth toes of the left foot. The lesions were extremely itchy and painful and more severe on the lower extremity (**b**, **c**). At the time of these photos, the patient still had swallowing difficulty secondary to blistering lesion in the throat

Fig. 3 This infant was born with blisters on his hands, fingers, ankles, feet, toes, and oral mucosa, and part of the body. A biopsy of the lesion was consistent with dystrophic epidermolysis bullosa. In addition, he had a single umbilical artery, esophageal atresia, a single kidney, penile hypospadias, and unilateral preaxial polydactyly. At 12-weeks of age, he still showed scars on the oral mucosa and the chest and dystrophic lesions on the fingers

Epidermolytic Palmoplantar Keratoderma

Epidermolytic palmoplantar keratoderma (EPPK), first described by Vörner in 1901, may be the most common form of diffuse keratoderma and is characterized by keratosis restricted to the palms and soles. The disease is also known as keratosis palmaris et plantaris familiaris. The estimated incidence is at least 4.4 per 100,000 in Northern Ireland (Covello et al. 1998)

Synonyms and Related Disorders

Keratosis of Greither; Keratosis palmaris et plantaris; Localized epidermolytic hyperkeratosis; Vorner type plamoplantar keratoderma

Genetics/Basic Defects

1. Inheritance:
   a. Autosomal dominant
   b. Highly penetrant
2. Cause
   a. Keratin 9 (K9)
      i. A type 1 keratin gene (*KRT9*, located at 17q12-q21), a type 1 keratin expressed exclusively in the suprabasal keratinocytes of palmoplantar epidermis
      ii. Nearly 20 distinct pathogenic mutation in KRT9 have been identified in various ethnic kindreds with EPPK (Chen et al. 2009)
   b. Mutations in keratin 1 gene (*KRT1*) underlies mild EPPK (Terron-Kwiatkowski et al. 2002, 2006)

Clinical Features

1. Characteristic hyperkeratosis (Covello et al. 1998)
   a. Early onset: present at birth or during the first months of life
   b. Diffuse thick yellowish hyperkeratosis, distinctly limited to the palms and soles, with sharply bordered erythematous margins (virtually diagnostic of EPPK)
   c. Absence of associated features
2. Differential diagnosis (Lee et al. 2008)
   a. Diffuse hereditary PPK without associated features (Hatsell et al. 2001)
      i. Diffuse nonepidermolytic PPK (NEPPK)
         a) NEPPK: an autosomal dominant disorder
         b) Clinically difficult to distinguish between EPPK and NEPPK
         c) Histologically, EPPK shows epidermolysis of keratinocytes in the suprabasal layers, a characteristic not observed in NEPPK
         d) In mild cases of EPPK, diagnosis can still be problematic as detection of epidermolysis can be difficult
      ii. Progressive PPK
         a) Hyperkeratosis extends onto the dorsa of the hands and the feet with characteristic involvement of the Achilles tendon
         b) Hyperhidrosis common
         c) Intrafamilial phenotypic variation common
         d) Course of the disease: worsen during childhood, static after puberty, and improves in the fifth decade of life

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iii. Gamborg-Nielson PPK
  a) An autosomal recessive disorder
  b) Severe form of PPK delineated in two families with six patients in Sweden
  c) Thick, diffuse keratoderma with knuckle pads
  d) Occasional keratosis on the dorsa of the hands
  e) Mutilating changes due to constricting bands surrounding the fingers have been described

b. Diffuse hereditary PPK with associated features
  i. Mal de Meleda
    a) Described initially in inhabitants of the Adriatic Island of Meleda (Miljet)
    b) An autosomal recessive disorder
    c) Diffuse, thick keratoderma with prominent erythematous border extending onto the dorsa of the hands and the feet
    d) Constricting bands around digits resulting in spontaneous amputation
    e) Well-circumscribed psoriasis-like plaques or lichenoid patches on the knees and the elbows
    f) Hyperhidrosis
    g) Periorbital erythema and hyperkeratosis
    h) Nail changes (koilonychias, subungual hyperkeratosis)
    i) Other associated features (lingua plicata, syndactyly, hair on the palms and the soles, high arched palate, left handedness)
  ii. Vohwinkel PPK mutilans
    a) An autosomal dominant disorder
    b) Honeycomb-like keratosis of the palms and soles in infancy
    c) Constricting fibrous bands on the digits, leading to progressive strangulation and autoamputation
    d) Starfish-shaped keratosis on the dorsa of the fingers and the knees
    e) Other associated features (alopecia, deafness, spastic paraplegia, myopathy, ichthyosiform dermatosis, and nail abnormalities)
  iii. Olmsted mutilating PPK with periorificial keratotic plaques (Olmsted syndrome) (Da Rosa Santos et al. 1997; Tao et al. 2008)
    a) An autosomal dominant disorder
    b) Onset in the first year of life
    c) Symmetric, sharply circumscribed PPK, surrounded by erythema with flexion deformities of the digits, leading to constriction and spontaneous amputation (Poulin et al. 1984)
    d) Presence of hyperkeratotic plaques with a periorificial pattern (Atherton et al. 1990; Lucker and Steijlen 1994)
    e) Onychodystrophy
    f) Universal congenital alopecia
    g) Oral leukokeratosis
    h) Joint hyperlaxity
  iv. PPK with sclerodactyly
    a) An autosomal dominant disorder
    b) Sclerodactyly
    c) Diffuse keratoderma more marked on the soles than the palms
    d) Nail abnormalities
    e) Hypohidrosis
    f) Associated with squamous cell carcinoma
  v. PPK with periodontitis
    a) An autosomal recessive disorder
    b) Diffuse trangrediens palmoplantar dermatosis
    c) Periodontosis, unless treated, results in severe gingivitis and loss of teeth by age 5 years
    d) Increased susceptibility to infection
    e) Scaly, erythematous lesions often observed over the knees, the elbows, and the interphalangeal joints
    f) Hyperhidrosis with malodor
  vi. Clouston hidrotic ectodermal dysplasia
    a) Diffuse, papillomatous PPK
    b) Nail dystrophy
    c) Universal sparsity of hair
    d) Other associated features (sensorineural deafness, polydactyly, syndactyly, finger clubbing, mental retardation, dwarfism, photophobia, and strabismus)
  vii. Diffuse NEPPK and sensorineural deafness
    a) An autosomal dominant disorder
    b) Diffuse palmoplantar hyperkeratosis
    c) Associated with a slowly progressive, bilateral, high-frequency hearing loss
    d) Deafness precedes the skin changes

c. Focal (nummular) PPK without associated features
   i. Focal NEPPK
      a) An autosomal dominant disorder
      b) Palmar keratosis with a nummular, linear, membranaceous, fissured, or periungual configuration
      c) Plantar keratosis with a nummular appearance, localized to pressure points
   ii. Focal epidermolytic PPK
      a) An autosomal dominant disorder
      b) Nummular keratotic lesions,located mainly on plantar pressure points
      c) Painful lesions
   iii. Siemens PPK areata/striata
      a) An autosomal dominant disorder
      b) Marked variable phenotypic expression
      c) Marked erythema initially, followed by islands of linear hyperkeratosis
d. Focal (nummular) hereditary PPK with associated features
   i. Oculocutaneous tyrosinemia (tyrosinemia type II)
      a) Focal, painful PPK
      b) Bilateral, pseudoherpetic corneal ulceration, leading to corneal scarring and glaucoma
      c) Mental retardation
      d) Occasional hyperkeratotic lesions on the elbows, knees, and tongue
      e) Hyperhidrosis
      f) Occasional bullous lesions
   ii. Pachyonychia congenita
      a) Autosomal recessive disorder
      b) Localized areas of hyperkeratosis on the palms and the soles
      c) Discoloration and thickening of the nails
   iii. Keratosis palmaris and plantaris with carcinoma of the esophagus
      a) Autosomal dominant disorder
      b) Age of onset: 5–15 years
      c) Focal PPK
      d) Increased susceptibility to developing carcinoma of the esophagus (38-fold increase)
      e) Variable oral leukokeratosis and follicular keratosis
   iv. Focal palmoplantar and oral mucosa hyperkeratosis
      a) Autosomal dominant disorder
      b) Focal PPK, especially on weight-bearing areas
      c) Oral hyperkeratosis
      d) Increased severity with age
      e) Subungual and circumungual hyperkeratosis
e. Papular PPK without associated features
   i. Keratosis palmoplantaris punctata
      a) Autosomal dominant disorder
      b) Asymptomatic, tiny hyperkeratotic papules present on the palmoplantar surface
      c) Absence of associated features in most patients
      d) Spastic paralysis, ankylosing spondylitis, facial sebaceous hyperplasia reported
      e) Possible association with gastrointestinal malignancy
   ii. Acrokeratoelastoidosis
      a) Autosomal dominant disorder
      b) Round or oval, yellowish, hyperkeratotic papules that can appear umbilicated
      c) Distribution of the lesions: along the border of the palms and the soles
      d) Associated hyperhidrosis
   iii. Focal acral hyperkeratosis
      a) Autosomal dominant disorder
      b) Condition similar to acrokeratoelastoidosis
      c) Insidious onset in childhood, reaching maximum in early life
      d) Race: African origin
f. Papular PPK with associated features
   i. Rare single-pedigree syndromes
      a) Syndrome of cystic eyelids, punctate PPK, hypotrichosis, and hypodontia (Schopf–Schulz–Passarge syndrome)
      b) Punctate PPK with ankylosing spondylitis
      c) Punctate PPK with facial sebaceous hyperplasia
      d) Punctate PPK with spastic paralysis
      e) PPK with lipomata
   ii. Punctate PPK and cancer
g. Acquired palmoplantar keratoderma
   i. Inflammatory and reactive dermatoses
      a) Hyperkeratotic eczema
      b) Psoriasis
      c) Reiter syndrome
      d) Lichen planus
      e) Pityriasis rubra pilaris

f) Lupus erythematosus
g) Callosities
h) Darier disease

ii. Infective causes
a) Dermatophytes
b) Viral (human papilloma virus) warts mimicking keratoderma
c) AIDS-related psoriasis with discrete keratotic pustular keratoderma
d) Late secondary syphilis in patients with HIV with diffuse, symmetric keratoderma or papular PPK
e) Yaws
f) Leprosy

iii. Drugs
a) Chronic arsenic exposure with multiple, irregular, warty keratosis
b) Lodine: manifestation of drug hypersensitivity

iv. Cutaneous features of systemic disease
a) Myoedema with hyperkeratosis
b) Diabetes with discrete plantar keratosis
c) Cutaneous T-cell lymphoma with subungual hyperkeratosis

v. Haxthausen keratoderma climactericum
a) Onset in the 40s
b) Initial lesion: pressure areas on the soles
c) Erythema and hyperkeratosis with fissuring making walking painful
d) Minimal pruritus
e) Discrete and centrally confined palmar involvement

vi. Keratoderma associated with internal malignancy
a) Keratoderma as a paraneoplastic phenomenon, such as acrokeratosis paraneoplastica of Bazex associated with squamous cell carcinoma of the upper gastrointestinal tract and acanthosis palmaris associated with gastric or pulmonary malignancy in 90% of cases
b) Keratoderma as evidence of predisposition to malignancy such as late-onset punctate keratoderma associated with cutaneous and internal malignancy

h. Syndromes with PPK as an associated features
i. Basal cell nevus syndrome
ii. Congenital bullous ichthyosiform erythroderma
iii. Congenital nonbullous ichthyosiform erythroderma
iv. Darier disease
v. Epidermodysplasia verruciformis
vi. Epidermolysis bullosa herpetiformis
vii. Ichthyosis vulgaris
viii. Incontinentia pigmenti
ix. Keratitis, ichthyosis, and deafness (KID) syndrome
x. Lamellar ichthyosis

Diagnostic Investigations

1. Histology and ultrastructures: cytolysis of keratinocytes and abnormal aggregation of tonofilaments in the suprabasal layers of the epidermis
2. Molecular genetic analysis
   a. *KRT9* mutations analysis
      i. Sequencing of entire coding region
      ii. Sequencing of select exons
      iii. Targeted mutations analysis
   b. *KRT1* mutation analysis for patients with no mutations in *KRT9*

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased unless a parent is affected in which case there is a 50% risk
   b. Patient's offspring: 50%
2. Prenatal diagnosis
   a. Not usually requested because of mild nature of the disease
   b. Possible to pregnancy at-risk, provided the disease-causing mutation has been identified in the proband
   c. Accomplished in a Chinese kindred affected by EPPK for detection of c. T470C (p.M157T) of the keratin 9 gene from fetal DNA obtained by amniocentesis (Chen et al. 2009)
3. Management
   a. Topical keratolytics
   b. Topical retinoids such as tretinoin

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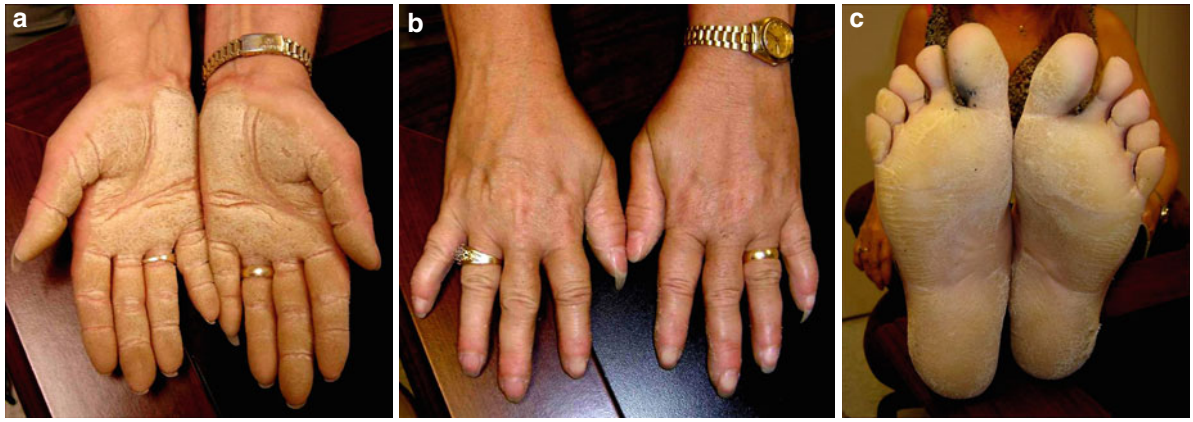

Fig. 1 (**a**–**c**) A 47-year-old woman with epidermolytic palmoplantar keratoderma showing diffuse keratoderma affecting both the palms and the soles. The keratoderma had erythematous border at the margins of both palms and soles and was completely restricted to the palms and soles. The dorsa of the hands and soles were spared. This patient has multiple affected relatives in several generations

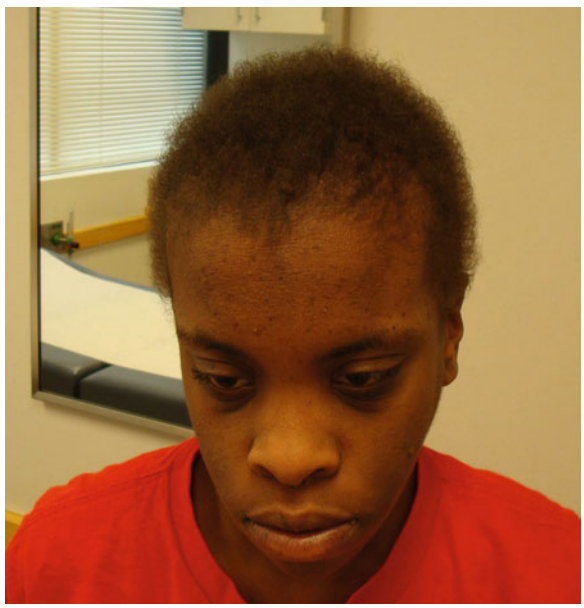

Fig. 2 This 17-year-old girl was seen for hyperkeratosis of the palms and soles associated with severe nail hyperplasia of the toes. She has mental retardation and short stature. Clinically she has type IV epidermolytic palmoplantar keratoderma with pachyonychia congenita

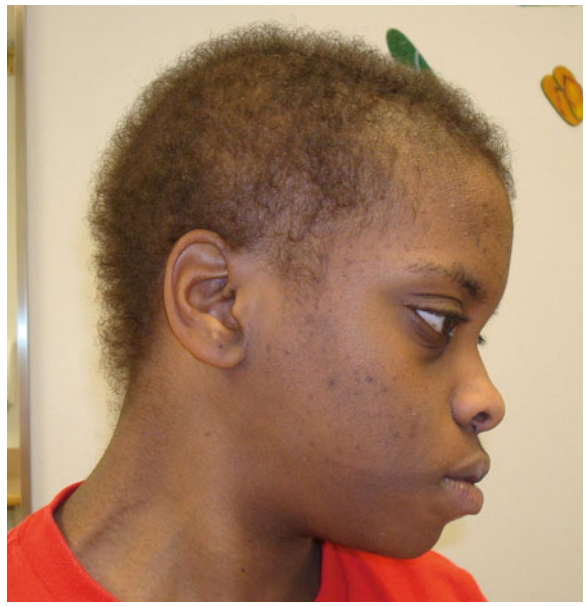

Fig. 3 She has marked midfacial hypoplasia

Fig. 4 Diffuse *thick* yellowish hyperkeratosis was noted on her palms. Her soles also have same *thick* yellowish hyperkeratosis

Fig. 5 Her toe nails show subungual keratinous mass pushing the nail bed upward

Faciogenital (Faciodigitogenital) Dysplasia

Faciogenital dysplasia (FGDY) was first described by Aarskog in 1970 (Aarskog 1970) as a familial syndrome of short stature associated with facial and genital anomalies. The occurrence of ligamentous laxity was emphasized by Scott in 1971 (Scott 1971). The syndrome is also known as Aarskog syndrome, Aarskog–Scott syndrome, and facio-digito-genital syndrome (Sugarman et al. 1973).

Synonyms and Related Disorders

Aarskog syndrome; Aarskog–Scott syndrome;

Genetics/Basic Defects

1. Inheritance
   a. X-linked recessive inheritance with occasional partial expression in the heterozygote
   b. Caused by mutations in the *FGDY* gene (*FGDY1*) affecting multiple skeletal structures including craniofacial bones, vertebrae, ribs, long bones, and phalanges
   c. First case of deletion of *FGD1* gene reported in a boy with Aarskog–Scott syndrome (Bedoyan et al. 2009)
2. The *FGDY1* gene (Schwartz et al. 2000)
   a. Mapped to the pericentromeric region of the X chromosome by the observation of an X;8 translocation in an affected mother and son (breakpoint at Xp11.21) (Pasteris et al. 1997)
   b. Encoding a guanine nucleotide exchange factor that specifically activates the P21 GTPase Cdc42, a member of the Rho (Ras homology) family of GTPase proteins (Gorski et al. 2000)

Clinical Features

1. Typical triad of the syndrome
   a. Facial appearance
      i. Rounded facies
      ii. Prominent metopic ridge
      iii. Widow's peak hair anomaly
      iv. Ocular hypertelorism
      v. Ptosis
      vi. Antimongoloid obliquity of palpebral fissures
      vii. Small and short nose
      viii. Anteverted nares
      ix. Broad nasal bridge
      x. Broad long philtrum
      xi. Maxillary and mandibular hypoplasia
      xii. Slight crease below lower lip
      xiii. Low-set ears with fleshy earlobes and incomplete outfolding of upper helices
   b. Digital anomalies
      i. Hands
         a) Short and broad hands
         b) Hypermobility of fingers
         c) Cutaneous syndactyly (interdigital webbing)
         d) Clinodactyly with hypoplasia of middle phalanges
         e) Transverse palmar crease
      ii. Feet
         a) Short and broad feet
         b) Bulbous toes
         c) Metatarsus varus
         d) Hypoplasia of the middle or terminal phalanges

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   c. Genital abnormalities
      i. Shawl scrotum (scrotal folds encircling the base of the penis)
      ii. Cryptorchidism
      iii. Phimosis
      iv. Hypoplasia
      v. Renal hypoplasia
2. Growth
   a. Failure to thrive
   b. Delayed puberty
   c. Slight to moderate (disproportionate acromelic) short stature (71%)
3. Intelligence and behavioral disorders
   a. Most individuals with normal intelligence: hyperactive and attention deficits present in 61% of these individuals, which usually regress after 12–14 years of age
   b. Individuals with subnormal to mentally retarded (30%): hyperactive and attention deficits present in 84% of these individuals
4. Dental abnormalities
   a. Hypodontia
   b. Retarded dental eruption
   c. Orthodontic problems
5. Ocular features
   a. Strabismus
   b. Nystagmus
   c. Amblyopia
   d. Bilateral blepharoptosis
   e. Astigmatism
   f. Hyperopia
   g. Anisometropia
   h. Corneal enlargement
   i. Deficient ocular elevation
   j. Blue sclera
   k. Posterior embryotoxon
   l. Ophthalmoplegia
   m. Tortuosity of the retinal vessels
6. Musculoskeletal anomalies
   a. Cervical vertebral anomalies
   b. Spina bifida occulta
   c. Mild pectus excavatum
   d. Genu recurvatum
   e. Joint restriction
   f. Prominent umbilicus
   g. Inguinal hernias
7. Other rare signs
   a. Gastrointestinal obstruction and volvulus in a few patients
   b. Rare perinatal occurrence of severe cerebrovascular accidents
8. Clinical variability and changing phenotype with age
9. Carrier females often present with minor manifestations of disorder, especially relatively short stature and subtle craniofacial anomalies (Pasteris et al. 1997)

Diagnostic Investigations

1. Ophthalmic examination
2. Radiography
   a. Ocular hypertelorism
   b. Short tubular bones with widened metaphysis
   c. Brachydactyly
   d. Clinodactyly of fifth fingers
   e. Hypoplastic middle phalanges
   f. Mild interdigital webbing
   g. Cubitus valgus
   h. Splayed toes with bulbous tips
   i. Metatarsus adductus
   j. Broad flat feet
   k. Cervical vertebral anomalies
      i. Odontoid hypoplasia
      ii. Fused cervical vertebrae
      iii. Spina bifida occulta
   l. Scoliosis
   m. Additional pairs of ribs
   n. Retarded bone age
3. Mutation analysis: by sequencing entire coding region of *FGD1* gene available clinically

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 50% risk of having affected brothers if the mother is a carrier; otherwise recurrence risk not increased
   b. Patient's offspring: 50% of his daughters to be carriers; no increased risk to his sons
2. Prenatal diagnosis
   a. Ultrasonography: possible with a positive family history of a previously affected child by demonstrating ocular hypertelorism, short long bones, vertebral defects, and digital anomalies in a male fetus
   b. Mutation analysis of fetal DNA from amniocytes or CVS provided the mutation has been previously identified in the proband

3. Management
   a. Supportive management
   b. Ophthalmological evaluation of the ocular problems for treatable causes of visual loss
   c. Surgery for cryptorchidism and inguinal hernia
   d. Reports of growth hormone treatment indicate a positive effect on growth and adult height in treated patients (Petryk et al. 1999)

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Fig. 1 (**a**–**c**) Two patients (*top* two photos are same patient) with faciogenital dysplasia showing short stature, round face, broad forehead, hypertelorism, mild ptosis, short nose with anteverted nostrils, long philtrum, low-set ears, and broad hands with webbing of fingers

Fig. 2 (**a**–**d**) Shawl scrotums observed in four patients with faciogenital dysplasia

Fig. 3 (**a**–**c**) A 3-year-old boy with faciogenital syndrome showing typical facial features (round face, prominent metopic ridge, ocular hypertelorism, low-set ears) and digital anomalies (short and broad hands and cutaneous syndactyly)

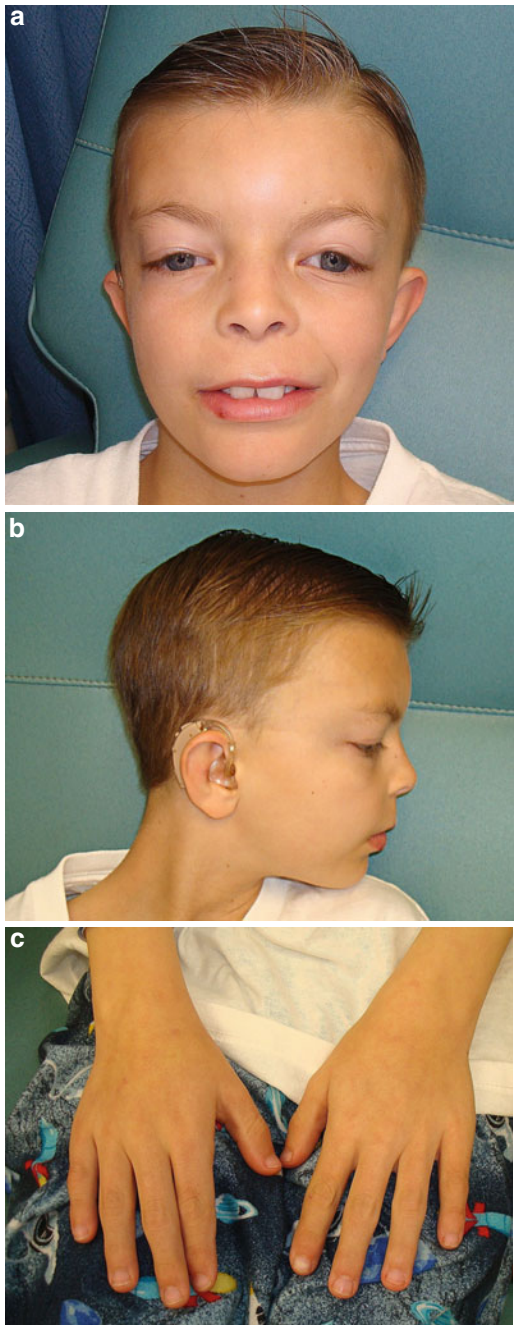

Fig. 4 (**a**–**c**) A 12-year-old boy was evaluated for short stature. On physical examination, he had ocular hypertelorism, ptosis, antimongoloid palpebral fissures, long philtrum, short and broad hands, and shawl scrotum. DNA sequencing identified a one basepair insertion at nucleotide 527 of the *FGDI* gene (c.527insC). This change is expected to cause a shift in the reading frame resulting in a truncated protein. This result is consistent with a diagnosis of Aarskog syndrome. In addition, he had sensorineural hearing loss. DNA sequence analysis indicated normal GJB2, connexin 26 (Cx26) gene

Fig. 5 His mother showed ocular hypertelorism, ptosis, and a long philtrum. She may represent a carrier with partial expression. Unfortunately, *FGS1* gene sequencing was not performed

Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common neuromuscular disorder after Duchenne muscular dystrophy and myotonic dystrophy. It is characterized by progressive weakness and atrophy of the facial and shoulder girdle muscles. The other muscles are also involved. Its prevalence is estimated to be 1 in 20,000 in Europe (Lunt and Harper 1991).

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant
   b. Almost complete penetrance (95%)
2. *FSHD1* gene
   a. Mapped to the subtelomeric region of chromosome 4q35
   b. Closely linked to the highly polymorphic locus D4F104S1
   c. Deletion of 3.3-kb tandemly repeated D4Z4 within the *Eco*RI fragment on chromosome 4q35: associated with the disease in 85–95% of FSHD families
   d. The deletion is pathogenic only when it is hypomethylated and resides in a 4qA161 allele (Lemmers et al. 2007)
   e. Candidate genes for FSHD not yet elucidated
   f. Nature of the precise mutation: still unknown
   g. Approximately 5% of FSHD families fail to exhibit linkage to 4q35, presumably indicating the presence of a second *FSHD1* locus (Upadhyaya et al. 1999)
3. Genotype-phenotype correlation
   a. Patients with a large gene deletion
      i. Tendency to have a higher chance of exhibiting severe clinical phenotypes
      ii. Higher chance of central nervous system abnormalities
   b. Patients with small *Eco*RI fragments
      i. Tendency to have earlier-onset disease
      ii. More rapid progression
   c. Correlation between the size of the disease-associated 4q35-*Eco*RI fragment and the following parameters
      i. Age at onset of symptoms
      ii. Age at loss of ambulation
      iii. Muscle strength as measured by quantitative isometric myometry
   d. De novo mutations
      i. Association with smaller *Eco*RI fragments (on average) than those segregating in families
      ii. Tendency of patients with de novo mutations to have findings the more severe end of the phenotypic spectrum
   e. Reduced penetrance in females bearing the FSHD small fragment as compared to the penetrance in males with the FSHD small fragment
4. Categories of FSHD (Padberg and van Engelen 2009)
   a. Severe disease, infantile form, onset usually before the age of 10 years with one to three residual D4Z4 repeats
   b. Moderate disease or classical phenotype with four to seven repeats and with a widely variable course, encompassing a large percentage of asymptomatic carriers older than 50 years, and 60% lower limb involvement with 20% wheelchair use after this age

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c. Mild disease with eight to ten residual D4Z4 repeats, probably with frequent nonpenetrant gene carriers and muscle involvement limited to the upper limbs

Clinical Features

1. Marked clinical variability
   a. Age at onset
      i. Usually between the first and second decade
      ii. Progress gradually over time
   b. Pattern of muscle involvement
      i. Progressive weakness and atrophy of the facial and shoulder girdle muscles
      ii. Other muscles affected in a specific order
         a) Abdominal muscles involved first
         b) Followed by foot-extensor and upper arm muscles
         c) Finally involving pelvic girdle and lower arm muscles
   c. Intrafamilial variability
   d. Inter-familial variability
   e. Phenotype ranging from almost asymptomatic forms to more severe wheelchair-bound forms
2. A distinctive distribution of progressive muscular weakness involving the following muscles (Kissel 1999)
   a. Facial muscles
      i. Typically involved:
         a) Orbicularis oculi
         b) Orbicularis oris
      ii. Clinical signs
         a) Often asymmetric involvement
         b) Facial weakness
         c) Unable to turn up the corners of the mouth when smiling
         d) Difficulty in whistling
         e) Unable to purse lips
         f) Sleeping with eyes partially open, the most common early sign
         g) Bury eyelashes when attempting to close eyelids tightly
         h) Sparing of extraocular, eyelid, and bulbar muscles
   b. Scapular stabilizer muscles
      i. Affected muscles
         a) Latissimus dorsi
         b) Trapezius
         c) Rhomboids
         d) Serratus anterior
      ii. Clinical signs
         a) Sloping shoulder posture at rest
         b) Anterior axillary folds
         c) Straight (horizontally placed) clavicles
         d) Pectoral muscle atrophy
         e) Scapular winging, the most common initial finding
         f) Preferential weakness of the lower trapezius muscle, resulting in characteristic upward movement of the scapula when attempting to flex or abduct the arms
   c. Proximal arm muscles
      i. Biceps and triceps selectively involved, resulting in atrophy of the upper arm
      ii. Distal progression of wasting and weakness of upper arm muscles, leading to eventual weakness of wrist and finger extensors
      iii. Deltoids minimally affected until late in the disease
      iv. Sparing of the forearm muscles, resulting in so-called "popeye arms" appearance
   d. Abdominal muscles
      i. Abdominal muscle weakness resulting in:
         a) Protuberance of the abdomen
         b) Exaggerated lumbar lordosis
      ii. Selective involvement of the lower abdominal muscles, resulting in Beevor's sign (upward displacement or occasionally downward movement of the umbilicus upon flexion of the neck in a supine position)
         a) Present in 90% of patients
         b) Helpful early sign in patients with equivocal findings, as it is rarely found in other muscle disorders
         c) Positive Beevor's sign may be caused by spinal cord injury at or below the level of Th10 (Eger et al. 2010)
   e. Lower extremity muscles
      i. Anterior compartment muscles of the distal leg (anterior tibial and peroneal muscles)
         a) Usually the first and most severely affected
         b) Resulting in the typical complaints of a foot slap while walking or frank foot drop

c) Frequent tripping or unstable walking, particularly on uneven ground
ii. Pelvic girdle muscles
a) Less common
b) Involving hip flexors and hip abductors
c) Resulting in early and relatively severe gait involvement
3. Degree of muscle involvement
a. Extremely variable
b. Wide range of muscle involvement
i. Very mildly affected patients unaware of the disease symptoms
ii. Isolated facial weakness
iii. Severe generalized weakness
iv. Eventually requiring a wheelchair in approximately 20% of patients
c. Sex difference in penetrance: males more severely affected than females
4. Clinical course of muscle involvement
a. Early involvement of facial and scapular muscles with eventual spreading to pelvic and lower limb muscles
b. A slowly progressive course
c. A stepwise course with periods of rapid deterioration occurring against a background of stability
d. Aggravation of muscle weakness during pregnancy but recover quickly in the puerperium
e. Bulbar and pharyngeal muscles, extraocular muscles, and respiratory muscles typically spared
5. Extra muscular involvement (uncommon)
a. Coats syndrome
i. Neurosensory hearing loss (64%)
ii. Retinal vasculopathy (49–75%)
a) Tortuosity of retinal arterioles (microaneurysms)
b) Telangiectasia
b. Mental impairment
c. Cardiac involvement (5%)
i. Conduction defects
ii. Supraventricular arrhythmia
d. Neurologic manifestations
i. Preserved sensation
ii. Often diminished reflexes
6. Diagnostic criteria include the following four main elements: The diagnosis of FSHD often remains a clinical diagnosis (Kissel 1999).
a. Onset of disease in the facial or shoulder girdle muscles, sparing the eyes, pharynx, tongue, and heart
b. Facial weakness in more than 50% of affected family members
c. Autosomal dominant inheritance in familial cases
d. Evidence of myopathic disease by electrodiagnostic studies and muscle biopsy in at least one affected family member

Diagnostic Investigations

1. Serum creatine kinase (CK)
a. Normal to elevated levels
b. Usually not exceeding three to five times the upper limit of the normal range
2. Audiogram for sensorineural hearing loss
3. Fluorescein angiography to demonstrate retinal vasculopathy
4. EMG: nonspecific myopathic features
a. Fibrillations
b. Positive waves in resting muscle
c. Early recruitment of short duration motor unit action potentials
5. Muscle biopsy: nonspecific features
a. Underlying process: myopathic and help to exclude the following primary muscle diseases that can present with a FSHD-like phenotype (Kissel 1999):
i. Congenital myopathies
a) Nemaline (rod) myopathy
b) Centronuclear myopathy
ii. Inflammatory myopathies
a) Polymyositis
b) Inclusion body myositis
iii. Other dystrophies
a) Scapuloperoneal dystrophy
b) Limb-girdle dystrophy
iv. Others: desmin-storage myopathy
b. Increased variation in fiber size
c. Increased internalized nuclei
d. Variable degrees of endomysial inflammatory cells
e. Angulated “neuropathic-like” myofibers
f. Mononuclear inflammatory reaction (75%)

6. Molecular genetic testing (Kissel 1999)
   a. Mutation analysis
      i. Detection of the short fragment in affected individuals
         a) High sensitivity and specificity of the 4q35 deletion for FSHD
         b) Using probe p13E-11 (D4F104S1), which hybridized to 4q35, to detect small *Eco*RI digestion fragments (Felice and Moore 2001)
         c) Deletion within the D4Z4 repeat region of chromosome 4q35 (demonstrable short fragment), observed in 95% of patients clinically affected with FSHD, whether familial or sporadic
         d) Approximately 98% of patients with such a short fragment have clinically demonstrable FSHD
         e) Confirms the diagnosis with a high degree of certainty
      ii. Large deletions in the 4q35 region (producing a smaller short fragment)
         a) Associated with more severe expression of the disease
         b) Manifest earlier onset of disease
         c) More severe degree of weakness
         d) Shorter fragment size generally associated with sporadic cases with an earlier age of onset than with familial cases
      iii. Variability in fragment size: unable to explain the significant clinical variability sometimes seen within FSHD families, since the deletion size appears to remain stable from generation to generation
      iv. Findings of a short but less intensively hybridizing p13E-11/*Eco*RI/*Bln*I fragment strongly suggest germinal mosaicism. Minor clinical signs in parents may point toward germline mosaicism
   b. Genetic diagnosis (Tawil et al. 2010)
      i. The large majority (>95%) of patients with FSHD have a partially deleted D4Z4 repeat array on one of their chromosomes 4 (FSHD1).
      ii. This repeat array is polymorphic in copy number, with alleles varying between 11 and 100 units in the general population
      iii. Patients with FSHD1 carry one allele with one to ten D4Z4 units (Tawil and van der Maarel 2006)
      iv. In order to be pathogenic, this shortened D4Z4 repeat array needs to reside on the 4qA background of chromosome 4
   c. Absence of identifiable D4Z4 deletions in approximately 5% of individuals with FSHD

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. 10% risk for a sib of a de novo case being a carrier. The figure of 10% is based on the observation that both somatic and germinal mosaics are detected, indicating that both types of mutations occur early in embryogenesis and therefore will give rise to a high percentage of mutated germ cells (Bakker et al. 1996)
      ii. 50% recurrence risk if a parent is affected
   b. Patient's offspring: Each offspring of an affected individual having a 50% chance of inheriting the deleted region within the D4Z4 repeat motif for FSHD
2. Prenatal diagnosis (Tawil et al. 2010)
   a. Available for fetuses at 50% risk for FSHD
   b. Molecular genetic testing: follow a de novo mutation in a subsequent generation by analyzing DNA extracted from fetal cells obtained by (Bakker et al. 1996):
      i. CVS: preferred over amniocentesis since genetic diagnosis for FSHD can take several weeks to complete
      ii. Amniocentesis
   c. Conditions for inclusion for prenatal diagnosis
      i. Confirmed FSHD1 in the family
      ii. Availability of DNA from parents and index case
   d. Preimplantation genetic diagnosis (PGD)
      i. Southern blot genetic test: not applicable to single cell PGD
      ii. Consequently, the disease-associated D4Z4 repeat can only be detected indirectly with the use of polymorphic markers, but the relatively high recombination frequency and the

availability of few polymorphic markers specific for the region proximal to D4Z4 hampers PGD significantly

3. Management (Kissel 1999; Figlewicz 2003)
   a. Lack of effective treatment
   b. Unpredictability of the clinical course
   c. Management of pain in the shoulders, back, abdomen, and leg
      i. Use of nonsteroidal anti-inflammatory drugs
      ii. Range-of-motion exercise
      iii. Gentle stretching through a physical therapy program
   d. Physiotherapy
   e. Supportive treatment of complications from progressive weakness
      i. Judicial use of bracing
      ii. Ankle and foot orthoses to improve mobility and prevent falls in patients with foot drop
      iii. Surgical fixation of the scapula to the chest wall (thoracoscapular fusion) or to the ribs (scapulocostal fusion)
         a) Often improving range of motion of the arms
         b) Short-lived effect in patients with rapidly progressive disease
   f. Pharmacologic treatment
      i. Limited to the use of corticosteroids in patients with evidence of inflammation on muscle biopsy
      ii. Possible effect of albuterol, a β2 adrenergic agent
         a) Improvement of lean body mass
         b) Modest improvement in strength
   g. Treat respiratory dysfunction which occurs in <1% of patients with FSHD (Wohlgemuth et al. 2004)
   h. Treat cardiac dysfunction which is seen in about 5% of patients (Laforet et al. 1998)
   i. Pregnancy in FSHD
      i. Pregnancy outcomes in FSHD: are generally good although two case series have conflicting reports about an increased incidence of operative deliveries and preterm births (Rudnik-Schoneborn et al. 1997; Ciafaloni et al. 2006)
      ii. Pregnant women with FSHD be followed by high risk obstetricians and that delivery occurs in a center that can provide comprehensive perinatal care
      iii. Additionally, it is recommended that pregnant women with FSHD and reduced lung function have serial monitoring of their FVC during the course of their pregnancy
   j. Required assistance in caring the infants after delivery due to weakness in the shoulder girdle

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Fig. 1 A child with FSHD showing periscapular wasting and weakness resulting in scapular winging and inability to abduct the arm above the horizon

Fig. 2 An adult with FSHD showing scapular winging and wasting of proximal arm muscles

Fig. 3 An adult with FSHD showing facial weakness and inability to smile, purse the lips, and whistle

Fig. 4 (**a–c**) A 14-year-old boy with FSHD showing sloping shoulders, inability to raise arms above shoulders, and inability to close his eyelids completely. In addition, he had difficulty in pursing the lips and could not whistle (onset at about 2 years of age). His CPK was 1,295 (normal: 0–200 U/L). Molecular genetic analysis revealed FSHD allele 1 of 18 kb and FSHD allele 2 of >48 kb (FSHD deletion, 12–37; marginal, 38–41; no deletion, ≥42). The mother and several other family members are also affected

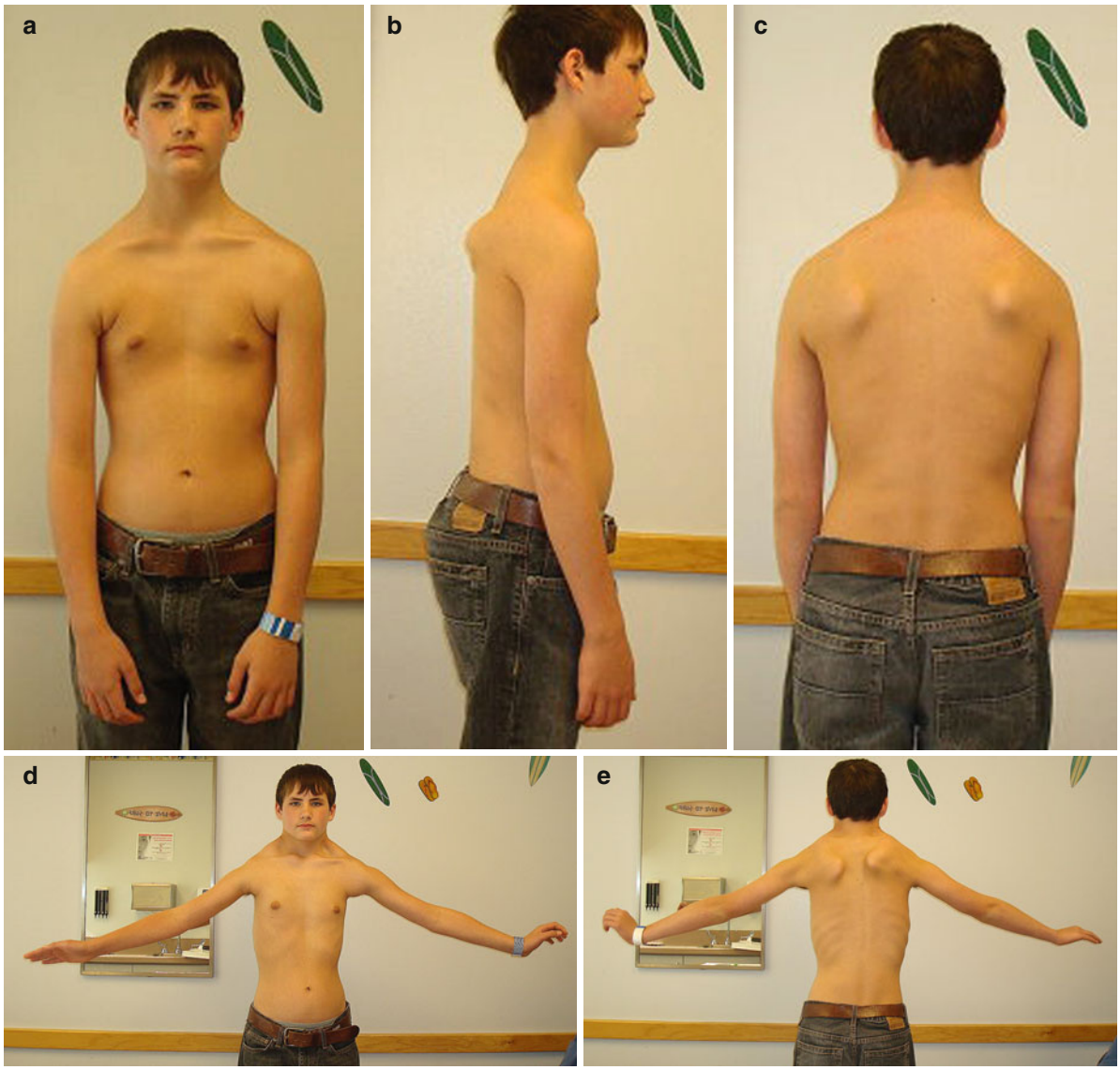

Fig. 5 (**a**–**e**) A 13-year-old boy was evaluated for his scapula deformities. He could not purse his lips, whistle, or smile. He could not raise his arms above his shoulders for the last 6 months. He had an elevated CK of 717 (normal: 35–232). On physical examination, he was noted to have sloping shoulder posture at rest, winging scapular, pectoral muscle atrophy, and mild atrophy of the upper arms. Molecular genetic testing revealed an FSHD gene mutation with allele 1 of 13 kb and allele 2 of >48 kb consistent with the diagnosis of facioscapulohumeral muscular dystrophy

Familial Adenomatous Polyposis

Germline mutations in the adenomatous polyposis coli (*APC*) gene cause the most common form of hereditary polyposis syndromes termed "familial adenomatous polyposis (FAP)." The incidence is approximately 1 in 8,300 to 1 in 13,000 live births.

Synonyms and Related Disorders

Adenomatous intestinal polyposis; Familial polyposis of the colon

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant with high penetrance (80–100%)
   b. Spontaneous mutations account for approximately 30% of cases
2. Caused by germline mutations in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21 (Lynch and Hoops 2002)
   a. More than 300 different disease-causing mutations of the *APC* gene are currently identified
   b. Nonsense or frameshift mutations that result in a truncated protein in nearly all of the germline mutations in APC
   c. Nearly 80% of FAP families have identifiable germline mutations in one allele of *APC* in affected individuals
   d. Similar high incidence of germline mutations is seen in the FAP variant, Gardner syndrome
3. *APC* gene
   a. A large gene consisting of approximately 6 kb in length
   b. A tumor suppressor gene encoding for a 2,843-amino acid protein with a putative role in:
      i. Cell adhesion
      ii. Signal transduction
      iii. Transcriptional activation
   c. The causative germline defect of *APC* gene predisposes to the following conditions:
      i. FAP
      ii. Nearly obligatory colorectal cancers
   d. Loss of second *APC* allele either by somatic mutation or loss of heterozygosity in the earliest premalignant lesions:
      i. Dysplastic aberrant crypt foci
      ii. Small adenomatous polyps
   e. Adenoma formation (Robbins and Itzkowitz 2002)
      i. Beginning with loss of function of the APC tumor suppressor gene
      ii. Followed by activation of the K-ras oncogene
      iii. Subsequent loss of function of genes on chromosome 18q and inactivation of p53 ushers in malignant degeneration
4. Colorectal carcinogenesis: involves two principal pathways (Robbins and Itzkowitz 2002):
   a. Chromosomal instability
      i. Deletion of portions of a chromosome results in loss of specific genes and abnormal amounts of DNA per cell (aneuploidy). This pathway accounts for:
         a) All cases of colorectal cancers associated with FAP
         b) Nearly 85% of sporadic colorectal cancers

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ii. The pathway of *c-myc* and *β-catenin* as downstream targets appears to impact on the kinetochore and microtubule attachment.
iii. Mutations in *APC* interfere with the way that epithelial cells divide and distribute their nuclear DNA.

b. Microsatellite instability
i. Produced by defects of the DNA base mismatch repair system
ii. This pathway accounts for:
a) 15% of sporadic colorectal cancers
b) Most cases of hereditary non-polyposis colorectal cancer

5. Genotype-phenotype correlation
a. FAP phenotype expressed in an individual depends in part on the site of the germline *APC* mutation
i. Attenuated familial adenomatous polyposis coli occurs when there is a truncating mutation in the extreme ends of the *APC* coding sequence
ii. Mutations between codons 169 and 1,393 resulting in classic FAP
iii. Mutations between codons 1,250 and 1,464, especially around codon 1,300, resulting in profuse colorectal polyposis and earlier onset of gastrointestinal polyps
iv. Retinal lesions (congenital hypertrophy of the retinal pigment epithelium, a condition present at any age in 60% of FAP families) occur only with mutations between codons 457 and 1,444 (Lynch and Hoops 2002; Cruz-Correa and Giardiello 2003)
v. Up to 60% of patients with mutations between codons 1,445 and 1,580 result in desmoids (Leggett 2002)
b. Limited clinical application of genotype-phenotype correlation: Considerable phenotypic variability exists even among individuals and families with identical genotypic mutations.

Clinical Features

1. Spectrum of disease activity (Half et al. 2009)
a. Attenuated FAP (AFAP): mild form of FAP
i. Fewer number of adenomatous polyps: less than 100
ii. A later age of adenoma development and onset for colorectal cancers
b. Fulminant FAP
i. With hundreds to thousands of polyps at a young age
ii. A nearly 100% risk of developing colorectal cancers by the age of 40
2. Usually asymptomatic until puberty when colonic polyps begins to develop, the adenomas become large and numerous so as to cause rectal bleeding or even anemia
3. Average age of onset of polyps: 25 years
4. Presenting signs and symptoms
a. Rectal bleeding: the most common symptom
b. Anemia
c. Abdominal pain
d. Change in bowel habits, constipation, or diarrhea, occurring approximately 8 years later
e. Palpable abdominal masses
f. Weight loss
g. Above signs and symptoms in young patients can lead to recto-sigmoid examination and identification of polyps suggestive of FAP
5. Relative and approximate contributions of familial causes to the incidence of colorectal cancer (Half et al. 2009)
a. About 85% of cases are sporadic
b. Approximately 10% are familial cancer
c. Three to five percent are hereditary nonpolyposis colorectal cancer (Lynch syndrome)
d. Less than one percent are FAP, familial juvenile polyposis, and Peutz–Jeghers syndrome
6. Colonic manifestations of FAP
a. Characterized by the presence of hundreds to thousands of colorectal adenomas of different sizes. Today this is rarely seen in countries with well-developed public health services
b. In the majority of patients polyps begin to develop during childhood, mostly in the distal colon (rectosigmoid) as small intramucosal nodules
c. By the time of adolescence, the polyps are usually identified throughout the colon and, thereafter, increase in size and numbers.
d. About half of FAP patients develop adenomas by 15 years of age and 95% by age 35 years (Petersen et al. 1991)
e. Generally, cancers start to develop a decade after the appearance of the polyps. So, if the

colon is left intact, the majority of patients with FAP eventually develop CRC by the ages 40–50 years.
f. Although uncommon, colorectal cancers can develop in children or in older adults
g. Other gastrointestinal manifestations
i. Gastric polyps (fundic gland polyps) develop in the stomach in 90% of patients with FAP
a) Typically benign
b) Adenomatous in rare cases
c) An increased rate of gastric cancer in some kindreds
d) Gastric cancer occur more frequently than duodenal cancer in Japanese FAP kindreds (Opposite is true for FAP kindreds with European Caucasian descent)
e) Gastric adenomas occur in 50% of Japanese FAP kindreds
ii. Duodenal or periampullary adenomatous polyps (5–10% lifetime risk)
a) May progress to cancer
b) Five percent of these patients develop malignant transformation within 20 years after the onset of polyps
iii. Other small intestinal tract polyps: rare
h. Adenomas of the ileal pouch may follow proctocolectomy
7. Extraintestinal manifestations
a. Pancreatic (2%) and biliary tract cancers: rare
b. Adrenal adenomas: rare
c. Papillary thyroid carcinomas
i. Affect about 1–2% of patients with FAP
ii. A hundred-fold increased risk in the women with FAP
iii. Activation of *ret*/*ptc1* oncogene in FAP-associated thyroid papillary carcinomas
d. Hepatoblastomas: a 1–3% risk of developing hepatoblastomas from birth until 6 years of age in infants and children who are at risk or known APC mutation carriers
e. Brain (medulloblastoma) (<1%)
f. Osteomas
g. Congenital hypertrophy of retinal pigment epithelium
i. Multiple and bilateral lesions: a sensitive phenotypic marker that can direct clinical screening tests prior to or in lieu of genetic screening in an at-risk member of an FAP kindred
ii. Generally a benign condition but low-grade adenocarcinoma of the retina has been reported in several individuals with this condition
h. Dental abnormalities
i. Unerupted teeth
ii. Congenital absence of one or more teeth
iii. Supernumerary teeth
iv. Dentigerous cysts
v. Odontomas
i. Cutaneous lesions: rarely malignant
i. Fibromas
ii. Lipomas
iii. Sebaceous and epidermoid cysts
iv. Nasopharyngeal angiofibromas
8. Desmoid tumors
a. Also known as mesenteric fibromatosis
b. A relatively common complication of FAP (Sturt and Clark 2006)
i. A lifetime risk for men: 8%
ii. A lifetime risk for women: 13%
c. No metastatic potential but can be both life-threatening or problematic in treatment when the lesions slowly expand:
i. To involve the intra-abdominal cavity
ii. To surround the nervous or vascular systems
d. Conditions which may accelerate the growth:
i. Surgery
ii. Estrogen receptor antagonists
iii. Radiation
iv. Chemotherapy
e. Common recurrence
9. FAP variants
a. Gardner syndrome
i. Refers to FAP with additional extra intestinal phenotypic manifestations accompanying colonic polyposis
a) Osteomas
b) Sebaceous cysts
c) Lipomas
d) Desmoids
e) Dental abnormalities
ii. Caused by mutations in the *APC* gene
b. Attenuated FAP
i. Characterized by the development of significantly fewer colonic adenomas (<100)
ii. Typically right-sided polyps

iii. Seventy percent of patients develop colorectal cancers by age 65 if polypectomy is not performed
iv. Presence of fundic gland polyps, a clue to the possible diagnosis of AFAP

c. Turcot syndrome
i. Characterized by medulloblastoma in association with colonic polyposis and colorectal cancers
ii. Caused by germline *APC* mutations
iii. Variable inter- and intrafamilial phenotypic expression

10. Differential diagnosis with two other main polyposis syndromes and one nonpolyposis syndrome, all of which are associated with an increased risk of GI cancer, especially colorectal cancer (Järvinen 2003)
a. Juvenile polyposis
i. An autosomal dominant disorder
ii. Caused by at least two separate genes
a) *SMAD4/DPC4* in chromosome 18q21
b) *BMPR1A/ALK3* in chromosome 10q21-22
iii. Characterized by multiple juvenile polyps of the colorectum
iv. Also involves the stomach and the small intestine
v. Large polyps
a) Commonly lobulated
b) Adenomatous dysplasia in 50% of cases, giving rise to the increased risk of colorectal cancer

b. Peutz–Jeghers polyposis
i. An autosomal dominant disorder
ii. Caused by mutations of the *LKB1* gene on 19p13.3
iii. Characteristics
a) Mucocutaneous melanin pigmentation
b) Hamartomatous intestinal polyposis
iv. Sites of polyps
a) Affect small intestine preferentially
b) Also affect stomach and large intestine

c. Hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome)
i. An autosomal dominant disorder
ii. Caused by mutations of three DNA mismatch repair genes
a) *MSH2* (2p21-23)
b) *MLH1* (3p21)
c) *MSH6* (2p16)
iii. More common than the polyposis syndromes
iv. Predominant tumors
a) Colorectal cancer
b) Endometrial cancer
v. Other cancer types: cancers of the stomach, ovary, ureter and renal pelvis, bile ducts, kidney, small intestine, and brain tumors

Diagnostic Investigations

1. Basis of diagnosis of classic FAP
a. Suggestive family history
b. Clinical findings
c. Confirmed by genetic testing whenever possible
2. Screening in FAP (Boardman 2002)
a. Colonoscopic examination for at-risk and *APC* mutation carriers, initiate at 10–12 years of age
b. Flexible sigmoidoscopy for at-risk individuals with unknown mutation status
i. Annually from age 10 to 15
ii. Biennially from age 26 to 35
iii. Every third year from age 36 to 50
c. Upper GI tract endoscopy for at-risk individuals with colorectal polyps and known gene carriers
d. Annual physical examination to assess thyroid nodules
e. Hepatoblastoma screening in children with FAP (at-risk or mutation-positive carriers until age 6)
i. Annual screening by liver ultrasonography
ii. Annual serum α-fetoprotein levels
f. Medulloblastoma screening: brain imaging for symptomatic or known Turcot syndrome kindreds
g. Imagings (King et al. 2000)
i. CT scan for desmoid tumors of the mesentery
ii. MRI to delineate vascular involvement and to predict desmoid growth
3. Screening in AFAP
a. Colonoscopy required for individual at risk for AFAP
b. Continued screening in the individual with AFAP because of the later age of onset of polyps
4. Detection of FAP in known kindreds
a. Retinoscopy: Presence of more than three pigmented ocular fundic lesions confirms the diagnosis of FAP

b. Flexible sigmoidoscopy
c. Presymptomatic *APC* gene testing
   i. Indications (Leggett 2002)
      a) Children and siblings of affected individuals with FAP or AFAP: usually delayed until the early teenage years (10 years or older) when screening by flexible sigmoidoscopy would normally commence
      b) Patients with an unusually high number of colorectal adenomas for their age but not enough to be clinically diagnostic of classical FAP ($\geq$20 cumulative colorectal adenomas, suspected AFAP)
      c) $\geq$100 colorectal adenomas
   ii. Methods (Boardman 2002)
      a) Protein truncation testing of peripheral blood lymphocytes: detects *APC* mutation in more than 80–90% of affected families
      b) Conformation strand gel electrophoresis
      c) Single-strand conformation polymorphism
      d) Direct sequencing
      e) Linkage analysis to markers on chromosome 5q
   iii. Germline *APC* testing: the most efficient means for identifying gene carriers within an FAP kindred
   iv. Direct sequencing targeted at the known region of the *APC* gene if a mutation has already been detected within one member of a kindred
      a) Cost-effective
      b) Nearly 90% accurate means of *APC* testing

5. Genetic tests for *MUTYH* (Half et al. 2009)
   a. A subset of patients that presents with clinical AFAP harbor a recessive disorder caused by the inheritance of mutations in the base-excision-repair gene *MUTYH* (Castellsagué et al. 2008)
   b. *MUTYH* mutation causes the polyposis condition known as *MUTYH* Attenuated FAP (MAP)
   c. It is recessively inherited and patients have either a homozygous or compound heterozygous germline mutations of the *MUTYH* gene.
   d. Recommended for all patients who have tens to hundreds of colorectal adenomas with no identified germline mutation in the *APC* gene and with a family history compatible with an autosomal recessive and rarely autosomal dominant modes of inheritance
   e. Therefore, DNA screening of the *MUTYH* gene should look for both heterozygous and homozygous mutations (Olschwang et al. 2007)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Not increased in a de novo case
      ii. 50% if a parent is affected
   b. Patient's offspring: a 50% risk of inheriting the condition and virtually all children who inherit the condition will develop polyposis (Leggett 2002)
2. Prenatal diagnosis
   a. Molecular genetic testing of the *APC* gene on fetal DNA obtained from amniocentesis or CVS for fetuses at 50% risk for FAP if a clinically diagnosed relative has an identified disease-causing *APC* gene alteration
   b. Linkage analysis if the family is informative for linked markers
3. Management (Boardman 2002)
   a. Pre- and post-test genetic counseling
      i. A pre-test counseling session covering:
         a) The nature of the disease itself
         b) The genetic aspects
         c) The implications of positive and negative test results on future screenings
         d) On insurability and family relationships
      ii. A post-test counseling session
         a) Disclosure of the results
         b) Addressing psychological consequences
   b. Potential consequences of genetic testing for hereditary colorectal cancer (Trimbath and Giardiello 2002)
      i. Positive consequences if the result is gene positive (the disease-causing mutation detected)
         a) Removal of uncertainty
         b) Early detection of polyps and prevention of cancer
         c) Greater ability to plan the future including family and career decisions

d) Increased compliance with colonic screening/surveillance
e) Greater choice of surgical and medical management

ii. Negative consequences if the result is gene positive (the disease-causing mutation detected)
a) Psychological distress, including anxiety, depression, anger, or denial
b) Changes in family psychosocial dynamics
c) Stigmatization
d) Increased fear about surgery or death
e) Children at 50% risk of disease
f) Guilt/worry about children
g) Colon surgery and possible lifestyle changes

iii. Positive consequences if the result is gene negative (truly negative for gene mutation identified in family)
a) Removal of uncertainty
b) Children not at risk
c) Fewer medical exams and costs
d) Better insurability

iv. Negative consequences if the result is gene negative (truly negative for gene mutation identified in family)
a) Survival guilt (guilt about being unaffected when other family members are affected)
b) Changes in family psychosocial dynamics

v. Negative consequences if the result is inconclusive (no pedigree mutation found or variant of unknown significance)
a) False sense of security
b) Does not rule out risk for disease
c) Need for continued screening
d) Confusion/anxiety

c. FAP
i. Prophylactic surgery remains the best means to minimize the risk of developing colorectal cancers
ii. Consider colectomy
a) By late teen years for cancer prophylaxis for both gene carriers and at-risk individuals with polyposis
b) Without colectomy, colorectal cancer is inevitable, appearing approximately 10–15 years after the onset of polyposis
iii. Specific surgical recommendation
a) Proctocolectomy with mucosectomy
b) Ileal pouch anal anastomoses
c) Ileorectal anastomosis
iv. Surgical removal of osteomas for cosmetic reasons
v. Treatments for desmoid tumors
a) Surgical excision: associated with high rates of recurrence
b) Non-steroidal anti-inflammatory drugs (sulindac, celecoxib) (use before colectomy): remains experimental
c) Antiestrogens
d) Cytotoxic chemotherapy
e) Radiation
vi. Celecoxib, a selective cyclooxygenase-2 (prostaglandin synthetase) inhibitor (Corredor et al. 2001)
a) Reduces by 28% the mean number of polyps in adult patients with FAP
b) Potential use of this class of drugs as chemopreventive and therapeutic agents: subject of intense current investigation

d. AFAP
i. Endoscopy and polypectomy
ii. Surgery: ileorectostomy rather than ileal pouch anal anastomosis is recommended because the rectum is relatively spared by polyposis
a) For recurrent, numerous polyposis
b) For the presence of aggressive histologic features
iii. Continued need for annual endoscopic evaluation of the rectal remnant

e. Prognosis (Half et al. 2009)
i. Most patients with clinical FAP can be identified and have their diagnosis confirmed by genetic testing
ii. Individuals with FAP carry a 100% risk of colorectal cancer that is reduced almost absolutely when patients enter a screening and treatment program
iii. Once proctocolectomy has been performed, the risk of ampullary and duodenal cancer is significant and requires lifelong upper gastrointestinal surveillance that has been shown to save lives of FAP patients
iv. Desmoids need to be identified early while small and not causing local perturbations

v. Duodenal cancer and desmoids are the two main causes of mortality after total colectomy has removed the risk for CRC
vi. The sociological, psychological, and physiological issues related to the diagnosis and treatment of FAP need to be addressed
vii. The colectomy and ensuing change in bowel habits frequently lead to dietary changes that can be unbalanced and lead to vitamin–mineral deficiencies.

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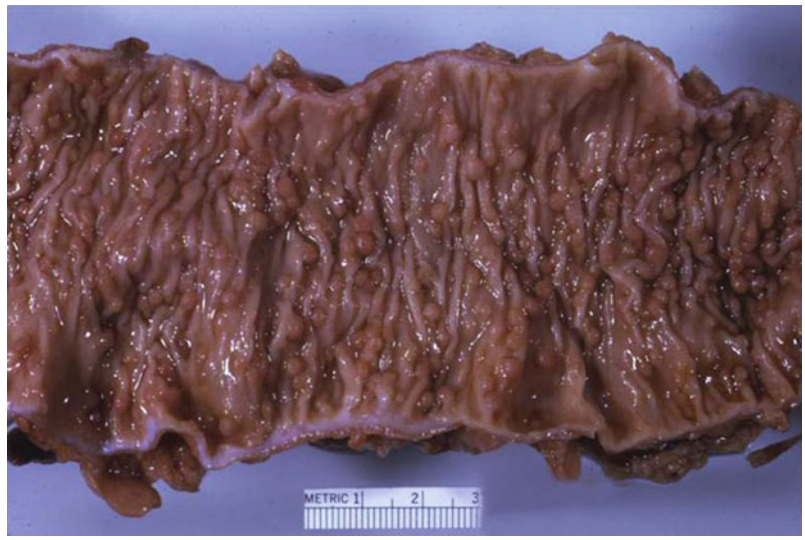

Fig. 1 Colon of an 8-year-old girl with familial adenomatous polyposis. Numerous small polyps were present on the mucosal surface of the entire colon. The polyps measured up to 3 mm in size. Occasional polyps had a slender stalk, up to 2 mm in length. Histologically, the polyps were of tubular (adenomatous) type

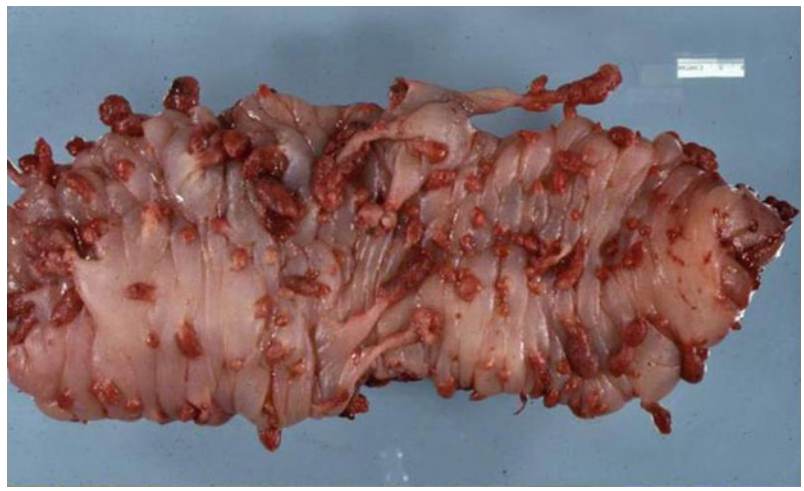

Fig. 2 A segment of colon showing juvenile polyposis. The polyps are large and lobulated. Stalks are present in some of them. The number of polyps is not as numerous as seen in Fig. 1 (AFP)

Fig. 3 A 50-year-old female had a history of multiple removals of numerous pedunculated and sessile polyps (adenomatous) during past 12 years. Her mother was diagnosed with colon cancers and had most colon surgically removed. Molecular testing of the patient showed intron 3 alteration [IVS3(−3)T > A]. Aberrations within the intron can affect normal splicing of RNA. Whether this is a disease-causing mutation or a normal variant cannot be determined without determination of the mother's DNA status

Familial Hyperlysinemia

Familial hyperlysinemia is an inborn error of metabolism caused by a defect in the bifunctional protein α-aminoadipic semialdehyde synthase.

Synonyms and Related Disorders

Alpha-aminoadipic semialdehyde synthase deficiency; L-lysine NAD-oxido-reductase deficiency; Lysine: alpha-ketoglutarate reductase deficiency

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. A heterogeneous group of at least three disorders
   a. Caused by mutations in the gene (mapped to 7q31.3) encoding α-aminoadipic semialdehyde synthase (AASS), the bifunctional protein that contains both lysine-ketoglutarate reductase (LKR) and saccharopine dehydrogenase (SDH) activity.
   b. Deficiency in lysine-ketoglutarate reductase (LKR) and/or saccharopine dehydrogenase (SDH) activities leads to a clinical phenotype characterized by hyperlysinemia, lysinuria, and variable saccharopinuria.
   c. Deficiency in saccharopine oxidoreductase activity, along with deficient LKR and SDH activities, is also observed in children with familial hyperlysinemia.

Clinical Features

1. Mental retardation of varying degree
2. Other neuromuscular manifestations
   a. Poor muscle tone (hypotonia)
   b. Muscle weakness
   c. Clumsy hand movements
   d. Cross adductor reflexes
   e. Ankles clonus
   f. High-arched feet
   g. Awkward gait
   h. Hyperactive deep tendon reflexes
   i. Seizures
   j. Progressive spastic paraparesis/diplegia
3. Developmental delay, especially speech delay
4. Hyperactive behavior
5. Ligamentous laxity
6. Ocular manifestations
   a. Bilateral subluxated lenses (ectopia lentis)
   b. Lateral rectus muscle paresis
   c. Bilateral spherophakia
7. Hyperlysinemia alone may not be associated with a clinical phenotype.
8. Differential diagnosis
   a. Hyperlysinemia: periodic hyperlysinemia with ammonia intoxication
   b. Ectopia lentis
      i. Marfan syndrome
      ii. Homocystinuria
      iii. Weill-Marchesani syndrome
      iv. Ehlers–Danlos syndromes
      v. Dominant and recessive forms of inherited subluxation of the lens

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Diagnostic Investigations

1. Plasma amino acid quantitative analysis: hyperlysinemia
2. Urinary amino acid quantitative analysis: hyperlysinuria
3. Urinary organic acid analysis: variable saccharopinuria
4. Cultured skin fibroblasts: absent lysine-ketoglutarate reductase and saccharopine dehydrogenase activities
5. Molecular genetic study: homozygous deletion in *AASS* gene
6. EEG for seizures

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is a carrier in which case 50% of the offspring will be affected
2. Prenatal diagnosis has not been reported.
3. Management
   a. Dietary control with reduction in lysine intake
   b. Other supportive therapies

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Fig. 1 A 27-year-old female with hyperlysinemia showing global delay, spasticity, rigidity, and multiple joint contractures. She was diagnosed to have hyperlysinemia since about 1 1/2 years of age with markedly elevated serum lysine of 1,618 μM (45–144). As a neonate, she had frequent emesis and noted to be stiff and irritable with progressive developmental delay. She began to walk with a ramp and rails until approximately 4 years of age when she started to develop increased spasticity and significant scissoring, necessitating adductor release. On the recent plasma amino acid analysis, lysine was markedly elevated at 1,252 μM (41–225)

Familial Mediterranean Fever

Familial Mediterranean Fever (FMF), also known as an autoinflammatory syndrome, is the most frequent periodic fever syndrome, affecting not only eastern Mediterranean people such as non-Ashkenazi Jews, Armenians, Arabs, and Turks but also reported throughout the world's populations.

Genetics/Basic Defects

1. An autosomal recessive disorder caused by missense mutations in the *MEFV* gene, located on the short arm of chromosome 16 (16p13.3). The *MEFV* gene is responsible for encoding a protein called pyrin or marenostrin.
2. Pathogenesis
   a. Partially elucidated only after the identification of pyrin or marenostrin
   b. A new macromolecular complex, called inflammasome, seems to play a major role in the control of inflammation and it might be involved in the pathogenesis of FMF.
3. Phenotype expression of the FMF should depend on the presence of a homozygote or heterozygote genotype for the *MEFV* gene mutations.
4. Genotype-phenotype correlation, however, is complex due to influence of genotype and the ethnic and environmental factors, playing a role in the clinical outcome with a very wide clinical spectrum
5. Etiology of the periodicity and the self-limited nature remain largely unexplained

Clinical Features

1. Clinical manifestations (Fonnesu et al. 2009)
   a. Onset of the disease: occurs before the age of 30 in almost all patients
   b. Recurrent attacks
      i. Last 1–4 days on average
      ii. Resolve spontaneously with a frequency varying from once a week to once every 3–4 months or, sometimes, years
      iii. Severity and frequency of attacks have an inter- and intra-individual variations
   c. Presence of fever: absent in rare cases
   d. Gastrointestinal symptoms
      i. Abdominal pain: localized or diffuse
      ii. Stypsis/diarrhea
      iii. Associated disease
   e. Musculoskeletal symptoms
      i. Arthralgia: transient or abortive
      ii. Arthritis
         a) Acute asymmetric nondegenerative mono/oligoarthritis
         b) Protracted arthritis
         c) Chronic degenerative arthritis
         d) Migrating polyarthritis: usually induced by exertion
      iii. Myalgias
      iv. HLA-B27 negative sacroiliitis during the prodromes or the attack
   f. Cardiopulmonary symptoms
      i. Pleuritis
      ii. Pericarditis

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   g. Cutaneous symptoms: erysipelas-like erythema
   h. Vasculitis
      i. Henoch–Schoenlein purpura
      ii. Polyarteritis nodosa
      iii. Behcet disease
   i. Other manifestations
      i. Acute orchitis
      ii. Mollaret's meningitis
      iii. Splenomegaly
      iv. Retinopathy
2. Known trigger factors
   a. Physical and emotional stress
   b. Exposure to cold
   c. Fat-rich meals
   d. Banal infections
   e. Drugs such as cisplatin
   f. Menstrual cycle
   g. Presence of *Helicobacter pylori*
3. Secondary amyloidosis: the most devastating and important long-term complication
   a. Predominantly renal
   b. Genetic risk factors
      i. Genetic factors linked to *MEFV* gene
      ii. Genetic factors linked to modifier genes (Seroamyloid A gene – SAA – and Major Histocompatibility Complex class 1 chain-related A gene – MICA)
   c. Nongenetic factors
      i. Male gender: males four times higher than in females
      ii. Environmental factors: country identified as the primary risk factor for renal amyloidosis (e.g., Armenians residing in Armenia have higher incidence than those who reside in the USA)
4. Two phenotypes of FMF (Shohat et al. 2009)
   a. FMF type I
      i. Characterized by recurrent short episodes of inflammation and serositis including:
         a) Fever
         b) Peritonitis
         c) Synovitis
         d) Pleuritis
         e) Rarely pericarditis and meningitis
      ii. Inter-individual and intra-familial variation of symptoms
      iii. Amyloidosis which can lead to renal failure is the most severe complication of FMF type I
   b. FMF type II: characterized by amyloidosis as the first clinical manifestation of disease in an otherwise asymptomatic individual (Pras 1998; Langevitz et al. 1999; Shohat et al. 1999; Koné Paut et al. 2000)
5. Differential diagnosis (Lidar and Livneh 2007)
   a. Abdominal attacks (recurrent peritonitis)
      i. Appendicitis
      ii. Diverticulitis
      iii. Cholecystitis
      iv. Pyelonephritis
      v. Pelvic inflammatory disease
      vi. Pancreatitis
   b. Recurrent abdominal attacks (without peritonitis)
      i. Peptic disease
      ii. Renal colic
      iii. Endometriosis
      iv. Menstruation pain
      v. Irritable bowel syndrome
   c. Chest attacks (recurrent pleuritic chest pain)
      i. Pulmonary embolism
      ii. Pleuritis (idiopathic, infectious, autoimmune)
      iii. Pericarditis (idiopathic, infectious, autoimmune)
   d. Joint attacks (recurrent synovitis)
      i. Gout
      ii. Pseudogout
      iii. Spondyloarthropathy
      iv. Juvenile idiopathic arthritis
   e. Febrile attacks (recurrent)
      i. Lymphoma
      ii. Infections (malaria, relapsing fever)
      iii. PFAPA (periodic fever, aphtous stomatitis, pharyngitis, adenopathy)
   f. Non-FMF inflammatory disorders (Ozen 2003)
      i. Inflammatory bowel disease
      ii. Hyper IgD syndrome
      iii. Tumor necrosis factor receptor–associated periodic fever syndrome
      iv. Acute intermittent porphyria
      v. Familial cold urticaria or familial cold auto-inflammatory syndrome
   g. Systemic lupus erythematosus
   h. Adult Still disease
   i. Muckle–Wells syndrome
   j. Chronic infantile neurological cutaneous arthropathy
   k. Neonatal onset multi-system inflammatory disease syndrome
   l. Periodic fever-adenopathy-pharyngitis-aphtosis syndrome

Diagnostic Investigations

1. Pras diagnostic criteria (Pras 2002)
   a. Recurrent short inflammatory attacks
   b. A favorable response to colchicine treatment
2. Tel-Hashomer diagnostic criteria (Livneh et al. 1997; Fonnesu et al. 2009)
   a. Major criteria
      i. Fever and serositis
      ii. Amyloidosis AA (without risk factors or other chronic inflammatory diseases)
      iii. Effectiveness of colchicine
   b. Minor criteria
      i. Recurrent attacks of fever
      ii. Erysipela-like erythema
      iii. Relatives affected by FMF
   c. Definitive diagnosis: two major criteria or one major criterion and two minor criteria
   d. Probable diagnosis: one major criterion and one minor criterion
3. Tel-Hashomer revised diagnostic criteria (Fonnesu et al. 2009)
   a. Presence of typical attacks
      i. Fever
      ii. Serositis
   b. Positive response to colchicine
4. Criteria for the diagnosis of FMF (Lidar and Livneh 2007)
   a. Major criteria: typical attacks (recurrent, febrile, and short)
      i. Peritonitis (generalized)
      ii. Pleuritis (unilateral) or pericarditis
      iii. Monoarthritis (hip, knee, ankle)
   b. Minor criteria
      i. Incomplete (painful and recurrent) attacks involving one or more of the following sites:
         a) Abdomen
         b) Chest
         c) Joint
      ii. Exertional leg pain
      iii. Favorable response to colchicine
   c. Supportive criteria
      i. Family history of familial mediterranean fever
      ii. Appropriate ethnic origin
      iii. Age <20 years at disease onset
      iv. Features of attacks
         a) Severe, requiring bed rest
         b) Spontaneous remission
         c) Symptom-free interval
         d) Transient inflammatory response with one or more abnormal test result(s) for white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen
      v. Episodic proteinuria/hematuria
      vi. Unproductive laparotomy or removal of "White" appendix
      vii. Consanguinity of parents
   d. Requirements for diagnosis of FMF
      i. Greater than or equal to one major criteria, or
      ii. Greater than or equal to two minor criteria, or
      iii. One minor plus >5 supportive criteria
5. Molecular genetic study of the MEFV gene to confirm the diagnosis
6. General clinical laboratory findings
   a. Leukocytosis
   b. Leukopenia associated with colchicine treatment
   c. Elevated acute-phase reactant proteins such as ESR, CRP, fibrinogen, haptoglobin, C3, C4, and serum amyloid A (SAA) protein
   d. Urinalysis for the presence of proteinuria
7. Diagnostic algorithm (Lidar and Livneh 2007)
   a. Clinical criteria
   b. Results of MEFV mutation analysis
   c. Therapeutic trial, monitored by clinical response and SAA levels
8. Renal biopsy: indicated in all FMF patients who develop proteinuria or nephrotic syndrome

Genetic Counseling

1. Recurrence risk
   a. Both parents carrying at least one *MEFV* gene mutation
   b. Patient's sib
      i. Twenty-five percent with MFM
      ii. Fifty percent with MFM carrier
   c. Patient's offspring
      i. All offspring inherit one *MEFV* gene mutation from the proband
      ii. Low recurrence risk unless the spouse is affected or a carrier of *MEFV* gene mutation
2. Prenatal diagnosis (Shohat et al. 2009)
   a. Possible for pregnancies at increased risk by analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus

sampling, giving that both disease-causing alleles of an affected family member must be identified or linkage established in the family before prenatal testing can be performed

b. Prenatal diagnosis of FMF, a treatable condition associated with a good prognosis with early treatment, may be controversial if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis

3. Management
   a. Colchicine
      i. Should be introduced as soon as the diagnosis is made and continued for life
      ii. Reduces the attack frequency, severity, and duration in most FMF patients
      iii. Can prevent, arrest, and even reverse renal amyloidosis, even if it fails to stop the attacks (Lidar et al. 2004; Kallinich et al. 2007)
      iv. Also recommended for treatment of amyloidosis
      v. Higher colchicines dosage, up to 2 mg/day, may be needed in high-risk patients such as after kidney transplantation or patients with amyloidosis
   b. No effective mean to treat acute attacks of FMF
      i. Methylprednisolone may relieve abdominal pain and tenderness (Erken et al. 2008), although steroids in general play no role
      ii. Interferon (IFN)-α injection at the earliest signs of an attack may provide some benefit (Tunca et al. 2004; Tweezer-Zaks et al. 2008)
   c. Controversy in treating asymptomatic individuals with mutations in the *MEFV* gene who may or may not develop FMF in the future

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Fig. 1 A 40-year-old female was diagnosed to have familial Mediterranean fever. She has a history of low grade fever, abdominal pain, joint pain, and peritonitis. She responded well to colchicine treatment. She is a compound heterozygote for two different mutations: MM680I and V726A, in exon 10 of the *MEFV* gene which confirms the clinical diagnosis. Her brother and sister are similarly affected. Her 5-year-old daughter was found to be heterozygous for the V726A FMF mutation. The parents are from Egypt

Fanconi Anemia

In 1927, Fanconi described a familial form of aplastic anemia in three brothers with short stature, hypogonadism, and skin pigmentation. The incidence of Fanconi anemia (FA) is estimated to be 1 in 360,000 births. The carrier frequency is estimated as 1 in 300 in Europe and the United States. Founder mutations have been described in Ashkenazi Jews, who have carrier frequency of 1 in 89 (Tischkowitz and Hodgson 2003).

Genetics/Basic Defects

1. Inheritance
   a. Autosomal recessive
   b. Genetically and phenotypically heterogeneous
2. Presence of at least 13 complementation groups delineated by cell fusion studies (Dokal 2000; Blom et al. 2004)
   a. FA-A (65–70%)
   b. FA-B (<2%)
   c. FA-C (10–15%)
   d. FA-D1
   e. FA-D2
   f. FA-E (2–5%)
   g. FA-F (<2%)
   h. FA-G (10%)
   i. FA-I
   j. FA-J
   k. FA-L
   l. FA-M
   m. FA-N
3. The FA pathway is composed of at least 13 genes. Each of these genes, when biallelically mutated causes FA. (Green and Kupfer 2009)
   a. *FANCA*, mapped to 16q24.3
   b. *FANCB*, mapped to Xp22.31
   c. *FANCC*, mapped to 9q22.3
   d. *FANCD1*, mapped to 13q12.13
   e. *FANCD2*, mapped to 3p25.3
   f. *FANCE*, mapped to 6p21.22
   g. *FANCF*, mapped to 11p15
   h. *FANCG*, mapped to 9p13
   i. *FANCI*, mapped to 15q25-26
   j. *FANCJ*, mapped to 17q22-24
   k. *FANCL*, mapped to 2p16.1
   l. *FNACM*, mapped to 14q21.3
   m. *FNACN*, mapped to 16p12
4. A candidate-gene approach leads to the breast cancer susceptibility gene BRCA2 as the gene defective in FA-D1 patients. The Fanconi–BRCA pathway is activated in response to certain kinds of DNA damage, particularly DNA agents that cause double-strand breaks in DNA such as ultraviolet light, ionizing radiation, and cisplatin.
5. FA cells are hypersensitive to cross-linking agents such as diepoxybutane (DEB), nitrogen mustard (NTM), and mitomycin C (MMC): induction of chromosomal aberrations (breaks and rearrangements) (Blom et al. 2004)
6. Reserved mosaicism
   a. Not infrequent in Fanconi anemia
   b. Presence of two populations of lymphocytes in mosaic Fanconi anemia patients
      i. One being hypersensitive to the clastogen
      ii. The other normal
   c. Phenotypic reversion to normal
      i. Correlated with intragenic homologous recombination in compound heterozygous

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patients giving rise to the segregation of a wild type allele at the disease locus
ii. The resulting cells are thus essentially cured from the disease.
iii. Progeny from a reverted stem cell expected to have a proliferative advantage over affected cells and thus may gradually expand and take over hematopoiesis
d. Patients with a high proportion of reverted cells may be falsely diagnosed as negatives.
7. Defective FA functional pathway
a. Defective DNA repair
b. Prolonged G2/M transition in the cell cycle
c. Increased oxygen sensitivity
d. Abnormally regulated apoptosis and accelerated telomere shortening
e. Defective hemopoiesis

Clinical Features

1. Variable clinical expression and severity
2. Hematological abnormalities secondary to bone marrow failure (>90%)
a. Clinical hallmark of Fanconi anemia
b. Usually starting in childhood
c. Increased incidence of aplastic anemia, myelodys plastic syndrome, and acute myeloid leukemia
d. Initial presentation
i. Pallor
ii. Bleeding
iii. Recurrent infections
e. Thrombocytopenia or leukopenia typically preceding anemia
f. Severe progressive pancytopenia due to loss of hematopoietic stem cells: the cardinal clinical feature
g. Increased risk of infections due to neutropenia
h. Sweet syndrome (neutrophilic skin infiltration) reported in a few patients with Fanconi anemia and myelodysplastic syndrome
3. Diverse congenital abnormalities (>63%)
a. Growth retardation
b. Short stature (60%)
c. Upper limb anomalies (50%)
i. Mainly radius and thumb abnormalities
a) Absent, hypoplastic, or supernumerary thumbs with hypoplastic thenar eminence
b) Absent, hypoplastic radii, and ulnae associated with abnormal thumbs
c) Absent first metacarpal
ii. Clinodactyly
iii. Polydactyly
iv. Short fingers
v. Transverse palmar crease
d. Other skeletal abnormalities
i. Short webbed neck with low hairline
ii. Spine anomalies
a) Spina bifida
b) Scoliosis
c) Sacrococcygeal sinus
d) Other vertebral anomalies
iii. Lower limb anomalies
a) Toe syndactyly
b) Pes planus
c) Abnormal toes
d) Congenital hip dislocation
e. Skin pigmentary changes (65%)
i. Generalized hyperpigmentation
ii. Café au lait spots
iii. Hypopigmentation
f. Eye anomalies (25%)
i. Microphthalmia
ii. Strabismus
iii. Epicanthal folds
iv. Hypertelorism/hypotelorism
v. Ptosis
vi. Cataracts
vii. Epiphora
viii. Nystagmus
g. Ear anomalies (10%)
i. Deafness, usually conductive secondary to middle ear abnormalities
ii. Abnormal pinna
iii. Stenosis or atresia of the external auditory meatus
iv. Low-set ears
h. Heart disease
i. Congenital heart disease
a) Patent ductus arteriosus
b) Ventricular septal defect
c) Pulmonary stenosis
d) Aortic coarctation

ii. Cardiomyopathy
i. Renal anomalies (25%)
i. Kidney
a) Pelvic kidneys
b) Horseshoe kidneys
c) Hypoplastic/dysplastic kidneys
ii. Collecting system (hydronephrosis, hydroureter, reflux)
iii. Abnormal artery
j. Gastrointestinal problems
i. Atresia
a) Esophagus
b) Duodenum
c) Jejunum
ii. Tracheoesophageal fistula
iii. Anteriorly placed anus
iv. Imperforate anus
v. Persistent cloaca
vi. Meckel diverticulum
vii. Umbilical hernia
viii. Abnormal biliary ducts
ix. Megacolon
x. Abdominal diastasis
xi. Budd–Chiari syndrome
xii. Annular pancreas
k. CNS abnormalities
i. Microcephaly
ii. Hydrocephalus
iii. Absent septum pellucidum
iv. Neural tube defects
l. Hypogonadism in males
i. Underdeveloped gonads
ii. Cryptorchidism
iii. Hypospadias
iv. Defective spermatogenesis (infertility)
v. A few males with Fanconi anemia fathered children
m. Hypogonadism in females
i. Hypogenitalia
ii. Bicornuate uterus
iii. Absent uterus or vagina
iv. Ovarian atresia
v. Delayed menarche
vi. Irregular menses
vii. Early menopause
viii. Successful pregnancies with live-born children observed
n. Absence of obvious congenital abnormalities in approximately 33% of patients with Fanconi anemia
4. Predisposition to malignancy
a. Hematologic tumors (60%)
i. Acute myelogenous leukemia (30%)
ii. Myelodysplastic syndrome (26%)
iii. Acute lymphocytic leukemia
iv. CMMOL
v. Burkitt lymphoma
b. Non-hematologic tumors (40%)
i. Liver tumors (9%)
a) Adenoma
b) Hepatocellular carcinoma
c) Adenocarcinoma
ii. Brain tumor (2%)
a) Medulloblastoma
b) Astrocytomas
iii. Renal tumors (3%)
a) Wilm tumor
b) Renal cell carcinoma
c) Nephroblastoma
iv. Squamous cell carcinoma (20%)
a) Head and neck
b) Vulvar
c) Cervix
d) Cutaneous
e) Anus
f) Esophagus
v. Miscellaneous tumors (6%)
a) Breast carcinoma
b) Basal cell carcinoma
c) Neuroblastoma
d) Desmoid tumor
e) Gonadoblastoma
f) Melanoma
g) Neurilemmoma
h) Osteogenic sarcoma
5. Cumulative probability of developing leukemia, liver tumors, and solid tumors in FA patients
a. Close to 40% by age 30
b. About 50% by age 45
c. An astounding 76% by age 45
6. Prognosis
a. Mean survival: 16 years
b. Main causes of death

i. Pancytopenia which develops in the first decade of life
ii. Associated progressive microcytosis
iii. Extremely high probability of developing bone marrow failure
iv. A predisposition to malignancy, particularly acute myeloid leukemia and aplastic anemia

7. Differential diagnosis (Tischkowitz and Hodgson 2003)
   a. VATER/VACTERL association overlap with FA
      i. Vertebral defects
      ii. Tracheo-esophageal atresia
      iii. Renal defects
      iv. Radial ray defects
   b. Diamond–Blackfan anemia (Aase syndrome)
      i. Defective erythroid progenitor maturation
      ii. Normochromic or macrocytic anemia
      iii. Congenital malformations in over one third of patients
         a) Head (micrognathia, cleft lip)
         b) Upper limb defects
         c) Genitourinary anomalies
      iv. A heterogeneous disorder
         a) Sporadic in most cases
         b) Autosomal dominant in some cases
         c) Rarely autosomal recessive inheritance
   c. Nijmegen breakage syndrome
      i. A rare autosomal recessive disorder
      ii. Resulting from mutations in NBS1, which codes for the nibrin protein
      iii. Clinical characteristics
         a) Immune deficiency
         b) Microcephaly
         c) Hypersensitivity to ionizing radiation
   d. Other chromosomal breakage syndromes (Bloom syndrome, ataxia-telangiectasia)
      i. Also exhibit high rates of spontaneous chromosomal breakage
      ii. Only FA cells exhibit increased chromosomal breakage in response to DEB
   e. Thrombocytopenia-absent radii (TAR) syndrome
   f. Holt–Oram syndrome

Diagnostic Investigations

1. Difficult to diagnose FA because of phenotypic diversity
2. Hematologic investigation
   a. Progressive decrease in peripheral blood counts, often present by 7–8 years of age
      i. Thrombocytopenia
      ii. Leukopenia
      iii. Anemia
   b. Macrocytic red blood cells, often with increased fetal hemoglobin
   c. Generally increased serum erythropoietin concentration
   d. Hypocellular or dysplastic bone marrow
   e. Bone marrow failure with pancytopenia
   f. Bone marrow cytogenetic testing: Cytogenetic abnormalities may progress to leukemia or myelodysplastic syndrome
3. DEB testing
   a. 10- to 100-fold increased chromosomal breakage (breaks, rearrangements, radials, exchanges) of Fanconi anemia cells after incubation of the patient's cells with chemical clastogen, DEB
   b. Highly sensitive and specific test for Fanconi anemia
   c. Allowing diagnosis of Fanconi anemia in persons with diverse clinical features including those without clinically detectable congenital abnormalities
   d. Used successfully in prenatal diagnosis of Fanconi anemia
   e. Remains underutilized mainly because there are some clinical conditions in which FA is not usually suspected
   f. Disadvantage
      i. Requires a high degree of cytogenetic expertise and meticulous attention to cell culture and safety conditions
      ii. Fails to distinguish among Fanconi anemia patients in different complementation groups
      iii. Fails to identify heterozygote carriers of mutant Fanconi anemia genes
4. Cell cycle test
   a. Alternative to cytogenetic testing
   b. Diagnostic potential of the cell cycle test for Fanconi anemia
   c. Based on the observation that Fanconi anemia cells experience difficulties in traversing the S and G2 compartments of the cell cycle
   d. Limitation of cell cycle test
      i. Applicable only to nonleukemic cells
      ii. Confirmatory DEB studies required in cases with evidence for G2-phase arrest

5. Molecular genetic testing
   a. Used primarily for carrier detection and prenatal diagnosis
   b. Complicated by the presence of 13 genes, which are responsible for the 13 FA complementation groups [A, B, C, D1 (BRCA2), D2, E, F, G, I, J, L, M, and N]
   c. Sequence analysis for *FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG*, and *FANCI*
   d. Mutation analysis for the common Ashkenazi Jewish *FANCC* mutation (IVS4+4A>T)
   e. Linkage analysis once a family has been assigned to a complementation group by a functional assay or by the detection of a specific mutant allele using highly polymorphic microsatellite markers located in close proximity to both FAA and FAAC genes
      i. Used for carrier detection
      ii. Used for prenatal diagnosis
6. Cancer surveillance
   a. Annual bone marrow examination provides early evidence for myelodysplastic syndrome or leukemia
      i. Aspirate for cell types
      ii. Biopsies for cellularity
      iii. Cytogenetics
   b. Liver function tests and ultrasound examinations to identify adenomas or hepatomas before becoming symptomatic
   c. Screening for solid tumors: more complex because of multiplicity of cancer types
      i. Direct visualization of the oropharynx and fiberoptic endoscopy for screening for aerodigestive cancers and precancerous lesions
      ii. Gynecologic examinations for vulvar and cervical tumors beginning with menarche

Genetic Counseling

1. Recurrence risk (Taniguchi 2008)
   a. Patient's sib
      i. Autosomal recessive inheritance in all but one of the FA complementation groups
         a) Twenty-five percent chance of inheriting both mutation alleles and being affected
         b) Two third chance of being carriers in unaffected sibs who have a normal DEB test
      ii. X-linked recessive inheritance (FANCB mutation)
         a) Risk to sibs depends upon the carrier status of the mother
         b) Fifty percent of male sibs who inherit the mutation will be affected
         c) Female sibs who inherit the mutation will be carriers and will usually not be affected
         d) Risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism if the disease-causing mutation cannot be detected in the DNA extracted from leukocytes of the mother of the only affected male in the family
   b. Patient's offspring: recurrence risk not increased unless the spouse is a carrier, in which case 50% of offspring will be affected; otherwise all offspring of the affected parent will be carriers who will be asymptomatic
2. Prenatal diagnosis
   a. Prenatal ultrasonography to evaluate fetal anomalies consistent with FA
   b. Prenatal diagnosis available to at-risk families by CVS, amniocentesis, or cordocentesis
      i. Demonstration of chromosome instability by DEB test
      ii. Molecular genetic testing of FA gene (*FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG*, and *FANCI*) mutations if the disease-causing mutations are previously characterized in a given family
      iii. Preimplantation genetic diagnosis possible for families in which the disease-causing mutations have been identified by using molecular methods, resulting in implantation of an embryo without FA mutations
3. Management
   a. Supportive care
      i. Developmental assessment
      ii. HLA typing of the patient, sibs, and parents in anticipation of possible bone marrow transplantation
      iii. Full blood typing
      iv. Packed red blood cells transfusions for symptomatic anemia
      v. Platelet transfusions for symptomatic thrombocytopenia
      vi. Antimicrobials for secondary infections

b. Surgical care
   i. Splinting and hand surgery indicated for thumb and radial anomalies
   ii. Surgery for congenital heart defects and gastrointestinal anomalies such as TE fistula
c. Transient response
   i. Androgens (oxymetholone) shown to improve the blood counts in approximately 50% of patients
   ii. Corticosteroids
   iii. Cytokines
   iv. Granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor (shown to improve the neutrophil count in some patients) for symptomatic Neutropenia
d. Hematopoietic stem cell transplantation may cure aplastic anemia and prevent myelodysplastic syndrome or leukemia
   i. Peripheral blood stem cells
   ii. Allogenic bone marrow transplant with a histocompatible sibling donor: treatment of choice
   iii. Umbilical cord blood offers a potential source of hematopoiesis stem cells for Fanconi anemia patients without sibling matches
e. Successful transplantation obtained by using in vitro fertilization and preimplantation genetic diagnosis of hematopoietic stem cells from a donor selected on the basis of specific, desirable disease and HLA characteristics
   i. Select embryos which are HLA-identical to the patient and unaffected by FA for intrauterine transfer and let the pregnancy continue to term
   ii. Obtain the umbilical cord blood from the healthy newborn infant and use it as the source of HLA-identical hematopoietic stem cells to reconstitute normal hematopoiesis in the affected sibling
f. Follow up surveillance for solid malignancies
g. Gene therapy not currently available

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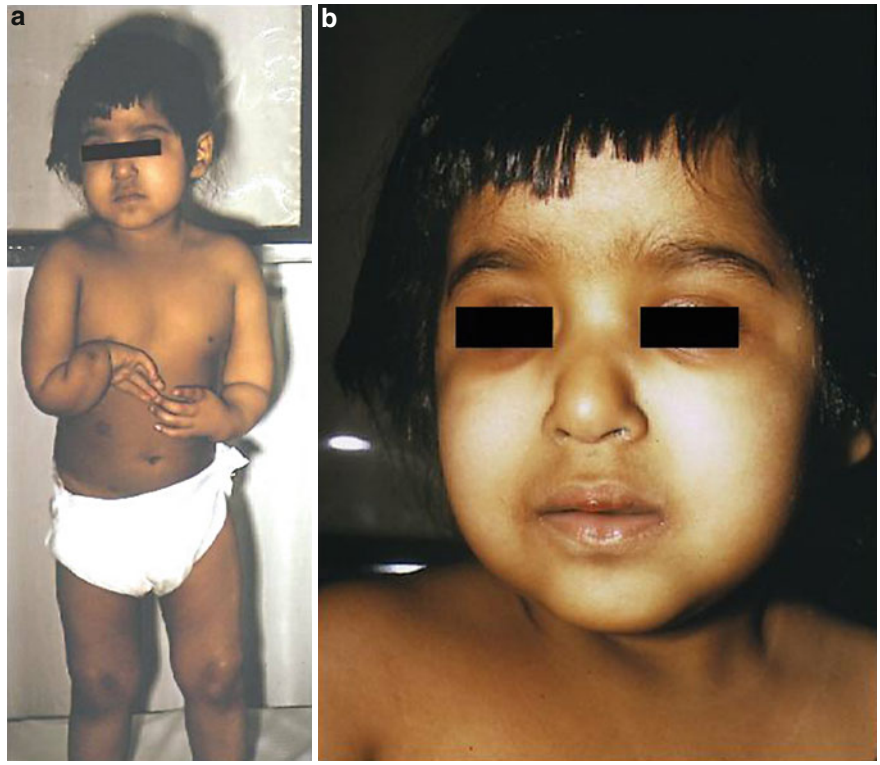

Fig. 1 (**a**, **b**) A young boy with Fanconi anemia showing pallor and radial ray defects of the upper extremities

Fig. 2 (**a**–**d**) An adolescent girl with Fanconi anemia showing similar phenotype

Femoral Hypoplasia – Unusual Facies Syndrome

In 1973, Daentl et al. delineate a distinctive pattern of malformation which includes femoral hypoplasia and unusual facies in four unrelated individuals. The syndrome is also known as femoral facial syndrome.

Synonyms and Related Disorders

Femoral-facial syndrome

Genetics/Basic Defects

1. Inheritance
   a. Sporadic in most cases
   b. Familial cases with autosomal dominant inheritance reported
   c. Multifactorial trait in some families
   d. Maternal diabetes causative in more than 20% of the reported cases
2. Possible causes
   a. Fetal constraint (deformation) due to severe oligohydramnios
   b. Maternal diabetes (disruption)
   c. Undetermined etiology

Clinical Features

1. Characteristic facial features
   a. Up-slanting eyes
   b. A short nose with broad tip
   c. Elongated philtrum
   d. Thin upper lip
   e. Micrognathia
   f. Cleft palate
   g. Low-set ears
2. Hypoplasia/aplasia of the femurs
   a. Usually asymmetric
   b. Presence of some degree of shortened lower extremities in most cases
   c. Variable shortening of the lower extremities depending on the absence or degree of hypoplasia of the femurs, with or without absent fibulas
3. Short stature due to reduced length of the lower extremities
4. Normal intelligence
5. Other anomalies
   a. Club foot in most cases
   b. Occasional polydactyly/syndactyly
   c. Sprengel's deformity
   d. Upper extremity hypoplasia
   e. Restricted motion of the elbows
   f. Stiff shoulders
   g. Pelvic and spinal abnormalities
   h. Inguinal hernia
   i. Genitourinary anomalies
      i. Hypoplastic/dysplastic kidneys
      ii. Polycystic kidneys
      iii. Cryptorchidism
      iv. Genital hypoplasia
         a) Hypoplastic penis
         b) Hypoplastic labia majora
      v. Inferiorly placed kidneys
      vi. Septated urinary bladder
   j. Rare cardiovascular anomalies
      i. Ventricular septal defect
      ii. Pulmonary stenosis
      iii. Truncus arteriosus

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6. Differential diagnosis (Pryde et al. 2003)
   a. Kyphomelic dysplasia
      i. Femur
         a) Symmetrically short
         b) Severe bowing
      ii. Other long bones
         a) Mild shortening
         b) Minimal bowing
      iii. Genitourinary: no abnormalities
      iv. Face: micrognathia
      v. Scapulae: normal
      vi. Others
         a) Mild small thorax
         b) Male sex predilection
      vii. Prognosis
         a) Good developmental prognosis
         b) Ambulatory
      viii. Genetics: autosomal recessive
   b. Campomelic dysplasia
      i. Femur
         a) Symmetric mild shortening
         b) Moderate-to-severe bowing/amputation
      ii. Other long bones
         a) Tibial bowing more marked than femora bowing
         b) Hypoplastic fibulae
      iii. Genitourinary
         a) Ambiguous genitalia
         b) Sex reversal in XY
      iv. Face
         a) Micrognathia
         b) Cleft palate
      v. Scapulae: hypoplastic
      vi. Others
         a) Occasional lateral ventriculomegaly
         b) Cardiac anomalies
         c) Talipes
      vii. Prognosis
         a) Often lethal in early infancy
         b) Survivors often severely disabled
      viii. Genetics
         a) Autosomal dominant
         b) *SOX*-9 mutations
   c. Antley–Bixler syndrome
      i. Femur; symmetric short, severely bowing
      ii. Other long bones
         a) Radiohumeral synostosis
         b) Joint contractures
      iii. Genitourinary: occasional abnormalities
      iv. Face
         a) Frontal bossing
         b) Depressed nasal bridge
      v. Scapulae: severely hypoplastic
      vi. Others
         a) Craniosynostosis
         b) Arachnodactyly
      vii. Prognosis
         a) Occasional death
         b) Normal neurodevelopment
         c) Severe orthopedic disability
      viii. Genetics: autosomal recessive

Diagnostic Investigations

1. Radiography
   a. Mandibular hypoplasia
   b. Femoral hypoplasia including proximal femoral focal deficiency
   c. Less frequent thoracocostovertebral anomalies
      i. Thorax: congenital elevation of the scapula (Sprengel's deformity)
      ii. Ribs
         a) Absent
         b) Hypoplastic
         c) Fused
      iii. Spine
         a) Dysplastic vertebrae
         b) Hemivertebrae
         c) Spina bifida occulta
         d) Lumbar scoliosis
         e) Sacral dysgenesis
      iv. Pelvis
         a) Small iliac wings
         b) Wide obturator foramen
         c) Hypoplasia/aplasia of the acetabula with dislocation of the hips
   d. Less frequent upper extremity anomalies
      i. Hypoplasia of the humerus
      ii. Radiohumeral/radioulnar synostosis
      iii. Ulnar deviation of the hands
2. Histopathology
   a. Femur from one infant showed hyaline cartilage with foci of fibrous dysplasia
   b. A disorganized growth plate and relative decrease in the resting cartilage matrix in another patient

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Sporadic cases: not increased
      ii. Autosomal dominant inheritance: not increased unless one of the parents is affected
      iii. Maternal diabetes: risk is significantly increased
   b. Patient's offspring: 50% if the patient has the autosomal dominant form of the syndrome
2. Prenatal diagnosis possible by ultrasonography in at-risk families
   a. Micrognathia
   b. Cleft palate
   c. Other facial features
   d. Short, bowed femora
3. Management
   a. Cleft palate repair
   b. Care for cardiovascular and genitourinary complications
   c. Orthopedic management of limb deformity and hip dysplasia

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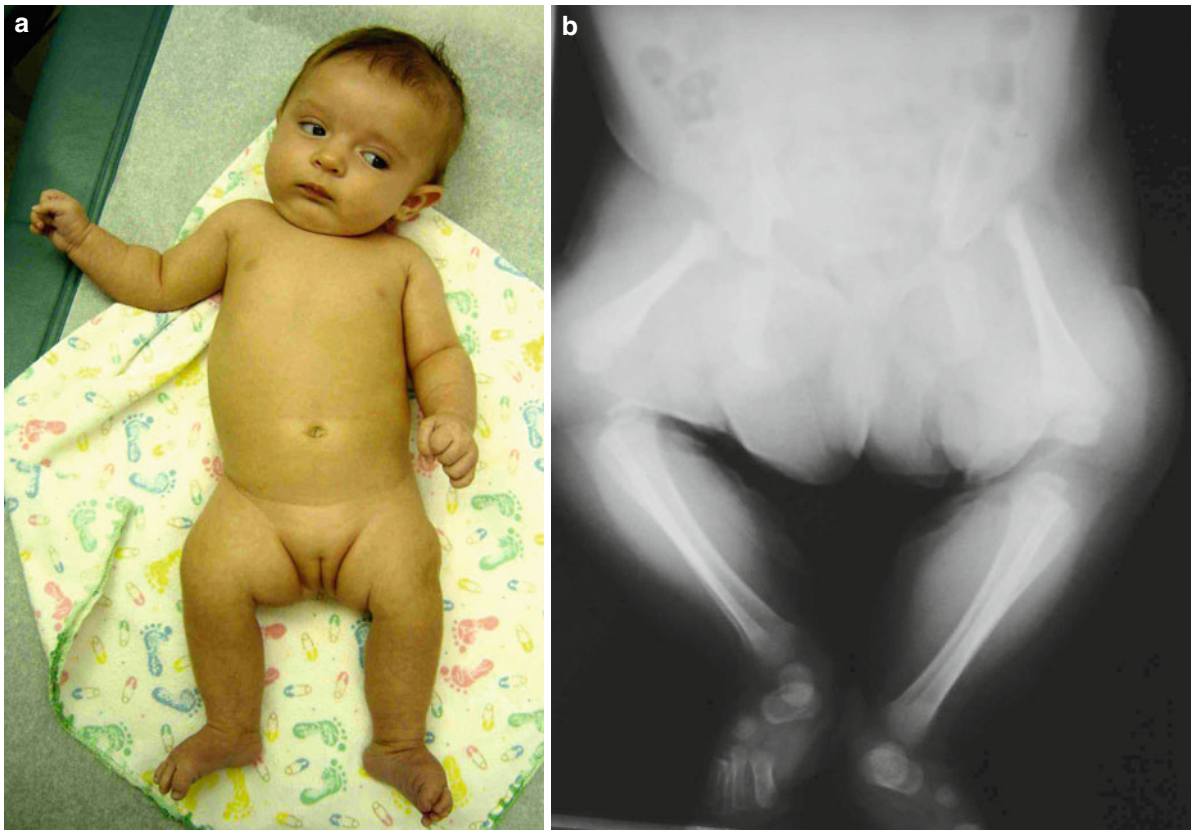

Fig. 1 (**a**, **b**) A 3-month-old infant with femoral hypoplasia – unusual facies syndrome showing short nose, long philtrum, thin upper lip, micrognathia, low-set ears, and marked bilateral rhizomelic shortening of the lower extremities. The radiograph showed hip dysplasia and bilateral proximal femoral hypoplasia

Fetal Akinesia Deformation Sequence

Fetal akinesia deformation sequence (FADS) refers to the condition of decreased intrauterine fetal movement and its consequent manifestations of multiple joint contractures, pulmonary hypoplasia, and abnormal face present at birth. It is also known as Pena–Shokeir phenotype (Hall 2009). The incidence is estimated to be 1 in 12,000, reflecting causal heterogeneity.

Synonyms and Related Disorders

Arthrogryposis multiplex congenita with pulmonary hypoplasia; Fetal akinesia sequence; Pena–Shokeir phenotype

Genetics/Basic Defects

1. Genetics
   a. Sporadic in majority of cases
   b. Familial cases
      i. Autosomal recessive inheritance
      ii. Possible X-linked recessive inheritance
2. Heterogeneous causes (Beemer 1990)
   a. Inadequacy of the intrauterine fetal environment
      i. Etiologic factors
         a) Ovarian cyst
         b) Bicornuate uterus
         c) Umbilical cord wrapping
         d) Twins
         e) Extrauterine pregnancy
         f) Insufficient placental circulation
         g) Maternal tetanus, drug treatment
         h) Amniotic bands
      ii. Oligohydramnios sequence
         a) Facial deformities (Potter's facies)
         b) Arthrogryposis
         c) Lung hypoplasia
      iii. Types of defects determined by the timing of constraint
         a) Early in pregnancy leading to limb reduction defects, syndactyly, and polydactyly
         b) Later in pregnancy (third trimester) leading to genu recurvatum, dislocated hips, and deviated wrists
         c) Various developmental defects occurring earlier in the upper than in the lower limbs
         d) Embryonic onset of immobility interferes with limb development and results in joint fixation and pterygium formation, in contrast to fetal-onset immobility, which causes joint contractures alone.
   b. Pena–Shokeir phenotype or sequence (Hall 2009)
      i. Pena–Shokeir syndrome
         a) Originally described by Pena and Shokeir in 1974
         b) Syndrome consisting of camptodactyly, multiple ankyloses, facial anomalies, pulmonary hypoplasia, and lethal outcome
         c) Currently the term "Pena–Shokeir phenotype or sequence" is recommended instead of Pena–Shokeir syndrome
         d) This form clearly exists as an autosomal recessive trait with frequent consanguinity and even incest reported

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ii. Curarization of fetal rats during pregnancy (study by Moessinger 1983) resulted in better understanding of fetal akinesia deformation sequence with the following features almost identical with those described in the Pena–Shokeir syndrome:
  a) Multiple contractures or arthrogryposis
  b) Pulmonary hypoplasia
  c) Craniofacial anomalies
  d) Polyhydramnios
  e) Intrauterine growth retardation
  f) Short umbilical cord
iii. Currently the term "Pena–Shokeir phenotype or sequence" is recommended instead of "Pena–Shokeir syndrome"

3. Fetal akinesia not associated with primary malformations (Grubben et al. 1990)
  a. Mechanical causes
    i. Oligohydramnios
    ii. Polyhydramnios
    iii. Premature rupture of the membrane
    iv. Chorioamnionitis
  b. Congenital infections
    i. Rubella
    ii. CMV
    iii. Toxoplasmosis
  c. Physical or chemical agents
    i. Toxic agents
    ii. Drugs
    iii. X-rays
    iv. Hyperthermia
  d. Fetal hypoxia
    i. Fetal anemia
      a) Blood loss
      b) Hemolysis
    ii. Compression of umbilical cord
    iii. Placental insufficiency
    iv. Severe toxemia
  e. Maternal myasthenia gravis
4. Role of fetal akinesia in heterogeneous syndromes and conditions (Grubben et al. 1990)
  a. Cerebro-oculo-facio-skeletal (COFS) syndrome
  b. Potter sequence
  c. Neu–Laxova syndrome
  d. Syndrome described by Herva et al. (1985)
  e. Osteochondrodysplasias
    i. Thanatophoric dysplasia
    ii. Achondrogenesis
    iii. Diastrophic dysplasia
  f. Lethal multiple pterygium syndrome
  g. CNS anomalies
    i. Hydranencephaly
    ii. Dandy–Walker malformation with hydrocephalus
    iii. Schizencephaly
    iv. Olivo-ponto-cerebellar degeneration
  h. Skin/connective tissue disorders
    i. Restrictive dermopathy
    ii. Epidermolysis bullosa
    iii. Congenital ichthyosis
  i. Metabolic disorders
    i. Lysosomal storage disorders
    ii. Generalized gangliosidosis syndrome type I
    iii. Glycogenosis type VII (Moerman et al. 1995)
  j. Neuromuscular disorders
    i. Congenital muscular dystrophy
    ii. Congenital myotonic dystrophy
    iii. Congenital spinal muscular atrophy
    iv. Central core disease
    v. Nemaline myopathy
  k. Other disorders causing restrictive fetal akinesia
    i. Loss of anterior horn cells
    ii. Radical disease
    iii. Peripheral neuropathy
    iv. Congenital myasthenia gravis
    v. Amyoplasia congenita
    vi. Prader–Willi syndrome
    vii. Cohen syndrome
    viii. Angelman syndrome
    ix. Neurofibromatosis I
    x. Moebius syndrome
    xi. Bilateral dislocation of the hips
    xii. Exstrophy of cloaca and bladder
    xiii. Chromosome abnormalities
      a) Fetal triploidy
      b) Trisomies 4p, 9, 9q, 9p, 10q, 11q, proximal 14, proximal 15, and 18
      c) Monosomies 4p and 13q
    xiv. Miscellaneous
      a) Cornelia de Lange syndrome
      b) Catel–Manzke syndrome
      c) Opitz–Frias syndrome
      d) Bowen–Conradi syndrome
      e) Marden–Walker syndrome
5. Pathogenesis of fetal akinesia sequence (Hageman et al. 1987)
  a. Spinal cord lesions observed most often (28%)
  b. Brain lesions (19%)

c. Miscellaneous or connective tissue disorders (11%)
d. Combined brain and spinal cord lesions (9%)
e. Mechanical restriction (7%)
f. Muscle disorders (5%)
g. Peripheral neuropathy and myasthenia gravis (1%)
h. No underlying defect observed in 14% of cases

6. Molecular basis of lethal fetal akinesia phenotype (Vogt et al. 2008, 2009)
   a. Mutations in the acetylcholine receptor subunits *CHRNA1*, *CHRNB1*, *CHRND*, and Rapsyn (*RAPSN*) can also result in a MPS (multiple pterygium syndrome)/FADS phenotype
   b. Whereas incomplete loss of *DOK7* function may cause congenital myasthenia, more severe loss of function can result in a lethal fetal akinesia phenotype

Clinical Features

1. Pregnancy history (Grubben et al. 1990)
   a. Feeble fetal movement
   b. Polyhydramnios
   c. Oligohydramnios
   d. Craniofacial abnormalities
      i. Ocular hypertelorism
      ii. Micrognathia
      iii. Low-set ears
      iv. Depressed nasal tip
      v. Short neck
   e. Limb anomalies
      i. Lack of normal growth
      ii. Limitation of joint movement
      iii. Abnormal shape
      iv. Abnormal position
      v. Decreased bone calcification
2. Phenotype present at birth
   a. Multiple joint contractures
   b. Limb pterygia
   c. Craniofacial abnormalities
   d. Pulmonary hypoplasia
   e. Short umbilical cord
   f. Growth retardation
3. Lethal outcome with pulmonary hypoplasia
4. Identifiable familial forms of Pena–Shokeir phenotype/fetal akinesia deformation sequence
   a. Classic Pena–Shokeir syndrome (type I)
      i. Classic signs of fetal akinesia deformation sequence (lack of normal fetal movement in utero)
         a) Intrauterine growth retardation
         b) Joint contractures
         c) Short gait
         d) Short umbilical cord
         e) Pulmonary hypoplasia
         f) Characteristic facial features: hypertelorism, prominent nasal bridge, posteriorly rotated low-set ears, depressed tip of the nose, micrognathia, and cleft palate (probably related to micrognathia and lack of in utero tongue movement)
      ii. Stick-like limbs with flexion or extension contractures
      iii. Feet usually in severe equinovarus position but rocker bottom feet may be present
      iv. Elbows usually flexed
      v. Hypoplastic dermatoglyphics
      vi. Normal CNS and most skeletal muscle, although muscle biopsies often show disuse atrophy, no myopathy changes and rarely fatty, fibrous replacement
      vii. Other often reported features
         a) Disproportionately large head
         b) Short limbs
         c) Thin ribs and long bones
         d) Clenched hands
         e) Ankylosis of large joints
         f) Thoracic kyphosis
   b. Lower motor neuron disorder with generalized decrease in anterior horn cells (Chen type) (Chen et al. 1983)
      i. Intrauterine growth retardation
      ii. Polyhydramnios
      iii. Lack of fetal movement in the early second trimester
      iv. Pulmonary hypoplasia
      v. Characteristic facial appearance
         a) Nasal bridge: depressed or high
         b) Long philtrum
         c) Small mouth
      vi. Limb abnormalities
         a) Flexion contractures
         b) Hyperextended and overlapping distal phalanges
         c) Ulnar deviation of fingers

d) Radioulnar synostosis
e) Clubfeet
vii. Other findings
a) Mild kyphosis
b) Hypoplastic adrenals
viii. Small muscles with disuse atrophy
ix. Cases reported by Abe et al. (1989), Moerman et al. (1983), Moerman and Fryns (1990), and possibly Imamura et al. (1981) and Gullino et al. (1993) appear to have this subtype

c. Lethal congenital contractures syndrome type 1 (LCCS-1) (GLE mRNA export mediator gene mapped at 9q34) (Herva et al. 1988, 1985; Vuopala et al. 1994)
i. An autosomal recessive disorder frequently seen in Finland
ii. Intrauterine growth retardation
iii. Pulmonary hypoplasia
iv. Micrognathia
v. Short neck
vi. Thin ribs
vii. Thin, stick-like limbs which may fracture, associated with decreased muscle mass
viii. Extended legs, often with flexed arms
ix. Dislocated hips always present
x. Striking and characteristic feature: decrease of anterior horn cells in the ventral part of the spinal cord with normal cerebellum
xi. Prenatal diagnosis possible by molecular testing of mutations in the messenger RNA export mediator GLE (*GLE1*) (Nousiainen et al. 2008)

d. Lethal congenital contracture syndrome type 2 (LCCS-2) (Landau et al. 2003)
i. Described in two Israeli Bedouin consanguineous kindreds
ii. Clinical features
a) Extended elbows
b) Flexed knees
c) Mild IGUR
d) Micrognathia
e) Hydronephrosis
f) Distended bladders
iii. Generally decreased anterior horn cells in the spinal cord and muscle wasting suggesting a neuropathic etiology
iv. *ERBB3* gene mapped at 12q13

e. Lethal congenital contracture syndrome type 3 (LCCS-3)
i. Represented by a large consanguineous Israeli Bedouin kindred
ii. Clinical features identical to LCCS-2 without bladder involvement
iii. *PIP5K1C* gene mapped at 19p13

f. Lethal lower motor neuron deficiency (Vuopala et al. 1995a)
i. Described in 11 families
ii. Considered to be a disorder of the degeneration of anterior horn cells leading to lethality
iii. Clinical features
a) Legs and arm: hyperextended or flexed
b) Mild IUGR
c) Usually born near term
d) Craniofacial: micrognathia, high nasal bridge, underdeveloped nasal tip, posteriorly rotated ears, short neck
e) Early death due to respiratory failure
iv. This disorder mapped to 5q

g. Families with apparent increase in monozygotic twinning (Chen et al. 1983; Lindhout et al. 1985; Ho 2000)
i. Affected twins and affected singletons occur in the same families
ii. Clinical features
a) Polyhydramnios
b) Increased fetal movement signal problems
c) Severe pulmonary hypoplasia
d) IUGR
e) Mildly webbed necks
f) Multiple flexion contractures including camptodactyly and clubfeet
g) Relatively large head compared to short trunk
h) Triangular face
i) Ocular hypertelorism
j) Clenched jaw
k) Posteriorly angulated ears
iii. Other features in some affected infants
iv. Relationship between MZ twinning and this type of PSP/FADS
a) Unclear
b) Potentially they are cases of classic Pena–Shokeir syndrome

h. Normal in utero growth, macrocephaly, and Pena–Shokeir phenotype (Lammer type)
   i. Affected brothers described by Lammer et al. (1989)
   ii. Clinical features
      a) Normal intrauterine growth
      b) Died with severe pulmonary hypoplasia
      c) Trismus
      d) Micrognathia
      e) Hydronephrosis
      f) Macrocephaly
      g) Choanal atresia in one brother
i. Absence of pyramidal cells, immature CNS development, adducted thumbs, kyphoscoliosis, and severe pulmonary hypoplasia (Biscegli type)
   i. Described in a consanguineous family
   ii. Clinical features
      a) Polyhydramnios
      b) IUGR
      c) Immaturity or delayed development of CNS
      d) Marked ocular hypertelorism
      e) Hypoplasia and atrophy of skeletal muscles
      f) Extension contractures of arms and legs
      g) Camptodactyly with abducted thumbs
      h) Clubfeet
      i) Marked congenital kyphoscoliosis
j. CNS dysgenesis and degeneration, seizures, trismus, and abdominal wall herniation (Erdl type)
   i. Sibs described by Erdl et al. (1989)
   ii. Clinical features
      a) IUGR
      b) Extended knees
      c) Trismus
      d) Seizures (intrauterine and after birth)
      e) Generalized edema at birth
      f) Severe lung hypoplasia
      g) Died shortly after birth
      h) Abdominal herniation (muscle defect) in the first sib
      i) A short and extremely thin umbilical cord
      j) Left lung trilobation and large thyroid and adrenal glands
      k) Polyhydramnios
      l) Fetal hydrops at 30–34 weeks of gestation
      m) CNS abnormalities: internal hydrocephalus, hypoplasia of basal ganglia, reduced or degenerating anterior horn cells, and other dystrophic brainstem and cerebellar changes
k. Skeletal muscle maturation defect
   i. Finish female siblings described by Vuopala et al. (1994)
   ii. Clinical features
      a) Polyhydramnios
      b) Severe pulmonary hypoplasia
      c) Congenital scoliosis
      d) Normal birth weight for gestation
      e) Edema
      f) One sib stillborn and other lived only 7 weeks
      g) Normal CNS
      h) Skeletal muscle immature with small muscle fibers and prominent atypical spindles
l. Pyramidal tract degeneration
   i. Two female sibs described by Vuopala et al. (1994)
   ii. Pena–Shokeir phenotype
   iii. Presence of pyramidal tract degeneration
   iv. Normal brain in one sib
   v. Holoprosencephaly in other sib
   vi. May represent an upper motor neuron disorder or a variation on holoprosencephaly
m. In utero seizures, scoliosis, together with cerebral and cerebellar hypoplasia in males (Persutte type)
   i. Two male sibs in a consanguineous family described by Persutte et al. (1988)
   ii. Clinical features
      a) Congenital scoliosis apparent at 18 weeks of gestation
      b) Decreased fetal movement
      c) Polyhydramnios
      d) IUGR
      e) Severe pulmonary hypoplasia leading to death within a few minutes after birth
      f) Flexion contractures
      g) Relatively large head
      h) Short neck
      i) Small low placed ears

j) CNS anomalies: agenesis of the corpus callosum and septum pellucida, hydrocephaly, hypoplastic cerebellum, and brain stem

iii. A family of male sibs with similar structural anomalies was described by Skrupski et al. (1996)

iv. This disorder could be X-linked recessive

n. Microphthalmia, microtia, and normal birth size (Thomas type)

i. Two male sibs described by Thomas et al. (1993)

ii. Clinical features

a) Polyhydramnios
b) Normal size at birth
c) Multiple congenital contractures
d) Died of respiratory insufficiency
e) Persistent truncus arteriosus
f) Micro-ophthalmia
g) Microtia
h) One had duodenal atresia, hydronephrosis, and dilated bladder

o. Olivo-ponto-cerebellar hypoplasia

i. A family of three siblings reported by Goutieres et al. (1977)

ii. Clinical features

a) Contractures
b) Anterior horn disease
c) Olivo-ponto-cerebellar hypoplasia
d) Death shortly after birth due to pulmonary hypoplasia

p. Failure to myelinate peripheral nerve

i. Affected male and female siblings reported by Penã et al. (1968)

ii. Clinical features

a) Multiple congenital contractures
b) Lack of myelination of peripheral nerve

q. Holoprosencephaly with hypokinesia and congenital contractures in an X-linked recessive pattern of inheritance

i. First reported by Morse et al. (1987) and then by Hockey et al. (1988)

ii. Other clinical findings with typical features of FADS

r. Hydrancephaly, calcification of basal ganglion, and proliferative Vasculopathy (Fowler type)

i. Families reported by Fowler et al. (1972), Harper and Hockey (1983), and Harding et al. (1995)

ii. Clinical findings

a) Polyhydramnios
b) Lack of fetal movements
c) Generalized edema
d) Cleft palate
e) Pterygia of large joints

s. Calcification of leptomeninges, the surface of cerebral convolutions, neurons, muscles, and vessels (Illum type)

i. A family of male and female siblings reported by Illum et al. (1988)

ii. Other clinical findings

a) Multiple congenital contractures
b) Camptodactyly with ulnar flare and clubfeet
c) Round face, depressed nasal bridge, long philtrum, short nose, puckered mouth, a deep horizontal crease below the lower lip, and trismus
d) Early lethality

t. Familial intrauterine anoxia and/or ischemia and PSP/FADS can be associated with the following situations

i. Maternal cocaine
ii. Monozygotic twins at increased risk for this type of change because of their vascular connection
iii. Polymicrogyri
iv. Oligogyri
v. Atrophy of cerebellum and cerebrum
vi. Cerebral neuronal loss and gliosis
vii. Cyst of the brain
viii. Heterotopia
ix. Decreased number of anterior horn cells with ferrigination
x. Dilated ventricles with calcification

Diagnostic Investigations

1. Radiography
   a. Thin tubular bones
   b. Gracile ribs

c. Multiple fractures possible at mid-diaphyses of humeri, distal diaphyses of femora, proximal diaphyses of tibiae, and fibulae
d. Camptodactyly

2. Histopathologic and other laboratory studies
   a. Trophoblastic inclusions in the chorionic villi of placenta:
      i. Triploidy
      ii. Lethal multiple pterygium syndrome
   b. Lung hypoplasia
   c. Bones
      i. Unremarkable resting cartilage
      ii. Normal cartilage cell columns at the chondro-osseous junctions
      iii. Marrow bony spicules often unusually thin and underossified
      iv. Irregular and focal areas of extreme diaphyseal thinning: a consistent finding
   d. CNS, muscles, and other organ systems
   e. Biochemical studies for lysosomal storage disease
   f. Analysis for chromosome abnormality
3. Molecular genetic diagnosis: *DOK7*- and *RAPSN*-related fetal akinesia deformation sequence available clinically

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal recessive inheritance: 25%
      ii. A recurrence risk of 10–15% suggested in the nonfamilial sporadic cases
   b. Patient's offspring: a lethal entity not surviving to reproductive age
2. Prenatal diagnosis by ultrasonography in high-risk pregnancies after the birth of a previous child with a heritable (mostly autosomal recessive) form of fetal akinesia sequence
   a. Marked decreased fetal activity
      i. Restricted limb movements
      ii. Decreased fetal chest movements
   b. Hydramnios/oligohydramnios
   c. Intrauterine growth retardation
   d. Hydrops noted in some affected babies late in pregnancy
   e. Some affected babies often die in utero if not shortly following birth
   f. Other echographic abnormalities associated with fetal akinesia
      i. Brain
         a) Microcephaly
         b) Holoprosencephaly
         c) Hydranencephaly
         d) Meningomyelocele
         e) Lissencephaly
         f) Dilated ventricles
         g) Absence of septum pellucidum
      ii. Spinal cord: sacrococcygeal agenesis
      iii. Gastrointestinal tract
         a) Omphalocele
         b) Gastroschisis
      iv. Renal
         a) Bilateral renal agenesis
         b) Renal malformations
      v. Craniofacial
         a) Hypertelorism
         b) Hypotelorism
         c) Micrognathia
         d) Cleft palate
      vi. Limbs
         a) Contractures (arthrogryposis)
         b) Camptodactyly
         c) Webbing
         d) Syndactyly
         e) Polydactyly
         f) Overlapping fingers and toes
         g) Abnormal position
         h) Clubfoot
         i) Partial absence or shortness
      vii. Cardiopulmonary
         a) Pulmonary hypoplasia
         b) Cardiac defects
3. Management: no effective treatment for pulmonary hypoplasia

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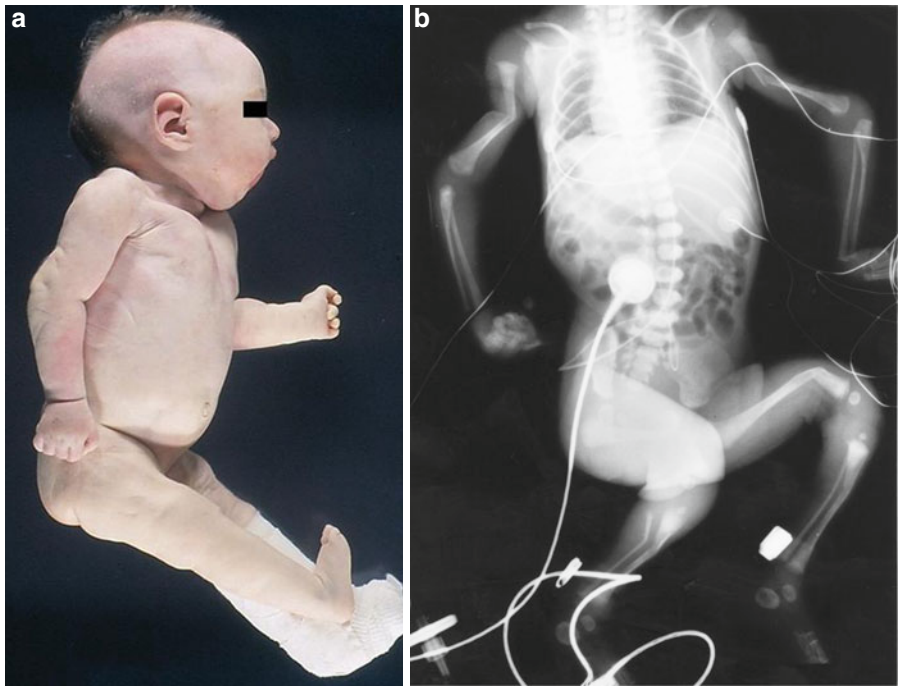

Fig. 1 (**a**, **b**) A neonate with fetal akinesia sequence showing micro/retrognathia, short neck, narrow thorax, flexion contractures of hips, fixed extension of the right knee, and inverted and rotated feet. The radiograph showed gracile ribs, thin long bones with multiple fractures at mid-diaphyses of humeri, distal diaphysis of femora, and proximal diaphyses of both tibiae and left fibula, and club hands

Fig. 2 (**a**, **b**) A neonate with fetal akinesia sequence showing micrognathia and multiple contractures. The radiograph showed gracile ribs and fractures at mid-diaphyses of humeri

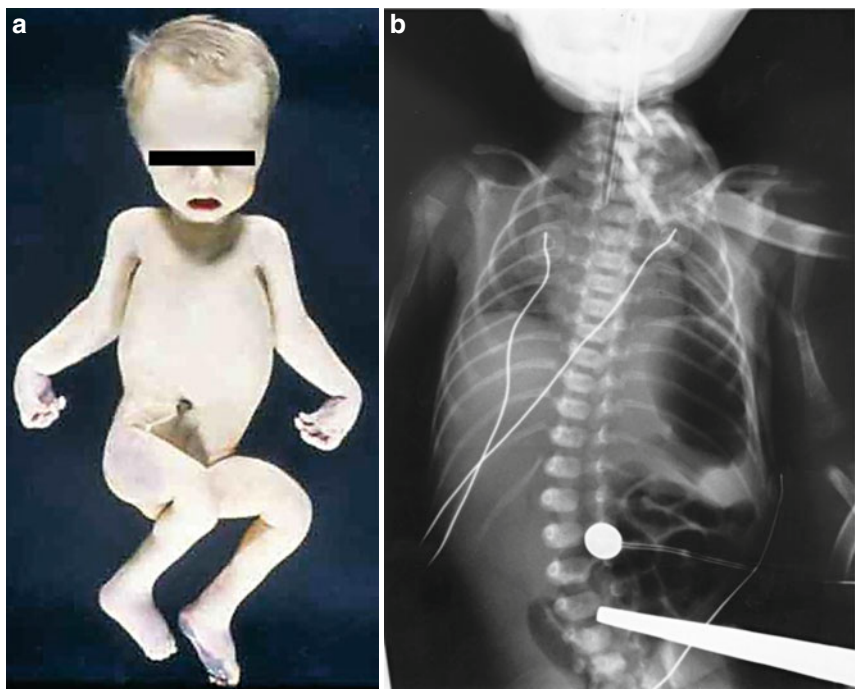

Fig. 3 (**a**, **b**) A neonate with Pena–Shokeir sequence (Chen type) showing hypertelorism, a short nose with depressed nasal bridge, long philtrum, a small and recessed jaw, low-set malformed ears, a short neck, clenched hands, multiple contractures at the hip, elbows, knees, ankles, and clubfeet. The infant had scalp edema and pulmonary hypoplasia. Neuromuscular histology showed lower motor neuron disorder with generalized decrease in anterior horn cells

Fig. 4 Radiographic study of the infant showed gracile ribs, thin long bones, and multiple contractures at the hip, elbows, knees, and ankles, and clubfeet

Fig. 5 Prenatal ultrasonography showed hydramnios, retrognathia, low-set ears, scalp edema, and flexion contractures at the elbows and knees

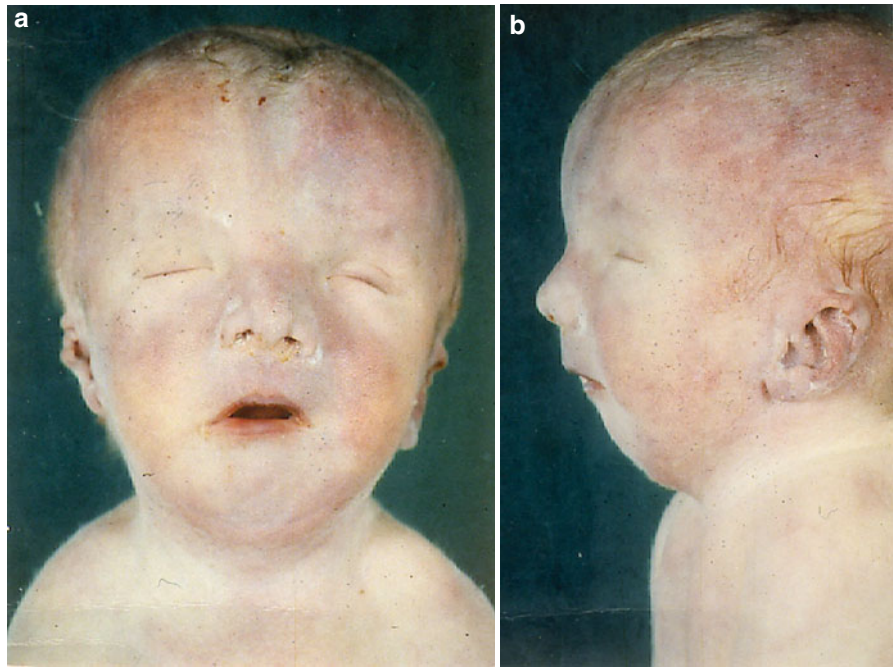

Fig. 6 (**a**, **b**) An infant in a family with MZ twinning. Note small jaw, ocular hypertelorism, antimongoloid slant of the palpebral fissures, high bridge of the nose, posteriorly rotated large ears, triangular shaped face, and short-appearing mildly webbed neck

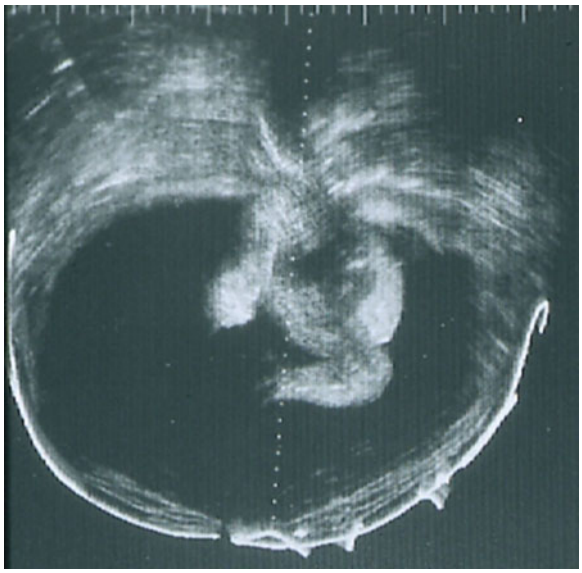

Fig. 7 Prenatal ultrasound of this fetus showed polyhydramnios, IUGR, and flexion contractures of the knees

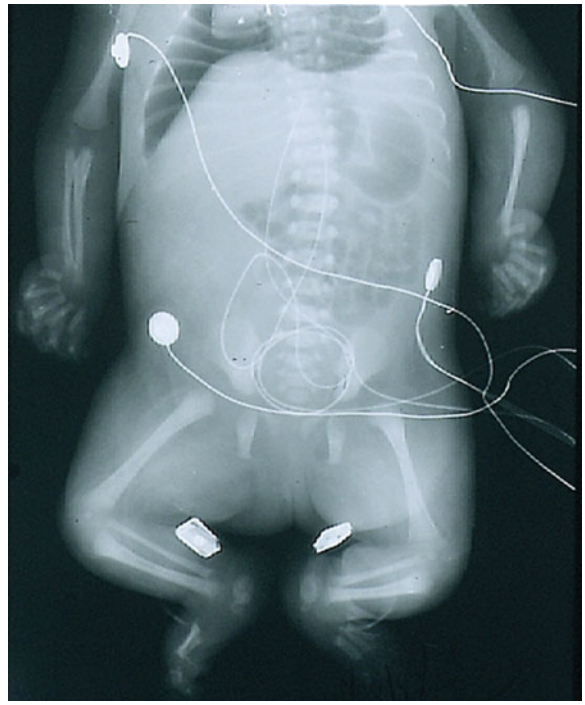

Fig. 8 Radiograph showed gracile ribs, thin long bones, flexion contractures at the elbows and knees, and clenched hands

Fetal Alcohol Spectrum Disorders

In 1973, Jones et al. described, in the American medical literature, a constellation of features in children born to alcoholic mothers, now known as fetal alcohol syndrome (FAS). In 1996, the Institute of Medicine further defined criteria of FAS and proposed two new terms: alcohol-related neurodevelopmental disorder (ARND) and alcohol-related birth defects (ARBD) to include structural CNS and cognitive abnormalities in children in whom fetal exposure to alcohol has been confirmed.

It is established that prenatal exposure to alcohol produces a range of morphological and cognitive-behavioral outcomes in the offspring, commonly referred to as fetal alcohol spectrum disorder (FASD) (Kodituwakku 2007). Fetal alcohol syndrome refers to severely affected children on the spectrum displaying a pattern of altered growth and morphogenesis, characterized by prenatal and postnatal growth retardation, craniofacial anomalies, abnormal brain function reflected by cognitive deficits, and developmental delays. The majority of children (about three times as many children as those with FAS) with substantial prenatal alcohol exposure show only some of the above mentioned features (Sampson et al. 1997), commonly referred to having fetal alcohol effects (FAE). The term FAE, however, has been replaced by two new terms: ARND and ARBD.

The incidence of FAS in the United States is estimated to be about 1–3 per 1,000 live births. The incidence is higher in certain population, such as Native Americans (Gleason 2001).

Synonyms and Related Disorders

Alcohol-related birth defects (ARBD); Alcohol-related neurodevelopmental disorder (ARND); Fetal alcohol syndrome

Genetics/Basic Defects

1. Genetics (Thackray and Tifft 2001)
   a. Genetic susceptibility
      i. Observation of differences in the severity and spectrum of FAS based on genetic background.
      ii. Higher concordance of FAS in monozygotic twins than in dizygotic twins supports the concept of genetic factors in the fetal effects of alcohol.
   b. Possible mechanism of heritable susceptibility to FAS: genetically encoded differences in alcohol dehydrogenase, the enzyme responsible for metabolizing alcohol in the liver
      i. Mother of children with FAS: possibly with less functional enzyme resulting in higher peak blood alcohol concentration after the ingestion of alcohol.
      ii. Fetuses with FAS: possibly with deficient alcohol dehydrogenase activity and thus less tolerance to elevated maternal alcohol levels.

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2. Pathogenesis (Thackray and Tifft 2001)
   a. Clinical features of FAS: result from exposure of the developing fetus to toxic levels of alcohol and its metabolites at critical periods in development.
   b. Specific pathophysiology unknown: may involve free radical formation that causes cellular damage in the developing tissues of the fetus.
   c. Exposure in the first trimester
      i. Affects organogenesis and craniofacial development, leading to minor and major malformations such as the characteristic facial features and ARBD.
      ii. Excessive cell death in the midline of the developing embryo may account for the development of these facial features.
   d. Continuous use of alcohol by the mother later in pregnancy resulting in low birth weight and affecting postnatal growth.
   e. Alcohol exposure at varying times in pregnancy may result in similar CNS neurodevelopmental effects.
   f. Detrimental defects on the fetus when there is concomitant maternal use of other drugs (marijuana, nicotine, caffeine).
3. Key risk factors for alcohol-induced brain damage
   a. Peak blood alcohol concentration rather than the length of alcohol exposure: the critical variable in determining risk for adverse effects on brain development.
   b. Cessation of drinking alcohol at any time during pregnancy likely to be beneficial on developing brain.
   c. Cerebellum particularly vulnerable to alcohol-induced growth restriction as well as neuronal loss following alcohol exposure during the brain growth spurt (third trimester in humans).
   d. Heavy alcohol consumption during the first trimester associated strongly with craniofacial abnormalities in humans.

Clinical Features

1. Characteristic craniofacial features in the young child (Clarren 1981; Gleason 2001)
   a. Discriminating features
      i. Short palpebral fissures
      ii. Flat midface
      iii. Indistinct (smooth, flat) philtrum
      iv. Thin upper lip
   b. Associated features
      i. Epicanthal folds
      ii. Low nasal bridge
      iii. Minor ear anomalies
      iv. Short nose
      v. Micrognathia
2. Growth retardation (Hanson et al. 1976)
   a. Low birth weight for gestational age (prenatal growth deficiency) (97%)
   b. Decelerating weight over time not due to nutrition (Postnatal growth deficiency) (97%)
   c. Disproportionate low weight to height
3. Alcohol-related birth defects (ARBD): birth defects associated with in utero alcohol exposure
   a. Ocular abnormalities
      i. Strabismus
      ii. Retinal vascular anomalies
      iii. Optical nerve hypoplasia
      iv. Refractive problems secondary to small globes
      v. Coloboma
   b. Cardiovascular abnormalities
      i. Atrial septal defect
      ii. Ventricular septal defect
      iii. Aberrant great vessels
      iv. Tetralogy of Fallot
   c. Hepatic abnormality: extrahepatic biliary atresia
   d. Skeletal abnormalities
      i. Hypoplastic nails
      ii. Shortened fifth digits
      iii. Radioulnar synostosis
      iv. Flexion contractures
      v. Camptodactyly
      vi. Clinodactyly
      vii. Pectus excavatum/carinatum
      viii. Klippel–Feil syndrome
      ix. Hemivertebrae
      x. Scoliosis
   e. Muscular abnormalities
      i. Hernias
         a) Diaphragm
         b) Umbilicus
         c) Inguinal
      ii. Diastasis recti
   f. Renal abnormalities
      i. Aplastic/dysplastic/hypoplastic kidneys
      ii. Horseshoe kidneys

iii. Ureteral duplications
iv. Megaureter
v. Hydronephrosis
vi. Cystic diverticula
vii. Vesicovaginal fistula

g. Genital abnormalities
i. Hypospadias
ii. Labial hypoplasia

h. Cutaneous abnormalities
i. Hemangiomas
ii. Hirsutism

i. Auditory abnormalities
i. Conductive hearing loss
ii. Neurosensory hearing loss

j. Neuroendocrine abnormalities
i. Altered hypothalamic-pituitary-adrenocortical axis-heightened stress response
ii. Abnormal thyroid function

k. Other abnormalities: include virtually any malformation

4. Alcohol-related neurodevelopmental disorder (ARND)
a. Structural CNS abnormalities associated with in utero alcohol exposure
i. Microcephaly
ii. Microencephaly
iii. Decreased size of cerebrum, cerebellum, basal ganglia, diencephalons
iv. Partial or complete agenesis of the corpus callosum
v. Neuroglial heterotopia
vi. Dendritic neuronal abnormalities
vii. Holoprosencephaly sequence
viii. Anencephaly
ix. Porencephaly
x. Ventricular enlargement
xi. Dandy–Walker malformation

b. Neurologic abnormalities associated with in utero alcohol exposure
i. Impaired fine motor skills
ii. Deficits in balance
iii. Poor tandem gait
iv. Neurosensory hearing loss
v. Poor hand–eye coordination
vi. Hypotonia

c. Neurobehavioral abnormalities associated with in utero alcohol exposure
i. Learning disabilities
ii. Decreased IQ scores
iii. Mental retardation
iv. Attention deficit/hyperactivity disorder
v. Poor impulse control
vi. Problems in memory, attention, or judgment
vii. Problems in social perception
viii. Deficits in higher level receptive or expressive language
ix. Poor capacity for abstraction or metacognition
x. Autism
xi. Adult mental illness
a) Alcohol or drug dependence
b) Psychotic disorders
c) Avoidant, antisocial, or dependent personality disorder
d) Depression
e) Suicide
xii. Alcohol or drug dependence
xiii. Psychotic disorders
xiv. Avoidant, antisocial, or dependent personality disorder
xv. Depression
xvi. Suicide

5. Neonatal alcohol withdrawal signs
a. Hypoglycemia
b. Irritability
c. Tremors
d. Seizures
e. Autonomic dysregulation, including temperature instability
f. Blood pressure abnormalities
i. Hypotension
ii. Hypertension
g. Excessive glucocorticoid release
h. Altered behavioral state organization

6. Medical risks for women who drink alcohol (Bradley et al. 1998)
a. Increased mortality and breast cancer in women who drink more than two drinks daily.
b. Increased menstrual symptoms, hypertension, and stroke in women with higher levels of alcohol consumption.
c. Increased infertility and spontaneous abortion in women who drink heavily.
d. Adverse fetal effects after variable amounts of alcohol consumption, making any alcohol use during pregnancy potentially harmful.

Diagnostic Investigations

1. Diagnosis of FAS based on clinical features in the setting of maternal alcohol use
2. Radiography for skeletal abnormalities
3. Neuroimaging in FASD (Norman et al. 2009)
   a. MRI imagings for CNS abnormalities
      i. Overall reduction in brain volume
      ii. CNS disorganization
      iii. Structural abnormalities
         a) Corpus callosum
         b) Cerebellum
         c) Caudate
         d) Hippocampus
   b. Neuroimaging techniques
      i. Regional increases in cortical thickness and gray matter volume
      ii. Decreased volume and disorganization of white matter in individuals
   c. Functional imaging studies: functional and neurochemical differences in those prenatally exposed to alcohol
4. Echocardiography for cardiovascular anomalies
5. Ultrasound for renal abnormalities
6. Neurologic and neurobehavioral evaluations

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: high if the mother abuses alcohol during the pregnancy
   b. Patient's offspring: high if the affected woman abuses alcohol during her pregnancy
2. Prenatal diagnosis
   a. Low maternal serum alpha-fetoprotein and low pregnancy-specific β_1-glycoprotein observed in one report possibly reflecting primary or secondary effects of ethanol abuse in pregnancy and possibly useful in predicting fetal alcohol syndrome.
   b. Prenatal ultrasound examination recommended for pregnant women who drink to detect fetal growth retardation and various birth defects associated with in utero alcohol exposure.
3. Management (Thackray and Tifft 2001)
   a. Beneficial effects of early diagnosis of FAS on medical intervention of affected infants and children.
   b. Management of issues (medical and surgical interventions) regarding specific birth defects.
   c. Implementation of resource programs for developmental delay, functional abilities, speech abilities, and social/behavioral interactions.
   d. Appropriate interventions with educational evaluation and support and community resources such as The National Organization on Fetal Alcohol Syndrome (NOFAS).
   e. Evaluate and manage the siblings who also have FAS.
   f. Prevention of alcohol-induced fetal brain damage (AAP 2000).
      i. Abstinence recommended for pregnant women and for those planning pregnancy since there is no known safe amount of alcohol consumption during pregnancy.
      ii. High-quality educational programs regarding the deleterious effects of alcohol on the unborn child.
      iii. High awareness of FAS and ARND and their prevention by health care professionals.
      iv. Appropriate support services including prevention of recurrence for parents and children diagnosed as having FAS or ARND.

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Fig. 1 (**a**–**c**) Two brothers with fetal alcohol syndrome showing prenatal and postnatal growth deficiency and characteristic facial features (short palpebral fissures, flat nasal bridge, flat midface, smooth philtrum, and thin upper lip)

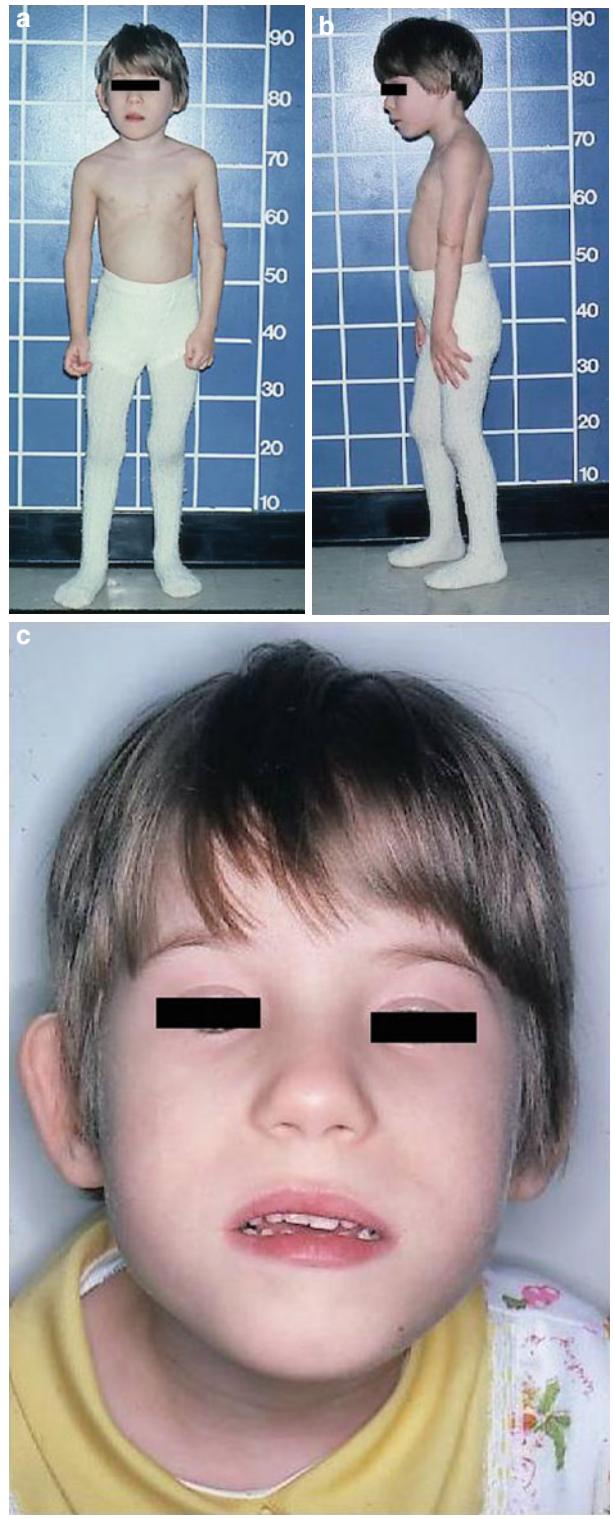

Fig. 2 (**a**–**c**) Another boy with fetal alcohol syndrome showing short stature and similar characteristic facial appearance

Fetal Hydantoin Syndrome

Fetal hydantoin syndrome is by far the best-characterized malformation complexes induced by anticonvulsant drugs used to treat maternal epilepsy.

Genetics/Basic Defects

1. Cause: maternal exposure to hydantoin anticonvulsant
2. Effect of prenatal exposure to hydantoin
   a. Fetal hydantoin syndrome in 11% of cases
   b. Fetal hydantoin effect in an additional 31% of cases
3. Teratogenicity of hydantoin
   a. Mediated not by the parent compound but by toxic intermediary metabolites that are produced during the biotransformation of the parent compound
   b. Epoxide (oxidative intermediates): the primary teratogenic agent of phenytoin
      i. Thought to occur before the formation of the dihydrodiol metabolite in a reaction catalyzed by the enzyme epoxide hydrolase
      ii. Highly reactive and capable of covalently binding to embryonic or fetal nucleic acids, which at critical periods of embryogenesis, are theoretically capable of disrupting normal development

Clinical Features

1. Eleven percent of infants exposed prenatally to hydantoin classified as having the fetal hydantoin syndrome
2. Presence of variable patterns of malformations
3. Classic features
   a. Growth and development
      i. Developmental delay
      ii. Mild to moderate mental retardation
      iii. Prenatal and postnatal growth deficiencies
      iv. Microcephaly
   b. Craniofacial anomalies
      i. Ridging of the metopic suture
      ii. Broad and low nasal bridge
      iii. Ocular defects
         a) Hypertelorism
         b) Ptosis
         c) Strabismus
         d) Wide epicanthal folds
         e) Congenital glaucoma
         f) Retinoschisis
         g) Nasolacrimal duct deformity and agenesis
         h) Coloboma of the iris and choroid
      iv. Short upturned nose
      v. Low-set ears
      vi. Wide mouth with prominent lips
      vii. Cleft lip and/or palate
   c. Limb defects
      i. Hypoplasia of distal phalanges and nails (most characteristic feature)
      ii. A finger-like thumb
      iii. Hyperphalangism
      iv. Adactyly/absent nails
      v. Acheiria (congenital absence of one or two hands)
      vi. Positional limb defects
         a) Calcaneovalgus deformity
         b) Pes cavus
      vii. Abnormal palmar creases

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4. Less frequently observed abnormalities
   a. Neck webbing
   b. Cardiovascular anomalies
      i. Aortic coarctation
      ii. Patent ductus arteriosus
      iii. Septal defects
   c. Gastrointestinal abnormalities
      i. Pyloric stenosis
      ii. Duodenal atresia
   d. Renal defects
   e. Genital abnormalities in males
      i. Hypospadias
      ii. Bifid or shawl scrotum
   f. Hernias
      i. Diaphragmatic hernia
      ii. Umbilical hernia
      iii. Inguinal hernias
   g. Other skeletal anomalies
      i. Spinal anomalies
         a) Scoliosis
         b) Segmentation defects of vertebral bodies
      ii. Rib and sternal anomalies
   h. Occasional tumor association
      i. Neuroblastoma
      ii. Melanotic neuroectodermal tumor of infancy
   i. Single umbilical artery

Diagnostic Investigations

1. Radiography for skeletal defects
2. Echocardiography for associated congenital heart defect
3. Renal ultrasound for renal defects
4. Developmental evaluation

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: minimal in the absence of maternal exposure to hydantoin during pregnancy
   b. Patient's offspring: minimal in the absence of maternal exposure to hydantoin during pregnancy
2. Prenatal diagnosis: prenatal ultrasound examination recommended for pregnant women who take hydantoin anticonvulsant to detect fetal growth retardation and various birth defects associated with in utero hydantoin exposure
3. Management
   a. Management of issues (medical and surgical interventions) regarding specific birth defects
   b. Implementation of resource programs for developmental delay, functional abilities, speech abilities, and social/behavioral interactions
   c. Appropriate interventions with educational evaluation and support
   d. Avoid hydantoin anticonvulsant during pregnancy

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Fig. 1 (**a**–**g**) Three patients with fetal hydantoin syndrome showing typical craniofacial features (ocular hypertelorism, flat nasal bridge, epicanthal folds, small upturned nose, wide mouth with prominent lips) and nail hypoplasia

Fibrodysplasia Ossificans Progressiva

Fibrodysplasia ossificans progressiva (FOP), an extremely rare and catastrophic genetic disorder of progressive heterotopic ossification, is the most disabling condition of extraskeletal ossification known to mankind. It is also known as myositis ossificans progressiva. The incidence of FOP was estimated to be approximately 1 in 1.64 million (Connor and Evans 1982b).

Synonyms and Related Disorders

Myositis ossificans progressiva

Genetics/Basic Defects

1. Inheritance
   a. Usually sporadic in occurrence: very few affected individuals have children because of the devastating nature of the disease
   b. Autosomal dominant inheritance
      i. Complete penetrance
      ii. Variable expression
2. Cause (Shore et al. 2006)
   a. FOP is caused by a recurrent heterozygous mutation (c.617G>A; p.R206H) of codon 206 in the glycine-serine (GS) activation domain of activin receptor 1A (ACVR1)/activin-like kinase (ALK2), a highly conserved BMP type I receptor, in all sporadic and familial cases of classically affected individuals worldwide, making this one of the most highly specific disease-causing mutations in the human genome.
   b. Chromosomal locus for the *FOP* gene: 2q23-24 by genome-wide linkage analysis.
3. Presence of two skeletons in patients with FOP (Mahboubi et al. 2001)
   a. A normotopic bone formation during embryogenesis
      i. Grossly normal normotopic skeleton
      ii. Exceptions
         a) Segmentation defects in the cervical spine
         b) Malformation of the great toes at birth due to shortening of the first metatarsal and proximal phalanx
         c) Monophalangic great toes due to synostosis: the earliest phenotypic feature of fibrodysplasia ossificans progressiva
   b. A heterotopic bone formation following birth
      i. Usually beginning in the first decade of life
      ii. Progressing in characteristic anatomic patterns
      iii. Typically involving upper back and neck
      iv. Heralded by large painful swellings of highly vascular fibroproliferative tissue involving ligaments, tendons, and skeletal muscle, often following minor trauma
      v. Early swelling regresses spontaneously but often matures to true heterotopic bone
4. Pathogenesis:
   a. p.R206H mutation in the *ACVR1* gene enhances ACVR1 activation and disrupts the highly conserved BMP signaling pathway (Groppe et al. 2007)
   b. When triggered by an inflammatory stimulus, some normal-functioning connective tissue may metamorphose into heterotopic bone (Kaplan et al. 2008)

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5. Precipitating factors for ectopic ossification (Kocyigit et al. 2001)
   a. Biopsies
   b. Intramuscular injections
   c. Dental therapy
   d. Prolonged pressure on the body, such as tight clothing
   e. Aggressive physical therapy
   f. Falls
   g. Injuries
   h. Exacerbation of bone formation common in response to surgery and other tissue trauma

Clinical Features

1. Appears to be normal at birth except for tell-tale malformations of the great toes (Kaplan et al. 2005)
2. Extraskeletal abnormalities (100%)
   a. Progressive widespread heterotopic ossification of muscles, tendons, ligaments, aponeurosis, and fascia. The heterotopic bony masses lead to progressive immobility/disability (100%)
   b. Onset: about 4 years of age in majority of patients
   c. Typical course of lesional progression at any site (Mahboubi et al. 2001)
      i. Early lesions during the first few weeks: characterized by pain, erythema, swelling, warmth, and tenderness
      ii. Intermediate lesions after several weeks
         a) Swelling beginning to subside
         b) Decrease in pain, tenderness, and erythema
      iii. Late lesions after approximately 12 weeks
         a) Disappearance of swelling
         b) A hard, non-tender lesion remains. It is roentgenographically a new area of heterotopic ossification
   d. Characteristic anatomical progression of heterotopic bone formation (Mahboubi et al. 2001)
      i. Typical earliest involvement: dorsal, axial, cranial, and proximal regions of the body
      ii. Later involvement: ventral, appendicular, caudal, and distal regions of the body
   e. Proximal medial tibial osteochondromas (>90%)
   f. Variation in size of soft tissue nodules involving the neck and back: often the first indication of heterotopic ossification in a child
   g. Progressive ankylosis
      i. Shoulder joints
      ii. Elbow joints
      iii. Hip joints
      iv. Knee joints
      v. Neck (>90%): painful swelling or stiffness of the neck in most patients
      vi. Spine
         a) Leading to complete fusion
         b) Mimicking ankylosing spondylitis
         c) Pain and stiffness of the spine present in most patients
      vii. Muscles of mastication
         a) Leading to limited mouth opening
         b) Inability to feed orally
         c) Poor oral hygiene
         d) Subsequent cachexia
   h. Severe restrictive pulmonary disease
      i. Causes
         a) Scoliosis of the thoracolumbar spine
         b) Ankylosis of costovertebral joints
         c) Ossification of the chest wall with resultant dependence on diaphragm for respiration
      ii. Severely reduced lung volume
      iii. Constrictive airway dysfunction developing over time
      iv. Recurrent pulmonary infections secondary to ineffective cough: a common cause of death in the third or fourth decade
   i. Eventual confinement to wheelchair
3. Congenital malformation (microdactylia) of the great toes (>95%) and thumbs (50%)
   a. Association with congenital great toe malformation
      i. Mainly short big toes with single phalanx (a cartilaginous anlage of the first metatarsal and proximal phalanx) present at birth
      ii. An important early diagnostic clue
   b. Shortened thumbs
   c. Clinodactyly of the fifth fingers
4. Other features
   a. Patients with FOP are prone to fractures with poor outcome
   b. Occasional baldness
   c. Conductive hearing loss (~50%) secondary to calcification and fusion of the ligaments, tendons, and bones of the middle ear
   d. Markedly reduced reproductive fitness

e. Life-threatening complications caused by thoracic insufficiency syndrome (95%) due to:
   i. Costovertebral malformations with orthotopic ankylosis of the costovertebral joints
   ii. Ossification of intercostals muscles, paravertebral muscles, and aponeuroses
   iii. Progressive spinal deformity
      a) Kyphoscoliosis
      b) Thoracic kyphosis
   iv. Pneumonia
   v. Right-sided congestive heart failure
f. Reduced life span but most patients survive to adulthood

5. Natural history
   a. Mobility becomes more restricted as the disease advances.
   b. A life-long rigid immobility caused by the progressive metamorphosis of skeletal muscle and soft connective tissue into a second skeleton of heterotopic bone.
   c. Typically confined to bed or wheelchair by early 30s.
6. Diagnostic criteria (Kartal-Kaess et al. 2010)
   a. Major characteristics
      i. Congenital malformation of the great toes (earliest phenotypic feature)
      ii. Progressive extraskeletal bone formation (episodic, begin during childhood)
      iii. Heterozygous *ACVR1* mutation
   b. Other features
      i. Early stage lesions associated with soft tissue swellings and inflammation in characteristic anatomic patterns
      ii. Predictable regional pattern of heterotopic ossification
      iii. Cervical spine fusions
      iv. Short/broad femoral necks
      v. Osteochondromas
      vi. Conductive hearing loss
7. Differential diagnosis of heterotopic ossification (Kartal-Kaess et al. 2010)
   a. Progressive osseous heteroplasia (Shore and Kaplan 2005)
      i. Presence of cutaneous ossification
      ii. Absence of congenital malformations of the skeleton
      iii. Absence of inflammatory tumor-like swellings
      iv. Asymmetric mosaic distribution of lesions
      v. Absence of predictable regional patterns of heterotopic ossification
      vi. Presence of dominance of intramembranous rather than endochondral ossification
      vii. Inherited only paternally
      viii. Carries inactivating mutations of the *GNAS* gene, a gene that is regulated through genomic imprinting and allele-specific gene expression
   b. Posttraumatic: myositis ossificans circumscripta
   c. Neurogenic
      i. After head trauma or spinal cord injury
      ii. After long coma
   d. Postsurgical: after total joint arthroplasties
   e. Reactive
      i. Bizarre parosteal osteochondromatous proliferation
      ii. Florid reactive periostitis
      iii. Subungual exostosis
   f. Neoplasms
      i. Sarcoma
      ii. Malignant fibrous histiocytoma
   g. Degenerative processes

Diagnostic Investigations

1. Radiography (Bridges et al. 1994)
   a. Extraskeletal ossification
      i. Progressive widespread heterotopic ossification of muscles, tendons, ligaments, and fascia
      ii. Ankylosis
         a) Shoulder joints
         b) Elbow joints
         c) Hip joints: prevent ability to ambulate
         d) Knee joints
         e) Muscles of mastication
   b. Phalangeal abnormalities
      i. Characteristically affecting the great toes
         a) Shortened first digits
         b) Delta-shaped proximal phalanges
         c) Often monophalangism with absence of the interphalangeal joint of the great toes
      ii. Shortened thumbs
      iii. Clinodactyly of the fifth fingers

   c. Less common congenital malformations
      i. Small vertebral bodies and enlarged pedicles in early childhood
      ii. Variable degrees of vertebral fusion, especially apophysial joint fusion in late childhood
      iii. Short, broad femoral necks
      iv. Ossification of ligamentous insertions producing exostoses of the proximal tibia
      v. Delay in skeletal maturation
      vi. Enchondroma formation
      vii. Association with synovial chondromatosis
2. Bone scintigraphy (radionuclide imaging) (Tulchinsky 2007)
   a. A very sensitive technique for new bone formation in FOP
   b. Reveals multiple foci of increased uptake in connective tissue at characteristic locations, in combination with pathognomonic microdactyly of the great toes (or thumbs): highly specific
3. CT scan
   a. Useful for diagnosis because CT scan is very sensitive for calcification.
   b. Soft tissue swelling in the fascial planes and muscle in the early course of FOP.
   c. Evidence of soft tissue calcification, typically in the form of shell seen within days to a few weeks.
   d. Calcification appearing as spicules in the soft tissue or in thin planes along the fascia often encircling muscle.
   e. Able to delineate the presence or absence of bone destruction, differentiating FOP from invasive processes such as infection and tumor.
4. MRI: a sensitive imaging technique for soft tissue abnormalities but not particularly useful for diagnosis
5. Ultrasonography to demonstrate echogenic and shadowing mass
6. Audiography: mixed-type hearing loss with prominent conductive component
7. Histopathology (Mahboubi et al. 2001)
   a. Earliest finding: an intense perivascular lymphocytic infiltration
   b. Followed by death of skeletal muscle and replacement by a highly vascular fibroproliferative soft tissue, which rapidly progresses through an endochondral process to form heterotopic bone
8. Molecular genetic diagnosis: mutational screening of *ACVR1* gene
   a. Detection of a specific heterozygous mutation (c.617G>A; p.R206H) in the activin A type I receptor gene (*ACVR1*) in all classically affected individuals
   b. Detection of a variant FOP phenotype (c.983G>A; p.G328E) (Carvalho et al. 2010)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased unless a parent is affected or has gonadal mosaicism
   b. Patient's offspring: 50%
2. Prenatal diagnosis: possible by molecular genetic testing of the *ACVR1* gene on fetal DNA obtained from amniocentesis or CVS for fetuses at 50% risk for FOP if a clinically diagnosed relative has an identified disease-causing *ACVR1* gene alteration
3. Management (Kocyigit et al. 2001)
   a. No effective treatment available
   b. FOP can often be recognized in children with or without previously affected family members at birth or in early years before the onset of heterotopic ossifications because of the presence of shortening of the great toe and short thumbs
   c. Early recognition allows protection of the child from injuries
      i. Avoid multiple biopsies, trauma, intramuscular injections, and dysfunctional IV catheters to prevent precipitating the heterotopic ossification and exacerbating the disease
      ii. Prevention of influenza-like illnesses
      iii. Minimal soft tissue trauma during routine dental care may precipitate permanent ankylosis of the jaw
   d. Physical therapy in general not recommended as stretching of the soft tissues around a joint can lead to a painful flare-up
   e. Steroids, nonsteroid anti-inflammatory agents, disodium etidronate, warfarin, and radiotherapy
      i. Used to halt the progression of disease
      ii. Without proven benefit
   f. Isotretinoin
      i. Principle based on its ability to inhibit differentiation of mesenchymal tissue into cartilage and bone

ii. Questionable benefit to decrease the incidence of heterotopic ossification at uninvolved anatomical sites

g. Etidronate (aminobisphosphonates)
   i. Blocks ectopic calcification and is approved by Food and Drug Administration for treatment of postoperative heterotopic ossification
   ii. Short-term effect of bone metabolism shows diminished bone turnover rate
   iii. Long-term effect on ectopic calcification is unchanged in most cases with few exceptions

h. Primary therapy for the debilitating disease: supportive care
   i. Active range-of-motion exercises encouraged if the movements are comfortable
   ii. Available adaptations or modifications prescribed to a disabled patient with FOP to achieve functional independence in the home and community
      a) Shoes
      b) Canes
      c) Wheelchairs

i. Surgery
   i. Nearly always contraindicated since new heterotopic ossification occurs at the operative site
   ii. Surgical removal of heterotopic bone
      a) Ineffective
      b) Leading to catastrophic exacerbation of the disease
   iii. Existence of intercurrent problems occasionally requiring surgery

j. Anesthesia
   i. Presenting numerous difficulties to the anesthesiologist including cervical spine ankylosis and restrictive pulmonary disease
   ii. Avoid tissue trauma in the form of local anesthetic injections
   iii. Presence of anatomical airway abnormalities
   iv. Alternative methods preferred
      a) Nebulized lidocaine
      b) IV sedation
      c) Nasotracheal intubation
   v. Proper positioning and padding perioperatively
   vi. Vigorous chest physiotherapy and pulmonary toilet postoperatively

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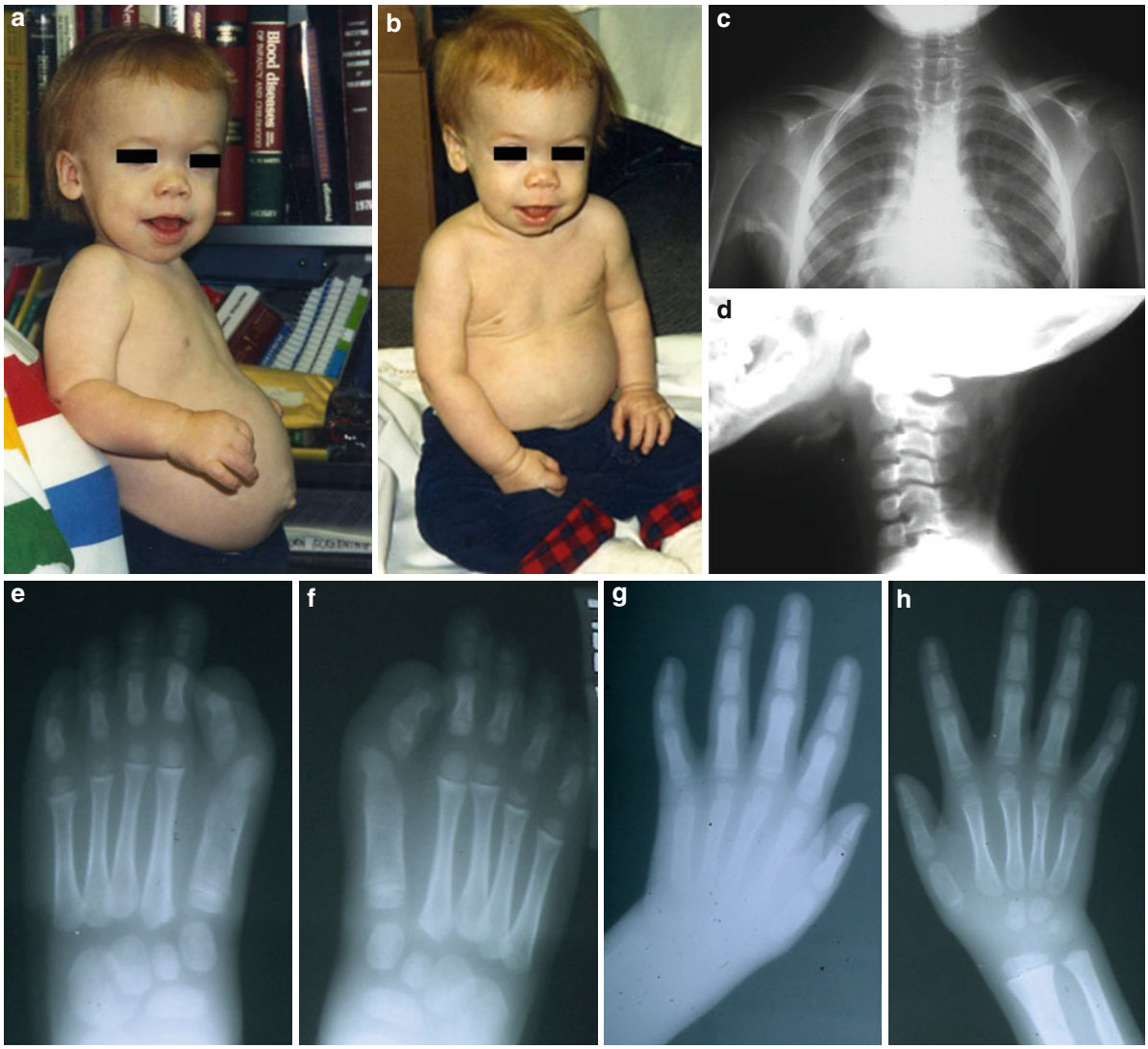

Fig. 1 (**a**–**h**) A boy with fibrodysplasia ossificans progressiva showing a stiff neck, a narrow chest, and inability to raise arms upward due to ossification of the soft tissues on the back of the neck, the lateral chest wall, and the axillary region, illustrated by the neck, chest, and pelvic radiographs. The radiographs of both feet showed shortened first toes and hallux valgus with delta-shaped proximal phalanges, monophalangism with absence of the interphalangeal joint of the great toes. The radiographs of both hands showed shortening of the first metacarpals and the middle phalanx of the fifth fingers with clinodactyly

Fig. 2 A 14-year-old girl was seen because of swelling and pain on the upper thigh, especially on the *left*. The pelvic radiograph showed extensive heterotopic calcifications on the inner upper thighs, worse on the *left*. Her father was also affected

Finlay–Marks Syndrome

In 1978, Finlay and Marks described the association of scalp defect, malformed ears, and absence of nipples in a family. The association is also known as scalp-ear-nipple syndrome.

Synonyms and Related Disorders

Scalp-ear-nipple syndrome

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant in most reports
   b. Severe autosomal recessive form: two children from an inbred Arab family with features suggestive of scalp-ear-nipple syndrome (Al-Gazali et al. 2007)
2. Lymphoid enhancer factor-1 (*Lef-1*), identified as a candidate gene for scalp-ear-nipple syndrome (van Steensel et al. 1999)
   a. *Lef-1*: an HMG-domain DNA-binding protein expressed in the neural crest, mesencephalon, tooth germs, and other sites during embryogenesis
   b. Homozygous deficiency of this gene causing postnatal lethality in mice
   c. Mutant mice lacking teeth, mammary glands, whiskers, and hair
   d. Lack of hair, missing teeth, and aplasia of breast tissue suggest that *Lef-1* may be a candidate gene for scalp-ear-nipple syndrome

Clinical Features

1. Scalp abnormalities (Edwards et al. 1994; Taniai et al. 2004)
   a. Raised firm nodules over the scalp in the occipital region, not covered by hairs
   b. The areas: raw at birth and heal during childhood
   c. Crumpled scalp over occipital region
2. External ear abnormalities
   a. Hypoplastic tragus, antitragus, and lobule
   b. Over-folding of the superior helix
   c. Flattening of the antihelix
3. Athelia (absent breasts and nipples)
   a. Rudimentary or absent nipples
   b. Breast hypoplasia or aplasia
4. Other reported features
   a. Ectodermal dysplasia features
      i. Dental anomalies
         a) Widely spaced teeth
         b) Missing secondary teeth
         c) Neonatal teeth
      ii. Reduction of axillary apocrine secretion and axillary hair growth
      iii. Hypohidrosis
      iv. Nail dysplasia
   b. Aplasia cutis vertices
   c. Renal hypoplasia
   d. Hypospadias
   e. Pyeloureteral duplication
   f. Cataract
   g. Coloboma of the iris
   h. Hypertension
   i. Diabetes mellitus
   j. Partial syndactyly

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5. Hypotonia and developmental delay in severe autosomal recessive form

Diagnostic Investigations

1. No specific laboratory tests available
2. Histology of scalp defect resembling aplasia cutis congenita (Finlay and Marks 1978)
   a. An excess of normal-appearing connective tissue
   b. Lack pilosebaceous elements
3. Renal sonography for renal hypoplasia
4. Diagnosis primarily by clinical features

Genetic Counseling

1. Recurrence risk
   a. Autosomal dominant
      i. Patient's sib: low unless a parent is affected
      ii. Patient's offspring: 50%
   b. Autosomal recessive
      i. Patient's sib: 25%
      ii. Patient's offspring: not increased unless the spouse is a carrier
2. Prenatal diagnosis: not been reported
3. Management: primarily supportive

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Fig. 1 A 7-month-old boy with Finlay–Marks syndrome showing absence of nipples and abnormal ears. He also had scanty eyebrows and eyelashes, neonatal teeth, which were extracted, nasolacrimal duct stenosis, and lumpy scalp on the occiput region

Floppy Infant

A floppy infant is an infant with poor muscle tone affecting the limbs, trunk, and the craniofacial musculature. The causes are numerous (heterogeneous etiologies) and the workup in many instances can be complex. The task of evaluating infants with hypotonia is difficult and complex.

Synonyms and Related Disorders

Congenital hypotonia

Genetics/Basic Defects

1. Heterogeneous causes of hypotonia (Prasad and Prasad 2003; Igarash 2004)
   a. Chromosome disorders: central hypotonia
      i. Aneuploidy: e.g., Down syndrome (one of the most frequently encountered cause of neonatal hypotonia)
      ii. Microdeletions: e.g., Prader–Willi syndrome (neonatal hypotonia, feeding problems, and failure to thrive with later onset of hyperphagia and obesity)
      iii. Subtelomeric cryptic deletions (relatively new category of disorders that account for unexplained mental retardation): e.g., terminal 22q13.3 deletion syndrome (neonatal hypotonia can be a prominent feature)
   b. CNS malformations/encephalopathies (associated with profound neonatal hypotonia)
      i. Congenital CNS malformations
         a) Lissencephaly
         b) Holoprosencephaly
      ii. Acquired CNS disorders
         a) Birth trauma
         b) Hypoxic–ischemic encephalopathy
         c) Spinal cord injury
   c. Disorders affecting anterior horn cells and peripheral nerves
      i. Spinal muscular atrophy (SMA1) (Werdnig–Hoffman disease): generalized weakness, often spares the diaphragm, facial muscles, pelvis, and sphincters
      ii. Charcot–Marie–Tooth disease
         a) CMT1A
         b) CMT4E (congenital hypomyelination syndrome)
         c) Dejerine–Sottas syndrome (CMT3)
   d. Neuromuscular junction disorders
      i. Transient myasthenic syndrome
      ii. Hypermagnesemia of the newborn
      iii. Infantile botulism
      iv. Congenital myasthenic syndromes (neuromuscular junction disorders): bulbar, oculomotor muscles exhibit greater degree of involvement (neonatal hypotonia, easy fatigability, recurrent aspiration, feeding difficulty, cyanosis, and apnea)
         a) Congenital myasthenic with episodic apnea
         b) Slow-channel and fast-channel syndromes
         c) Endplate cholinesterase deficiency
   e. Congenital muscular dystrophies (CMD) and myopathies: hypoactive reflexes. For example,
      i. Classical congenital muscular dystrophy
      ii. Fukuyama muscular dystrophy
      iii. Walker–Warburg syndrome

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iv. Muscle-eye-brain disease
v. Ullrich congenital muscular dystrophy
vi. Bethlem myopathy
vii. Rigid spine-muscular dystrophy (SEPN1 selenoprotein deficiency)
viii. Congenital myotonic dystrophy
a) Triplet repeat CTG expansion of the *DMPK* and *SIX5* genes
b) Abnormal splicing of chloride channels mRNA leading to the myotonia

f. Congenital myopathies: prominent weakness. For example,
i. Central core myopathy
ii. Nemaline myopathy
iii. Myotubular (centronuclear) myopathy
iv. Multicore myopathy
v. Congenital myopathy with fiber type disproportion

g. Metabolic disorders/myopathies: proximal musculature weakness. For example,
i. Acid maltase deficiency (Pompe disease)
ii. Pyruvate dehydrogenase complex deficiency
iii. Pyruvate carboxylase deficiency
iv. Respiratory chain defects (mitochondrial disorder)
v. Zellweger syndrome
vi. Smith–Lemli–Opitz syndrome
vii. Congenital disorders of glycosylation
viii. Phosphomannomutase-2 deficiency

h. Combined CNS and motor unit disorder
i. Metachromatic leukodystrophy
ii. Giant axonal neuropathy
iii. Familial dysautonomia
iv. Mitochondrial encephalopathy
v. Congenital muscular dystrophies

i. Congenital hypotonia with a favorable outcome (benign congenital hypotonia): characterized by an early neonatal onset and a benign clinical course: No longer considered as a specific diagnostic entity

j. Acute and systemic diseases especially in the newborn period
i. Sepsis
ii. Congestive heart failure

k. Chronic
i. Hypothyroidism
ii. Connective tissue disorder

2. Localization of hypotonia in the floppy infant (Bodensteiner 2008)
a. Supraspinal/suprasegmental hypotonia in which deep tendon reflexes are preserved:
i. Central hypotonia caused by brain lesions
a) Sepsis
b) Congenital heart failure
c) Hypoxic–ischemic encephalopathy
ii. Syndromic central hypotonia caused by brainstem lesions (extensive list of etiologic possibilities associated with constellation of dysmorphic features)
iii. Nonsyndromic central hypotonia
a) Cerebral dysgenesis (developmental anomalies of the brain).
b) Grossly normal brain by MRI includes myelination within normal range, normal development (essential hypotonia), delayed myelination, motor delay only (usually catch up to peers in tone and development by school age), developmental delay (may later be diagnosed as nonsyndromic mental retardation, frequently labeled as autistic), or global developmental delay (usually do not catch up intellectually and cognitively to peer by school age).
iv. Central hypotonia caused by craniocervical junction lesions
a) Spinal cord injury (critically ill infant with severe hypotonia at first and the nature of the injury is not usually suspected until the development of the hyperactive reflexes and the lack of the expected maturation of the corticospinal tract influences on the motor unit).
b) Chiari I malformation (may be an isolated finding that may cause hypotonia early on by compression of the lower brainstem at the level of the foramen magnum).
c) Chiari II malformation (usually associated with spina bifida and easily suspected).

b. Segmental or motor unit hypotonia in which deep tendon reflexes are depressed or lost
i. Anterior horn cell (spinal muscular atrophy)
ii. Peripheral nerve (hereditary motor sensory neuropathy)

iii. Neuromuscular junction
  a) Myasthenia gravis
  b) Congenital myasthenic syndromes
  c) Botulism
iv. Muscle
  a) Congenital myopathies
  b) Metabolic myopathies
  c) Neonatal presentation of muscular dystrophy

Clinical Features

1. Hypotonia (decreased or loss of muscle tone)
   a. Full abduction and external rotation of the legs.
   b. Flaccid extension of the arms.
   c. Prominent head lag on pull to sit (normally diminished or absent by about 2 months of age): "Pull to sit" maneuver tests axial tone of the neck and back and appendicular tone of the shoulder and arms and also tests strength to some extent. Normal response from the infant being tested is to resist the pull on the arms and shoulder.
   d. Scarf sign: produced by grasping the supine infant's hand and pulling it across the chest and bring the baby's elbow well beyond the baby's chin and the midline of the chest before encountering the resistance. The maneuver tests the appendicular tone in the shoulder and is somewhat sensitive to the gestational age of the infant, the degree of laxity of the ligaments, and the state of alertness of the child.
   e. Shoulder suspension test: produced by picking the infant up holding under the infant's arms and observe the tendency of the hypotonic infant to slip through the examiner's hands. The maneuver tests the appendicular tone but also gives some indication of head control (axial) as well as strength.
   f. Ventral suspension test: produced by lifting off the infant from the table by examiner's one hand under the infant's chest and abdomen and observe the hypotonic infant unable to lift the head above the horizontal plane and unable to flex the arms and legs.
2. Central hypotonia (disorders of central nervous system that cause decreased tone by interrupting pathways involved in the modulation) with following general characteristics:
   a. Hypotonia
   b. Obtundation
   c. Neonatal seizures
   d. Hyperactive deep tendon reflexes
   e. Neonatal encephalopathy
   f. Clinical or neuroimaging evidence for hypoxia–ischemia
3. Peripheral hypotonia (disorders of the motor unit)
   a. General characteristics
      i. Hypotonia (absence of features of central hypotonia)
      ii. Areflexia or diminished reflexes
      iii. Convincing weakness
      iv. Decreased antigravity limb movements
      v. Weak cry
      vi. Weak suck
      vii. Fasciculations
      viii. External ophthalmoplegia
      ix. Alert look
      x. Arthrogryposis
   b. Anterior horn cell disease
      i. SMA: the most common serious cause of hypotonia in the infant and child
      ii. Very few conditions other than SMA that would result in widespread denervation on EMG in the clinical setting of hypotonia and weakness in infancy
      iii. Muscle biopsy no longer necessary to make the diagnosis of SMA in the clinical situation
   c. Peripheral nerve diseases, such as CMT, rarely cause hypotonia in infancy
   d. Neuromuscular junction disease
      i. Not a common cause of hypotonia in infancy
      ii. The only category of motor unit disease in which the reflexes may be preserved
      iii. Neonatal myasthenia gravis
        a) Uncommon cause of hypotonia in infancy in recent years
        b) Caused by antibodies to the acetylcholine receptor (AchR) which are passively transferred to the infant by the mother who has autoimmune myasthenia gravis
      iv. Congenital myasthenic syndromes
        a) Much more common cause of hypotonia in infancy

b) Caused by genetic defects of neuromuscular transmission resulting in a decrease in the safety margin in neuromuscular transmission
c) Manifest clinically by easy fatigability and weakness to variable degree depending on the severity of the defect in transmission
d) Diagnosis based on fatigue with exercise
e) Affected infants may be very sensitive to neuromuscular blocking agents and may respond to AchE antagonists

v. Selected congenital myasthenic syndromes
a) AchR deficiency: early onset, variable severity, ptosis, extraocular palsy, and involvement of bulbar, arm, and legs.
b) Slow-channel syndrome: selective severe weakness of neck, wrist, and finger extensor, variable onset and severity, and common, often progressive ventilatory problems.
c) Fast-channel syndrome: variable onset and severity and may respond to AchE inhibitors.
d) Endplate rapsyn deficiency: early onset with hypotonia, respiratory failure, apnea, and arthrogryposis.
e) Congenital myasthenia syndrome with episodic apnea: early respiratory failure, episodic apnea, improvement with age, and may respond to AchE inhibitors.
f) Endplate acetylcholinesterase deficiency: ophthalmoparesis, severe axial musculature weakness, slow papillary responses.

e. Abnormalities of muscle structure or function
i. A major cause of motor unit hypotonia, second only to SMA in overall frequency
ii. Congenital myopathies
a) More likely than Duchenne muscular dystrophy as a cause of hypotonia in the first year
b) Comprised of a group of muscle diseases that typically only slowly progressive over time, although present at birth with variable severity
c) Classical congenital myopathies (central core disease, nemaline myopathy, centronuclear myopathy)
d) Other well-established congenital myopathies (multicore, congenital myopathy with fiber-type disproportion (CFTD, reducing body, fingerprint, cytoplasmic body)
e) Congenital muscular dystrophies (CMD): CMD is an important subgroup of congenital myopathies. The conditions are usually present at birth, often quite severe with muscle weakness, wasting, respiratory difficulty, and contractures, with variable involvement of brain, eyes, and other tissues. Muscle biopsies show dystrophic muscle with muscle fiber necrosis and regeneration with replacement of muscle with fibrous and fatty connective tissue. The CMD is typically subdivided into two categories: those with brain involvement (syndromic CMD, comprised of merosin-deficient CMD, CMD with partial merosin deficiency, CMD 1C, CMD with ITGA7 mutations, CMD with spine rigidity) and those without brain involvement (nonsyndromic CMD, comprised of Fukuyama CMD, muscle-eye-brain disease, Walker–Warburg syndrome 2, congenital muscular dystrophy)

iii. Central core disease
a) Variable presentation
b) Somatic abnormalities
c) Characteristic malignant hyperthermia
d) Occasional cardiomyopathy

iv. Nemaline myopathy
a) Variable presentation
b) Somatic abnormalities (infantile)
c) Muscle wasting
d) Ocular muscle weakness
e) Adult onset of pain/cramp
f) Rare cardiomyopathy

v. Centronuclear (myotubular) myopathy
a) Variable presentation
b) Somatic abnormalities (infantile)
c) Muscle wasting
d) Ocular muscle weakness with ptosis

vi. Multicore myopathy
a) Mild early presentation
b) Somatic abnormalities

c) Ocular muscle weakness with ptosis
d) Malignant hyperthermia reported
e) Cardiomyopathy reported

vii. Congenital myopathy with fiber-type disproportion (CFTD)
a) Variable presentation
b) Muscle wasting
c) Somatic abnormalities
d) Stiffness
e) Mental retardation

viii. Reducing body myopathy (X-linked)
a) Variable presentation
b) Somatic abnormalities
c) Ocular muscle weakness with ptosis
d) Cardiomyopathy reported

ix. Fingerprint body myopathy
a) Mild early presentation
b) Muscle wasting
c) Somatic abnormalities
d) Mental retardation

x. Cytoplasmic inclusion body myopathy
a) Early, moderate to severe onset
b) Somatic abnormalities
c) Cardiomyopathy

xi. Merosin-deficient DMD
a) Severe manifestation
b) Hypotonia
c) Global weakness
d) Contractures
e) Scoliosis
f) Inability to walk
g) Normal intelligence
h) Abnormal white matter signal (MRI)

xii. CMD with partial merosin deficiency
a) Milder manifestation
b) Ability to walk in most cases
c) Cardiomyopathy
d) Contractures of elbow, knees, and fingers
e) Normal intelligence
f) Normal MRI of the brain

xiii. CMD type 1C
a) Severe weakness
b) Global involvement
c) Contractures of elbow, knees, fingers
d) Cardiomyopathy
e) Normal intelligence
f) Normal MRI of the brain

xiv. CMD with ITGA7 mutation
a) Proximal muscle weakness
b) Torticolis
c) Congenital hip dislocation

xv. CMD with spine rigidity
a) Rigid spine, elbows, hips, and ankles
b) Progressive sleep hypoventilation

xvi. Ullrich CMD
a) Global weakness with contractures
b) Distal hyperextensibility
c) Calf atrophy
d) Normal intelligence

xvii. Fukuyama CMD
a) Severe generalized weakness
b) Contractures
c) Cobblestone lissencephaly

xviii. Muscle-eye-brain disease
a) Mild presentation early (ability to walk in some cases but lose walking by age 20)
b) Eye malformations (without cataracts)
c) Hydrocephalus
d) White matter abnormality (MRI)
e) Cobblestone lissencephaly

xix. Walker–Warburg syndrome
a) Severe generalized weakness
b) Contractures at elbows only
c) Lissencephaly
d) Dandy–Walker malformation or cerebellar hypoplasia, flat pons (MRI)
e) Early demise

xx. CMD 1D
a) Global delay
b) Proximal weakness greater than distal weakness
c) Muscle hypertrophy
d) Facial sparing
e) White matter changes (MRI)

4. Differentiating congenital hypotonia of central versus peripheral origin (Harris 2008)
a. Weakness
i. Central: mild to moderate
ii. Peripheral: significant (“paralytic”)
b. Deep tendon reflexes
i. Central: decreased or increased
ii. Peripheral: absent
c. Placing reactions
i. Central: sluggish or slow
ii. Peripheral: absent

d. Motor delays
   i. Central: present
   ii. Peripheral: present
e. Antigravity movements in prone and supine
   i. Central: some but less than a typical infant
   ii. Peripheral: often absent
f. Pull to sit
   i. Central: some head lag (more so than typical infant)
   ii. Peripheral: marked head lag
g. Cognition/affect
   i. Central: delayed
   ii. Peripheral: typical
h. Ability to "build up" tone, e.g., tapping under knees with infant in supine to assist them in holding hips in adduction
   i. Central: present
   ii. Peripheral: absent

5. Pattern of muscle weakness and localization in the floppy infant (Prasad and Prasad 2003)
   a. Central nervous system
      i. Corresponding disorders
         a) Chromosome disorders
         b) Inborn errors of metabolism
         c) Cerebral dysgenesis
         d) Cerebral/spinal cord trauma
      ii. Pattern of weakness and involvement
         a) Central hypotonia
         b) More prominent axial weakness
         c) Hyperactive reflexes
   b. Motor neuron
      i. Corresponding disorders (SMA)
      ii. Pattern of weakness and involvement (generalized weakness, often sparing diaphragm, facial muscles, pelvis, and sphincters)
   c. Nerve
      i. Corresponding disorders: peripheral neuropathies
      ii. Pattern of weakness and involvement (weakness with wasting involving distal muscle)
   d. Neuromuscular junction
      i. Corresponding disorders
         a) Myasthenia syndrome
         b) Infantile botulism
      ii. Pattern of weakness and involvement (weakness with greater involvement of bulbar and oculomotor muscles)
   e. Muscle
      i. Corresponding disorders
         a) Congenital myopathies
         b) Metabolic myopathies
         c) CMD
         d) Congenital myotonic dystrophy
      ii. Pattern of weakness and involvement
         a) Prominent weakness
         b) Proximal musculature
         c) Hypoactive reflexes
         d) Joint contractures
6. Congenital hypotonia with a favorable outcome (benign congenital hypotonia)
   a. No longer considered as a specific diagnostic entity
   b. The term applied to a group of patients in whom a specific diagnosis cannot be made despite best effort in workup
   c. Common features
      i. Generalized hypotonia since birth
      ii. Mild delayed or normal developmental milestones
      iii. Active movement with preserved reflexes
      iv. Significant joint laxity or hypermobility
      v. Normal investigations (muscle enzymes, EMG, nerve conduction studies, muscle biopsy)
      vi. Favorable outcome common
7. Other diagnostic features
   a. Areflexia, decreased limb movement, and demonstration of denervation on EMG suggest anterior horn cell disorders such as SMA type I.
   b. Decreased conduction velocities on nerve conduction test suggest a demyelinating neuropathies such as Charcot–Marie–Tooth (CMT) type 2 (also known as Dejerine–Sottas disease), congenital hypomyelinating neuropathy (CMT 4E), other subtypes of CMT4.
   c. Demonstration of cerebral myelin abnormalities and peripheral demyelination suggest Pelizaeus–Merzbacher disease or other known leukodystrophies such as Krabbe disease.
   d. Pompe disease (acid maltase deficiency).
      i. Can easily mistaken for a primary myopathy in the first year
      ii. Major differential clinical features
         a) A large heart
         b) Firm skeletal muscles secondary to glycogen stored in the muscle fibers
         c) Distinctive EMG findings

8. Differential diagnosis of hypotonia based on specific associated features (Dubowitz 1985)
   a. Hypotonia and respiratory difficulties
      i. Muscular disorders
         a) Spinal muscular atrophy
         b) Myotonic dystrophy
         c) Myotubular myopathy (especially X-linked form)
         d) Nemaline myopathy
         e) Congenital muscular dystrophy
         f) Other
      ii. Nonmuscular disorders
         a) Intracranial hemorrhage
         b) Intracranial ischemia
   b. Hypotonia and facial weakness: muscular disorders
      i. Congenital myotonic dystrophy
      ii. Myotubular myopathy
      iii. Congenital muscular dystrophy
      iv. Congenital facial diplegia syndrome
   c. Hypotonia and swallowing difficulty
      i. Muscular disorders
         a) Spinal muscular atrophy
         b) Myotubular myopathy
         c) Myotonic dystrophy
         d) Myasthenia gravis (neonatal)
      ii. Nonmuscular disorders
         a) Prader–Willi syndrome
         b) Intracranial hemorrhage
         c) Intracranial ischemia
   d. Hypotonia and ptosis/ophthalmoplegia: muscular disorders
      i. Myotubular myopathy
      ii. Mitochondrial myopathy
      iii. Myotonic dystrophy
      iv. Congenital muscular dystrophy
      v. Myasthenia gravis
   e. Hypotonia and arthrogryposis
      i. Muscular disorders
         a) Congenital muscular dystrophy
         b) Myotonic dystrophy
         c) Congenital fiber-type disproportion
         d) Denervation syndromes
      ii. Nonmuscular disorders
         a) Oligohydramnios
         b) Bicornuate uterus
         c) Renal agenesis
   f. Hypotonia and CNS dysfunction/convulsions
      i. Hypoxic–ischemic encephalopathy
      ii. Intracranial hemorrhage
      iii. Intracranial ischemia
      iv. Organic acidurias
      v. Mitochondrial encephalopathies
      vi. Zellweger disease
      vii. Other rare metabolic disorders

Diagnostic Investigations

1. A stepwise approach to the evaluation of a neonate with hypotonia (modified from Paro-Panjan and Neubauer 2004)
   a. Step 1 comprised of history taking and physical examination
      i. Family history
         a) Drug or teratogen exposure
         b) Breech presentation
         c) Reduced fetal movements
         d) Polyhydramnios
         e) Maternal diseases such as diabetes and epilepsy
         f) Parental age
         g) Neuromuscular disease
         h) Affected siblings
      ii. Prenatal history
         a) Decreased fetal movement
         b) Abnormal ultrasonographic findings such as hydrocephalus or polyhydramnios
         c) Possible evidence for hypoxic–ischemic insult, either in utero or during birth: detail perinatal birth trauma, birth anoxia, delivery complications, low APGAR scores (lower scores for tone, reflexes, and respiratory effort) and onset of hypotonia
      iii. Neonatal history
         a) A shortened umbilical cord and abnormal fetal presentation: reflects poor fetal movement or immobility.
         b) Infants requiring ventilator assistance soon after birth to maintain respiration in addition to hypotonia: suggest the presence of significant muscle weakness.
         c) In addition to hypotonia, infants with severe CNS abnormalities develop signs of impairment in level of consciousness, feeding difficulties, seizures, apneas, abnormal posturing,

abnormalities of ocular movements and of brain stem reflexes.
d) Presence of congenital malformations in other organ systems, deformations, and craniofacial dysmorphic features: need to establish a syndromic diagnosis.
iv. Postnatal history
v. Clinical and neurological examinations
b. Step 2 comprised of neurological imaging tests: important to determine whether there is evidence for a cerebral lesion contributing to hypotonia
i. Computed tomography (CT)
ii. Magnetic resonance imaging (MRI)
c. Step 3 comprised careful search of dysmorphology databases
d. Step 4 comprised of karyotyping with fluorescence in situ hybridization (FISH) for chromosome anomalies
e. Step 5 comprised of biochemical investigations for inborn errors of metabolism
f. Step 6 comprised of other specific studies
i. Specific nerve and muscle investigations
a) Serum kinase levels
b) Electromyography
c) Nerve conduction velocities
ii. DNA markers
a) Spinal muscular atrophy
b) Congenital myotonic dystrophy
c) Duchenne muscular dystrophy
iii. Muscle and nerve biopsy with mitochondrial enzymes

2. Initial workup of the floppy infant based on clinical presentation, localization, and diagnostic yield (Prasad and Prasad 2003)
a. Clinical history and physical examination
i. Central hypotonia
a) Hypotonia
b) Obtundation
c) Seizures
d) Hyperactive deep tendon reflexes
ii. Disorders of the lower motor unit
a) Hypotonia
b) Weakness
c) Areflexia
d) Fasciculations
e) Weak cry
f) Weak suck
g) External ophthalmoplegia
h) Alert look
i) Arthrogryposis
b. Multidisciplinary assessment including pedigree/family history and targeted investigations
i. CT/MRI, EEG, infection screen (CSF, blood)
a) Birth trauma
b) Hypoxic–ischemic encephalopathy
c) Sepsis
d) Cerebral dysgenesis
ii. Genetic studies (karyotyping, FISH, methylation studies, mutation analysis)
a) Chromosomal rearrangements
b) Prader–Willi syndrome
c) Congenital myotonic dystrophy
d) Subtelomeric deletions
iii. Creatine kinase assay, electrophysiology, nerve conduction studies, EMG
a) Nerve biopsy and/or direct mutation analysis (inherited neuropathies, disorders of neuromuscular junction)
b) Muscle biopsy followed by DNA-based mutation analysis when available (congenital muscular dystrophy, congenital myopathies)

3. Investigation scheme in the floppy infant with multisystem involvement (Prasad and Prasad 2003)
a. Cranial MRI, echocardiography, abdominal ultrasound, ophthalmic examinations for infants with hypotonia plus manifestations.
i. CNS obtundation
ii. Abnormal odors
iii. Seizures
iv. Craniofacial dysmorphisms
v. Cataracts
vi. Hepatomegaly
vii. Renal cysts
viii. Retinopathy
ix. Arthrogryposis
x. Lipodystrophy
b. Plasma lactate levels, mt DNA mutations, DNA depletion studies, respiratory chain analysis (muscle), DNA-based mutation analysis for mitochondrial and "energy deficient" encephalopathies (e.g., congenital lactic acidosis).
c. Plasma ammonia, amino acids (blood, urine), urine organic acids, blood acylcarnitine profile, plasma uric acid, urinary sulfites, enzyme assays in skin fibroblasts for

aminoacidopathies, organic acidemias, sulfite oxidate/molybdenum cofactor deficiency.
   d. Lysosomal enzyme assay in WBC, skin biopsy (EM for inclusion), skin fibroblast culture + enzyme assays for lysosomal disorders (e.g., Pompe disease).
   e. Phytanic acid, plasma VLCFA for peroxisomal disorders (e.g., Zellweger syndrome).
   f. Isoimmune electrophoresis for transferrin for congenital disorders of glycosylation.
   g. 7-dehydrocholesterol for Smith–Lemli–Opitz syndrome.
4. Cytogenetic analyses: for floppy infants with dysmorphic features and/or multiple congenital anomalies
   a. Aneuploidy disorders such as Down syndrome
   b. Microdeletion disorders such as Prader–Willi syndrome
      i. Methylation patterns study to determine the presence of PWS
      ii. FISH and mutation analysis to identify the class of mutation
   c. Subtelomeric deletion disorders: easily detected using in situ hybridization using chromosomal telomeric probes
5. Molecular analyses: genetic testing aid significantly in timely diagnosis for a critically ill newborn and allow for anticipation of medical interventions by the multidisciplinary team caring for the infant
   a. Chromosomal microarray studies
   b. Mutation or deletion analysis of the survival motor neuron gene (*SMN*) for SMA
      i. All patients with SMA have deletions or mutations of *SMN1* (also known as SMN_t, the telomeric copy of *SMN* gene). Homozygous deletion of exon 7 in the telomeric survival motor neuron gene found in 95% of SMA type I patients
      ii. The major phenotype determinant is the presence of the number of copies of *SMN2* (also known as SMN_c, the centromeric copy of *SMN* gene)
         a) One copy: likely to produce SMA1
         b) No copy of SMA1: likely results in spontaneous abortion or fetal wastage
         c) Five or six copies: likely allow normal survival with little or no progressive weakness
   c. Mutation analysis in CMT hereditary motor sensory neuropathies
      i. CMT 1A: mutations in the peripheral myelin protein-22 gene
      ii. CMT 1B: mutation in the myelin protein zero gene
      iii. CMT 2B: mutation in the RAS-associated protein RAB7
      iv. CMT 4A: mutation in the ganglioside-induced differentiation-associated protein-1 gene
      v. CMT-X1: mutation in the connexin-32 gene
   d. Mutation analysis for disorders of neuromuscular junction (congenital myasthenic syndromes)
      i. Congenital myasthenia with episodic apnea
      ii. Slow-channel and fast-channel syndrome
      iii. Endplate cholinesterase deficiency
   e. Mutation analysis for disorders with prominent muscle involvement
      i. Bethlem myopathy
      ii. Triplet repeat CTG expansion of the DM protein kinase mutations (>37)
      iii. Congenital DM protein kinase repeat expansion (>750)
   f. Gene sequencing, mutation analysis, or mutation scanning
      i. Dystrophinopathies
      ii. Muscular dystrophies
      iii. Myopathies
   g. mtDNA mutation analysis or mutation analysis in nuclear gene for mitochondrial disorders
6. Electrophysiological studies
   a. Needle electromyogram (EMG)
      i. Neurogenic changes
         a) Spontaneous fibrillation at rest
         b) Long duration polyphasic motor unit potentials
         c) Decreased interference pattern
      ii. Myopathic changes: consider muscle biopsy
         a) Low amplitude, short duration polyphasic
         b) Normal interference pattern
      iii. Myopathy plus muscle irritability (large amplitude of CMAPs, increased insertional activity) should consider Pompe disease (acid maltase enzyme assay)
      iv. Demonstration of denervation on EMG (large amplitude of CMAPs, fasciculation, positive sharp wave) should prompt

investigation for anterior horn cell disorders (proceed to SMA genetic test, SMN type I and type II copy number)

b. Motor and sensory nerve conduction studies (NCS): Decreased nerve conduction velocities on NCS suggest a demyelinating neuropathy

7. Pathologic studies of muscles (muscle biopsy):
   a. The most useful test in the diagnosis of motor unit hypotonia
   b. Used much less often today with the availability of specific gene test for many of the conditions under consideration
   c. A sequential scheme for the proper use of the muscle biopsy
      i. Nonspecific myopathy: consider myotonic, dystrophinopathy, and other congenital myopathy
      ii. Characteristic pathology
         a) Central core disease
         b) Nemaline rod myopathy
         c) Centronuclear myopathy
      iii. Dystrophic muscle
         a) Brain involvement: consider muscle-eye-brain disease, Fukuyama congenital muscular dystrophy, and Walker–Warberg syndrome
         b) Without brain involvement: consider histoimmunological stain for merosin-deficient and merosin-positive muscular dystrophies
   d. SMA: extensive large grouped atrophy involving both type I and type II fibers and scattered clusters of enlarged type I fibers
   e. Congenital muscular dystrophy: considerable variations in fiber size with extensive fatty infiltration
   f. Glycogen storage disease: vacuolar myopathy with muscle fibers containing type vacuoles of varying sizes
   g. Central nuclear myopathy: presence of central nucleus in the majority of muscle
   h. Central core myopathy: deficient oxidative enzyme in the center of many fibers
   i. Nemaline myopathy: muscle fibers with thickened striations and aggregates of rod bodies
   j. Congenital fiber-type disproportions: increased number of small lightly stained type I fibers and reduced number of larger darkly stained type II fibers
8. Biochemical studies
   a. Muscle enzymes (creatine kinase)
      i. Rarely helpful in workup of a floppy infant
      ii. Elevated in:
         a) Congenital muscular dystrophies
         b) Some forms of congenital myopathies
   b. Inborn errors of metabolism screening
      i. Categories of biochemical defects
         a) Toxic encephalopathies
         b) Energy deficient encephalopathies
         c) Disorders affecting intracellular processing of complex molecules
      ii. Blood ammonia
         a) Urea cycle defects
         b) Organic acidemias
         c) Fatty acid oxidation disorders
      iii. Lactate (blood, urine, CSF)
         a) Carbohydrate metabolism disorders
         b) Mitochondrial disease
      iv. Blood and urine quantitative analysis of amino acids for aminoacidopathies
      v. Blood organic acid and acylcarnitine profiles using tandem mass spectrometry
         a) Organic acidemias
         b) Fatty acid oxidation defects
      vi. Plasma very long chain fatty acids (VLCFA) for peroxisomal disorders
      vii. Transferrin (low in glycosylation disorders)
      viii. Blood 7-dehydrocholesterol (elevated in Smith–Lemli–Opitz syndrome)
9. Cranial ultrasound or CT studies (Rumack 1985): to detect CNS lesions causing infantile hypotonia
   a. Hypoxic–ischemic encephalopathy
      i. Fetal or neonatal hypoxia
      ii. Sudden infant death syndrome
      iii. Infarction from other causes
   b. Neonatal intracranial hemorrhage
      i. Subependymal hemorrhage (premature infants)
      ii. Subarachnoid hemorrhage or atypical intracranial hemorrhage (term infants)
   c. Intracranial infection
      i. Prenatal
         a) Cytomegalovirus
         b) Toxoplasmosis
         c) Herpes
         d) Rubella
      ii. Neonatal and infant: bacterial

d. Trauma
   i. Subdural hematoma
   ii. Epidural hematoma
   iii. Parenchymal hemorrhage or edema
10. Cranial CT/MRI studies
   a. Structural malformations
   b. Altered signals
      i. White matter: Laminin deficiency
      ii. Basal ganglia: mitochondrial cytopathies
      iii. Brain stem and cerebellar abnormalities
         a) Joubert syndrome
         b) Pontocerebellar hypoplasia

Genetic Counseling

1. Recurrence risk: depends on underline etiology
   a. Patient's sib
      i. Autosomal recessive (e.g., spinal muscular atrophy, congenital muscular dystrophy): 25%
      ii. Autosomal dominant (e.g., congenital myotonic dystrophy): not increased unless a parent is affected
      iii. X-linked recessive (e.g., severe infantile form of myotubular myopathy): 50% of male sibs affected if the mother is a carrier
      iv. Mitochondrial: All sibs are at risk of being affected if the mother has the mitochondrial DNA mutation
      v. Chromosomal: increased risk, especially a parent is a translocation carrier
   b. Patient's offspring
      i. Autosomal recessive: not increased unless the spouse is also a carrier
      ii. Autosomal dominant: 50%
      iii. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal
      iv. Mitochondrial:
         a) Offspring of males with a mtDNA mutation are not at risk
         b) All offspring of females with a mtDNA mutation are at risk of inheriting the mutation
         c) A female harboring a heteroplasmic mtDNA point mutation may transmit a variable amount of mutant mtDNA to her offspring, resulting in considerable clinical variability among sibs within the same nuclear family (Poulton and Turnbull 2000; Chinnery 2006)
      v. Chromosomal: an increased risk
2. Prenatal diagnosis: not reported to date
3. Management (Pediatric Care Online 2008)
   a. Supportive treatment in most causes of hypotonia
   b. Multidisciplinary team approach for coordination of interventions
   c. Infantile progressive spinal muscular atrophy
      i. Physical therapy
      ii. Respiratory therapy
      iii. Nutritional support as needed
      iv. Scoliosis treatments: e.g.,
         a) Body jacket
         b) Molded back support
         c) Surgery
         d) Motorized wheelchair for children with type II at approximately 2–3 years of age
   d. Peripheral nerve disorders: bracing for children with foot drop
   e. Neuromuscular junction disorders: hospitalization, with respiratory and nutritional support as needed
      i. Passively acquired autoimmune myasthenia gravis (transient neonatal myasthenia): give pyridostigmine until asymptomatic, then taper over 1–2 weeks
      ii. Acquired autoimmune myasthenia gravis (juvenile myasthenia)
         a) Anticholinesterase drugs
         b) Immunosuppressive treatment
         c) Intravenous γ-globulin
         d) Corticosteroids
         e) Thymectomy
      iii. Nonautoimmune myasthenic syndromes (congenital myasthenia gravis)
         a) Anticholinesterase inhibitors
         b) Corticosteroids
         c) Diaminopyridine (experimental)
      iv. Infantile botulism: antibotulism immune globulin may be therapeutic
   f. Myopathies
      i. Infantile form of myotonic dystrophy–type hypotonia
         a) Assisted ventilation as indicated
         b) Gastrostomy tube feedings as indicated

ii. Glycogen storage disease: consider enzyme replacement therapy (prognosis dismal without such therapy)

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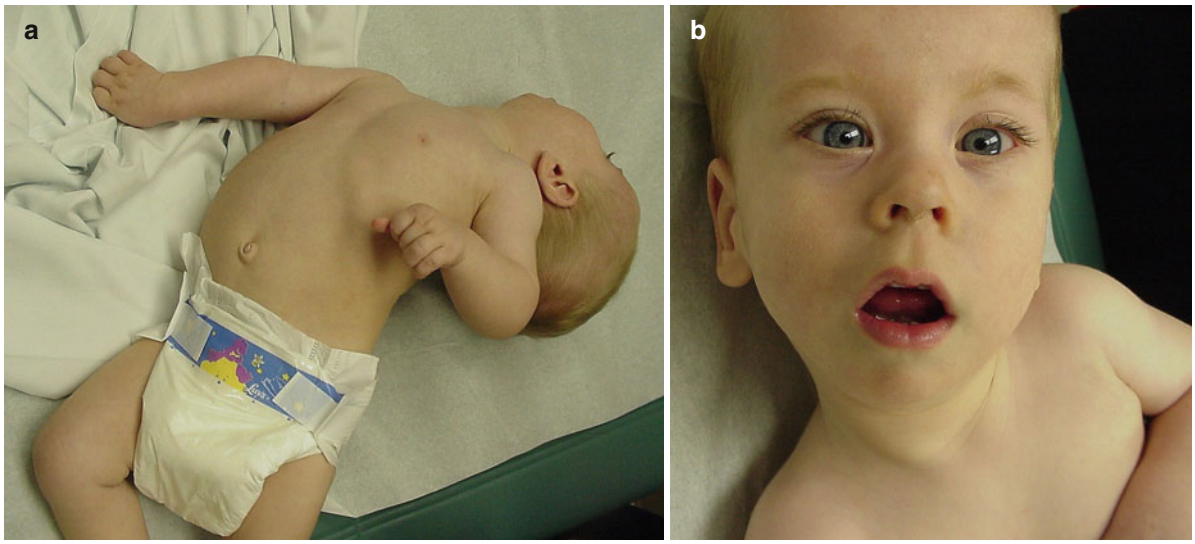

Fig. 1 (**a**–**b**) An infant boy with hypotonia

Fig. 2 The same boy with hypotonia at 6 years of age

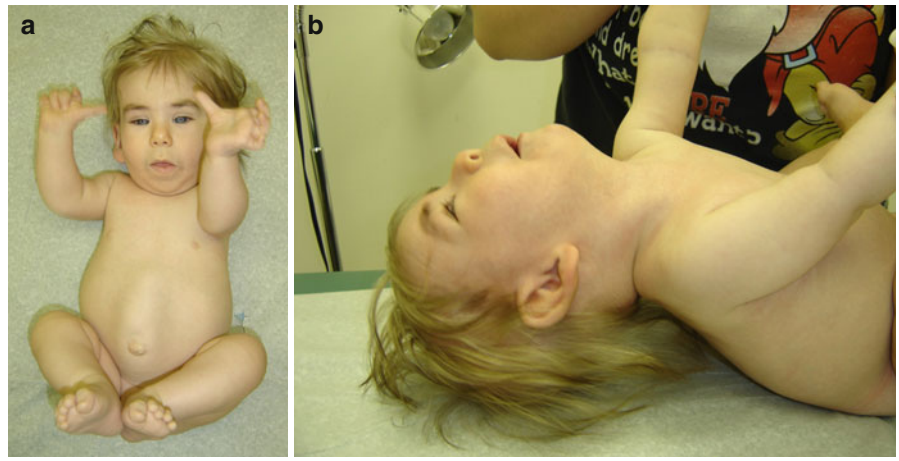

Fig. 3 (**a**–**b**) Hypotonia associated with cerebellum and optic nerve hypoplasia in an infant at 9 months of age

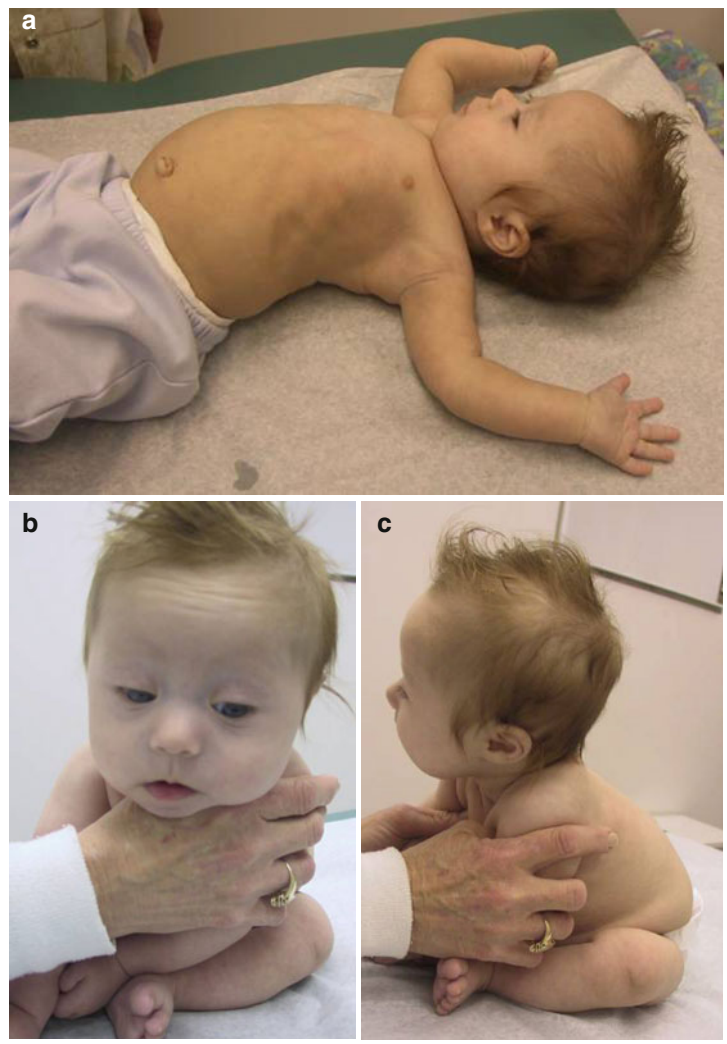

Fig. 4 (**a**–**c**) Hypotonia associated with Down syndrome in an infant

Fig. 5 (**a**–**b**) Hypotonia associated with Prader–Willi syndrome in a 7-month-old boy

Fig. 6 (**a**–**b**) Hypotonia associated with dysmorphic facies (ocular hypertelorism, slightly upslanted palpebral fissures, bulbous nose, micro/retrognathia, and small ears) secondary to microdeletion of 15q demonstrated by chromosome microarray analysis [arr cgh l5q11.2q13.1 n19,623,685 → 26,605,469) × 1]. Regular chromosome analysis was normal

Fig. 7 A 28-month-old infant with metachromatic leukodystrophy with hypotonia

Fig. 8 (**a**–**b**) "Congenital benign hypotonia" in a 7-month-old infant

Fragile X Syndrome

Fragile X syndrome is the most common form of heritable mental retardation affecting approximately 1 in 1,250 males and 1 in 2,000 females (Webb 1989). The prevalence appears to be 1 in 4,000–6,000 males and 1 in 8,000–10,000 females. Martin and Bell first documented X-linked mental retardation in 1943. Subsequent identification of a fragile site on the long arm of the X chromosome (Lubs 1969), discovery of cell culture medium-dependent fragile site, and recognition of a unique constellation of physical features served to distinguish fragile X syndrome from other X-linked mental retardation syndromes.

In Verkerk et al. (1991) identified a single gene that was associated with symptoms of the disorder. The gene, known as fragile X mental retardation gene 1 (*FMR1*), exhibited a novel form of mutation, a sequence of three nucleotides (CGG) that was repeated many times in patients with fragile X syndrome.

Synonyms and Related Disorders

Fragile X mental retardation syndrome; Marker X syndrome; Martin-Bell syndrome; X-linked mental retardation and macroorchidism

Genetics/Basic Defects

1. Inheritance not conforming to usual rules governing X-linked traits
   a. Presence of asymptomatic transmitting males
   b. Presence of affected female carriers who inherited the gene
2. Caused by mutations in a trinucleotide $(CGG)_n$ repeat found in the coding region of the *FMR1* gene, mapped to Xq27.3
   a. Expanded CGG repeats >200 (full mutation): associated with fragile X syndrome.
   b. High repeat number (full mutation) leads to hypermethylation of an upstream promoter region and subsequent silencing (inactivating) of the *FMR1* gene.
   c. A small expansion (premutation) with approximately 50–200 CGG repeats: usually not associated with cognitive deficits.
   d. Expansion to a full mutation from the premutation in normal carriers occurs only when it is transmitted by a female.
   e. Presence of anticipation phenomenon.
3. The Sherman paradox (Laxova 1994)
   a. A perplexing and confusing fragile X pedigree pattern was discovered during mid-1980s by Sherman et al. who discovered the large discrepancy in risks for mental retardation within fragile X families containing transmitting males. This phenomenon was termed the "Sherman paradox" by Opitz (1986).
      i. 20% of males within fragile X families who carried the mutation are unaffected clinically and intellectually and became known as transmitting males.
      ii. An increasing risk of mental retardation in grandsons of normal transmitting males: a special form of genetic anticipation (the increase in disease severity through successive generations).
      iii. About a third of obligate carrier females are mentally impaired.

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iv. More than half of known carrier females are either mildly impaired or expressed the fragile site on one of their X chromosomes.

b. Possible explanations of the Sherman paradox.
   i. An unaffected transmitting male who inherits a premutation from his unaffected carrier mother, who has 50–200 repeats but probably a number closer to the lower end of the premutation range.
   ii. Offspring of a carrier mother with the number of repeats still within the premutation range, even if amplification occurs during oogenesis.
   iii. Transmission of the premutation to the daughters by the transmitting male. No amplification has occurred during spermatogenesis; hence, the daughters also have a premutation and are unaffected.
   iv. Amplification to more than 200 repeats occurs during oogenesis of the transmitting male's daughters whose sons will receive a ull mutation and be affected and their daughters may or may not be affected.

4. Genotypic–phenotypic correlations (Kaufmann and Reiss 1999)
   a. Fragile X full mutation and mental retardation with a wide spectrum of phenotypic effects in both sexes
      i. Mental retardation in 100% of males
      ii. Usually a milder form of retardation in 60% of females
   b. Large CGG amplification
      i. Associated with hypermethylation
      ii. Almost invariably correlated with the most severe fragile X phenotype
      iii. Seen in males with the full mutation pattern
   c. Premutation expansions that are not usually accompanied by methylation: minimal or no neurologic repercussion
   d. Correlation of methylation in *FMR1* expression and cognitive function
      i. Individuals with full mutation without methylation scored better than those with full mutation and complete methylation
      ii. Individuals with full mutation and partial methylation showed intermediate values
   e. Presence of the *FMR1* protein (FMRP) responsible for:
      i. Lack of neurologic abnormalities in individuals with premutation
      ii. Milder phenotype of males having full mutation without full methylation
5. Pathogenesis
   a. A consequence of the absence or deficit of the FMRP
   b. Absence of FMRP in the brain: the likely cause of mental retardation in patients with fragile X syndrome

Clinical Features

1. Affected males (Hagerman and Cronister 1996)
   a. CNS involvement
      i. Delayed developmental milestones
      ii. Mild to severe mental retardation
      iii. Difficulty with abstract thinking, sequential processing, mathematics, short-term memory, and visual motor coordination
      iv. Seizures
   b. Connective tissue dysplasia
      i. Hyperextensible finger joints
      ii. Double-jointed thumbs
      iii. Flat feet
      iv. High-arched palate
      v. Mitral valve prolapse (55%, diagnosed by echocardiography)
      vi. Dilatation of the ascending aorta
      vii. Inguinal hernia
      viii. Soft and velvet-like skin
   c. Typical facial features
      i. Long face
      ii. Prominent forehead
      iii. Prominent/long ears
      iv. Prominent jaw
   d. Other features
      i. Macroorchidism present in over 80% of adult fra(X) males
      ii. Pectus excavatum
      iii. Scoliosis
      iv. Strabismus
      v. Recurrent otitis media in early childhood
      vi. Reproduction documented but rare because of significant mental retardation

e. Behavior abnormalities
   i. Stereotyped with odd mannerisms (hand flapping/biting)
   ii. Tactile defensiveness
   iii. Poor eye contact (excessive shyness)
   iv. Attention-deficit/hyperactivity disorder
      a) Hyperactivity
      b) Temper tantrums
      c) Distractibility
      d) Mood lability
   v. Speech disorder
      a) Perseveration
      b) Litany speech
      c) Echolalia
   vi. Autism
   vii. Autistic-like features
   viii. Schizotypal personality disorder
   ix. Anxiety disorder
2. Females heterozygous for full mutation alleles
   a. Fifty percentage with cognitive deficits with learning disabilities, borderline IQ, or mental retardation
   b. Fifty percentage with normal intellectual function
3. Females heterozygous for premutation alleles (carriers) at risk for premature ovarian failure (early onset of menopause before age 40 years) (*FMR1*-related premature ovarian failure
4. Fragile X-associated tremor/ataxia syndrome (FXTAS) (Saul and Tarleton 2010)
   a. A definite diagnosis based on the following three observations
      i. Presence of FMR1 premutation
      ii. White matter lesions on MRI in the middle cerebellar peduncles and/or brain stem (the major neuroradiologic sign)
      iii. Presence of two major clinical signs
         a) Intention tremor
         b) Gait ataxia
   b. Other minor clinical criteria
      i. Parkinsonism
      ii. Moderate to severe working memory deficits
      iii. Executive cognitive function deficits
   c. A probable diagnosis: requires either one major neuroradiologic sign and one minor clinical sign or two major clinical signs
   d. A possible diagnosis: based on one minor neuroradiologic sign and one major clinical sign

Diagnostic Investigations

1. Pedigree analysis
2. Karyotyping of cells grown in folate- or thymidine-depleted cell culture media
   a. A "fragile" site on one of the X chromosomes (Xq27.3) that appeared as a constriction on the distal long arm in many patients
   b. Cells exhibiting fragile X chromosome: 5–50%
   c. Cytogenetic studies now rendered obsolete by direct DNA testing
3. Indications for molecular genetic testing (Park et al. 1994)
   a. Individuals of either sex with mental retardation, developmental delay, or autism
      i. Any physical or behavioral characteristics of fragile X syndrome
      ii. A family history of fragile X syndrome
      iii. Male or female relatives with undiagnosed mental retardation
   b. Individuals seeking reproductive counseling who have a family history of fragile X syndrome or undiagnosed mental retardation
   c. Fetus of a known carrier mother
   d. Patients with cytogenetic fragile X test result discordant with phenotype
      i. Patients with a strong clinical impression of being affected with or carrier of fragile X syndrome but had a negative or ambiguous cytogenetic test result
      ii. Patients with an atypical phenotype of fragile X syndrome but had a positive cytogenetic test result
4. Direct DNA analysis for point mutation or deletion in *FMR1* gene. Mutation analysis to determine the CGG repeat size by Southern blot hybridization and polymerase chain reaction (PCR): mutation detection rate >99% (commercially available)
5. Methylation analysis by Southern blot analysis to determine the *FMR1* methylation status
6. Types of *FMR1* repeat expansion mutations (Tarleton and Saul 1993; Saul and Tarleton 2010)
   a. Normal alleles: 5–40 CGG repeats
      i. Stably transmitted without any increase or decrease in repeat number

ii. In stable normal alleles, the CGG region is interrupted by an AGG triplet after every nine or ten CGG repeats. These AGG triplets are believed to maintain repeat integrity by preventing DNA strand slippage during replication
iii. Normal alleles with more than 35 CGG repeats are associated with increased risk of *FMR1*-related premature ovarian failure

b. Mutable normal alleles (intermediate alleles, also termed "gray zone"): broadly defined as 41–58 repeats (no consensus exists regarding the precise size)
c. Premutation alleles
i. 59–200 CGG repeats
ii. Methylation status of *FMR1*: Premutation alleles are usually unmethylated and FMRP production is normal
iii. Therefore, individuals (males or females) with permutation are clinically unaffected
iv. Do convey increased risk for FXTAS and POF, because of:
a) Potential repeat instability upon transmission of premutation alleles
b) Women with alleles in this range are considered to be at risk of having children affected with fragile X syndrome
d. Full mutation alleles
i. >200 CGG (several hundreds to several thousands) repeats. Expansion of the repeat more than 200 generally results in hypermethylation of both the CpG island and the CGG repeat within the *FMR1* gene
ii. Methylation status of *FMR1*: completely methylated
iii. Males: affected
iv. Females: affected in about 50% of cases; unaffected in about 50% of cases
e. Mosaicism
i. Number of CGG repeats varies between premutation and full mutation in different cell lines.
ii. Methylation status of *FMR1*: partially methylated (unmethylated in the premutation cell line and methylated in the full mutation cell line)
iii. Males: affected but may function higher than individuals with full mutation
iv. Females: highly variable clinical expression ranging from normal intellect to affected
f. Methylation mosaicism
i. Number of CGG repeats >200
ii. Methylation status of *FMR1* gene: partially methylated (mixture of methylated and unmethylated cell lines)
iii. Males: affected but may function higher than individuals with full mutation
iv. Females: highly variable clinical expression ranging from normal intellect to affected
g. Unmethylated full mutation
i. Number of CGG repeats >200
ii. Methylation status of *FMR1* gene: unmethylated
iii. Males: Nearly all are affected but may have high functioning mental retardation to low normal intellect
iv. Females: highly variable clinical expression ranging from normal intellect to affected

7. Immunocytochemical tests based on the direct detection of FMRP using monospecific antibodies. This FMRP detection assay is based on the presence of FMRP in cells from unaffected individuals and its absence in cells from patients with fragile X syndrome. This assay is proven to be a reliable alternative method to identify male patients with fragile X syndrome. The new test on hair roots is suitable for use in large screening programs among males. The immunocytochemical tests can also be used in patients with mosaic pattern, affected premutation males, and intragenic mutations
8. Molecular genetic testing
a. Targeted mutation analysis
i. PCR analysis
ii. Southern blot analysis
b. Methylation status
c. Sequence analysis
d. Deletion/duplication analysis
e. FISH analysis
f. X-chromosome inactivation

Genetic Counseling

1. Recurrence risk: Adequate genetic counseling depends on accurate diagnosis at the molecular level
   a. Individuals identified as noncarriers: The zero risk of transmitting fragile X syndrome to the next generation.
   b. Individuals identified as carriers: The risk of having children with fragile X syndrome depending on the sex of the carrier parent, the sex of the child, and the size of the CGG repeats.
      i. Premutation carrier males: considered "transmitting males." All daughters of transmitting males are unaffected premutation carriers. However, the grandsons and granddaughters of a transmitting male are at risk for developing fragile X syndrome.
      ii. All mothers of a child with *FMR1* full mutation (expansion >200 CGG trinucleotide repeats), considered carriers of an *FMR1* gene expansion (either full mutation or premutation and may be affected).
      iii. Females with premutation: an increased risk of passing on the full mutation and having offspring with the fragile X phenotype (the fragile X premutation can expand to the full mutation during maternal meiosis).
      iv. Carrier males who may reproduce: essentially zero risk of having male offspring with fragile X syndrome, since all their sons receive their Y chromosome [except in the rare instance of the fragile X chromosome coming into the family from the other source (mother)]. All the daughters of male carriers will have premutations regardless of the size of paternal amplifications and will not have fragile X syndrome. Only a few reports with premutation males have full mutation daughters.
   c. Females with full mutation: Her offspring, if they inherit the fragile X locus, all will have full mutation.
      i. All her sons will have fragile X syndrome.
      ii. About 50–60% of her daughters will have fragile X syndrome, exceeding the 35% applicable to all female carriers of the fragile X chromosome. Affected females generally have less severe intellectual disability than found in affected males.
   d. Males with full mutations.
      i. Mentally retarded
      ii. Generally do not reproduce
2. Risks to pregnant women with an expanded *FMR1* gene
   a. A repeat size of 40–59: safe (0% risk) with no fetal full mutations
   b. A repeat size of 60–80: low risk (14%) of full mutation in the fetus
   c. A repeat size of over 80–100: a significant increase in risk (89%) of developing full mutation in the fetus
   d. A repeat size of 100–200: 100% risk of developing full mutation in the fetus
3. Prenatal diagnosis by amniocentesis or CVS
   a. Available to at-risk pregnancies: requires prior confirmation of the presence of an expanded (or altered) *FMR1* allele in the family
   b. Prenatal diagnosis using direct DNA analysis to women discovered to be premutation carriers
   c. The limitation: inability to accurately predict phenotype in female fetuses with full mutation
   d. CVS: follow-up amniocentesis or testing using PCR, necessary to determine the size of the *FMR1* alleles in a methylation-independent manner
4. Preimplantation genetic diagnosis: available to at-risk pregnancies in which prior confirmation of the presence of an expanded (or altered) *FMR1* allele was identified in the family
5. Management
   a. Early intervention programs for developmental delay including speech and language therapies, physical therapy, and occupational therapy
   b. Behavioral interventions including psychopharmacological therapy
   c. Special educations
   d. Vocational planning
   e. Anticonvulsants for seizure control

f. Prophylactic antibiotics for surgical or dental procedures in patients with mitral valve prolapse
g. Orthopedic care for joint dislocations, flat feet, and scoliosis

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Fig. 1 Two brothers with fragile X syndrome showing large ears, accompanied by their mother

Fig. 2 A pair of brothers with fragile X syndrome showing a long face with large ears

Fig. 3 Another pair of male siblings with fragile X syndrome

Fig. 4 A chromosome spread showing a fragile X chromosome (arrow)

Fig. 5 A large family affected by fragile X syndrome. The first boy (**a**, age 15) is the most affected one with CGG repeats of >1,500. He was not toilet trained until age 5 or 6 years. He never spoke until after auditory training. He may watch TV for 6–8 h straight and get agitated if someone approaches him. The brother (**b**, age 10) and sister (**c**, age 16) have CGG repeats of 1,200 and 600 respectively. Another sister (**d**) is a carrier with CGG repeats of 110 who has four children. The daughter (age 3, the first one from the left) has CGG repeats of 700. She has a long face with prominent ears, a high-arched palate, and flat feet. She suffers from hyperactivity, tactile/oral/olfactory defensiveness, gaze aversion, poor postural alignment, food cramming, hand biting, excessive drooling, poor self-regulation, and speech difficulties including echolalia. The other three children are normal with normal CGG repeats. The maternal grandmother has CGG repeats of 126

Fig. 6 A 66-year-old male with fragile X syndrome. The patient has mental retardation, a long face with large ears, and macroorchidism. Molecular analysis revealed CGG repeats of about 400

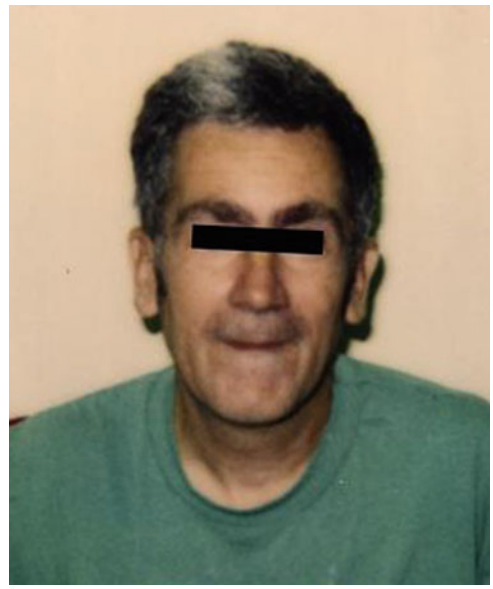

Fig. 7 A 46-year-old male with methylation mosaic fragile X syndrome (mixture of methylated full mutation allele of approximately 450 repeats in some cells and unmethylated premutation size allele of approximately 200 repeats in some cells). He is tall and has mental retardation, a long narrow face, slightly large ears, and macroorchidism

Fraser Syndrome

Fraser syndrome is a malformation syndrome characterized by cryptophthalmos ("hidden eye," a term coined by Zehender et al. 1872), cutaneous syndactyly, and anomalies of the genitourinary system. It was first described by Fraser in 1962. It is also known as cryptophthalmos-syndactyly syndrome, cryptophthalmos syndrome, or Fraser cryptophthalmos syndrome. Fraser syndrome occurs with a minimal estimated frequency of 0.43 per 100,000 liveborn infants and 11.06 per 1,000,000 stillbirths (Martínez-Frías et al. 1998).

Synonyms and Related Disorders

Cryptophthalmos with other malformations; Cryptophthalmos-syndactyly syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Caused by mutations in *FRAS1* and FRAS1-related extracellular matrix protein 2 (*FREM2*) genes
   a. *FRAS1* gene, encoding a putative extracellular matrix (ECM) protein, located on the long arm of chromosome 4 (4q21)
   b. *FREM2* gene located on the long arm of chromosome 13 (13q13.3)
3. Genotype–phenotype correlations (van Haelst et al. 2008)
   a. Patients with an *FRAS1* mutation
      i. More frequently skull ossification defects
      ii. Low insertion of the umbilical cord
   b. Mutations were identified in only 43% of the cases suggesting that other genes syntenic to murine genes causing blebbing may be responsible for Fraser syndrome as well
4. Familial cases (56%)
   a. Presence of consanguinity, estimated to be as high as 15%
   b. Multiple affected sibs born to the same parents (Slavotinek and Tifft 2002; Singh et al. 2007)
5. Three forms of cryptophthalmos, classified based on ophthalmic findings (Francois 1969)
   a. Complete (typical) cryptophthalmos
      i. The eyelids replaced by a sheet of skin running from forehead to cheek with absence or poor development of the eyebrow
      ii. Absence of the eyelashes or the gland structures
      iii. The elevated skin covering the globe moves when eye movements occur
      iv. The skin adherent to the underlying cornea
      v. Absence of the conjunctival sac
      vi. Microphthalmia usually present
      vii. Often associated with numerous congenital abnormalities, including anomalies of the head, ears, nose and genitalia, and syndactyly. This pattern of anomalies is termed Fraser syndrome (Ferri and Harvey 1999)
   b. Incomplete (atypical) cryptophthalmos
      i. Presence of rudimentary eyelids
      ii. Lateral placement of a small conjunctival sac
      iii. The palpebral aperture about one-third of normal length
      iv. Usually small globe, covered almost completely by the skin

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   c. Abortive form or congenital symblepharon
      i. The upper eyelids, without a defined margin, covers and adherent to up to 75% of the upper cornea
      ii. Absence of punctum in the eyelid
      iii. Absence of the upper conjunctival fornix
      iv. Free part of the cornea often keratinized or opaque
      v. Globes: usually normal or small size
6. Pathogenesis (Ferri and Harvey 1999)
   a. Primary failure of differentiation during embryogenesis
   b. Compression of the amniochorionic band
   c. Intrauterine inflammation
   d. Failure of lid fold development
   e. Inactivation of glutamate receptor interacting protein 1 (GRIP1), a cytoplasmic multi-PDZ scaffolding protein, leads to the formation of subepidermal hemorrhagic blisters, renal agenesis, syndactyly or polydactyly, and permanent fusion of eyelids (cryptophthalmos), Fraser syndrome-like defects in mice (Takamiya et al. 2004)

Clinical Features

1. Intrafamilial clinical heterogeneity (Chattopadhyay et al. 1993; Slavotinek and Tifft 2002)
2. Eyes
   a. Cryptophthalmos (a developmental anomaly in which the skin is continuous over the eyeballs without any indication of the formation of eyelids): the most common feature of Fraser syndrome (84–93%)
      i. Bilateral (more common) or unilateral
      ii. Total or partial
   b. Microphthalmia
   c. Absent or malformed lacrimal ducts
   d. Ocular hypertelorism
   e. Coloboma of the upper eyelid
   f. Supernumerary eyebrows
   g. Blindness
3. Head: unusually low lateral hairline on temples extending to lateral eyebrow
4. Nose
   a. Hypoplastic and notched nares
   b. Broad nasal bridge
   c. Midline nasal cleavage
   d. Choanal atresia
5. Mouth
   a. Cleft lip
   b. Cleft palate
   c. High-arched palate
   d. Crowding of the teeth
6. Ears
   a. Malformation of middle and external ears (cup shaped and low set)
   b. Microtia
   c. Low-set ears
   d. Absent pinna
   e. Skin of the upper helix contiguous with scalp
   f. Conductive hearing loss
7. Laryngeal stenosis/atresia
8. Chest: widely spaced nipples
9. Lungs
   a. Lung hyperplasia (Stevens et al. 1994)
   b. Lung hypoplasia
10. Cardiac anomalies (Thapa and Bhattachakya 2008)
   a. Hypertrophy of the left ventricle
   b. A variant of Ebstein anomaly
   c. Coarctation of the aorta
   d. Atrial septal defect
   e. Interventricular communication
   f. Truncus arteriosus
   g. Ventricular septal defect
   h. Complex heart disease
   i. PDA
   j. Patent foramen ovale
   k. Dextrocardia
   l. Transposition of the great vessels
   m. Partial anomalous pulmonary venous connection
11. Gastrointestinal anomalies (Slavotinek and Tifft 2002)
   a. Imperforate anus
   b. Anal atresia and anal stenosis
   c. Rectal atresia
   d. Displaced anus
   e. Umbilical hernia
   f. Intestinal malrotation
   g. Colonic atresia
12. Urogenital anomalies
   a. Renal agenesis/hypoplasia
      i. Unilateral
      ii. Bilateral
      iii. Hypoplastic bladder

b. Male genital anomalies
   i. Small penis
   ii. Hypospadias
   iii. Cryptorchidism
c. Female genital anomalies
   i. Bicornuate uterus
   ii. Hypoplastic uterus
   iii. Vaginal atresia
   iv. Hypoplastic labia majora
   v. Clitoral enlargement

13. Limbs: syndactyly of the fingers (cutaneous in 54% of cases) and toes
14. CNS involvement
    a. Mental retardation
    b. Microcephaly
    c. Meningomyelocele
    d. Encephalocele
15. Natural history
    a. Stillborn: 25% of affected infants
    b. Additional 20% of affected infants die before 1 year of age
    c. Survival to 96 years of age reported (Impallomeni et al. 2006)
    d. Commonest causes of death
       i. CNS malformations
       ii. Laryngeal stenosis or atresia
       iii. Respiratory insufficiency
       iv. Obstructive uropathy or bilateral renal agenesis
16. Diagnostic criteria (Thomas et al. 1986): requires at least two major and one minor, or one major and four minor criteria for the diagnosis
    a. Major criteria
       i. Cryptophthalmos
       ii. Syndactyly
       iii. Abnormal genitalia
       iv. Sib with Fraser syndrome
    b. Minor criteria
       i. Congenital malformation of nose
       ii. Congenital malformation of ears
       iii. Congenital malformation of larynx
       iv. Cleft lip/palate
       v. Skeletal defects
       vi. Umbilical hernia
       vii. Renal agenesis
       viii. Mental retardation
17. Revised diagnostic criteria for Fraser syndrome (van Haelst et al. 2007): requires either three major, or two major and two minor, or one major and three minor diagnostic criteria present in a patient
    a. Major criteria
       i. Syndactyly
       ii. Cryptophthalmos spectrum
       iii. Urinary tract abnormalities
       iv. Ambiguous genitalia
       v. Laryngeal and tracheal anomalies
       vi. Positive family history
    b. Minor criteria
       i. Anorectal defects
       ii. Dysplastic ears
       iii. Skull ossification defects
       iv. Umbilical abnormalities
       v. Nasal anomalies

Diagnostic Investigations

1. Radiography
   a. Poor ossification of the calvarium
   b. Orbital structures
   c. Pulmonary hypoplasia
   d. Diastasis of the symphysis pubis
   e. Syndactyly
2. Renal ultrasound for renal anomalies
3. Hearing test
4. Molecular genetic testing (van Haelst et al. 2008; Shafeghati et al. 2008)
   a. Linkage analysis in consanguineous families indicated possible linkage to *FRAS1* and *FREM2* in 60% of the cases
   b. Mutation analysis identified 11 new mutations in *FRAS1* and one *FREM2* mutation

Genetic Counseling

1. Recurrence risk
   a. Patient's sibs: 25%
   b. Patient's offspring: recurrence risk not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis
   a. Prenatal diagnosis made in the follow-up of a pregnancy with a previous sibling having had the same syndrome (Feldman et al. 1985; Ramsing et al. 1990; Schauer et al. 1990; Fryns

et al. 1997; Berg et al. 2001; Rousseau et al. 2002; Vijayaraghavan et al. 2005)
   b. Prenatal diagnosis made in families with a negative history (Boyd et al. 1988; Serville et al. 1989; Maruotti et al. 2004)
   c. Prenatal ultrasonography
      i. Major findings
         a) Microphthalmia
         b) Syndactyly
         c) Ambiguous genitalia
      ii. Other findings
         a) Oligohydramnios
         b) Ear defects
         c) Renal abnormalities
         d) Uropathy
         e) Hyperechogenic lungs
         f) Laryngeal stenosis/atresia
         g) Ascites
         h) Intrauterine growth retardation
         i) Polyhydramnios
   d. Fetoscopy (Kabra et al. 2000)
3. Management
   a. Immediate ocular management: frequent use of artificial tears to maintain corneal luster and clarity (Dinno et al. 1974)
   b. Intubation or tracheotomy to provide an adequate airway when laryngeal atresia/stenosis is present. Final repair of the laryngeal stenosis is deferred until about 1–2 years of age when adequate thyroid cartilage development has occurred (Karas and Respler 1995)
   c. Surgical correction of associated anomalies
   d. Goals of reconstruction, considering the poor probability of restoring visual function (Ferri and Harvey 1999)
      i. To protect the cornea (if present) from infection and ulceration
      ii. To enhance cosmetic appearance
      iii. To preserve the globe
   e. Surgical treatment at a later age (Dibben et al. 1997)
      i. Reconstruction in partial cryptophthalmos
         a) Dissection of the eyelids from the cornea
         b) Reconstruction of the conjunctival fornices with buccal mucosa
         c) Repair the upper lid coloboma in a flap reconstruction using the inferior eyelid margin
      ii. Reconstruction without grafting in complete cryptophthalmos (Ferri and Harvey 1999)
   f. Surgical strategy for correction of cryptophthalmos (Saleh et al. 2009)
      i. The main indication for early surgery: presence or risk of corneal exposure in eyes with visual potential, as may occur in abortive cryptophthalmos
      ii. Surgery deferred for painless eyes with no potential for vision and where there is a low risk of corneal exposure. These include:
         a) Complete cryptophthalmos
         b) Incomplete cryptophthalmos with completely keratinized corneas
         c) Patients without corneal exposure

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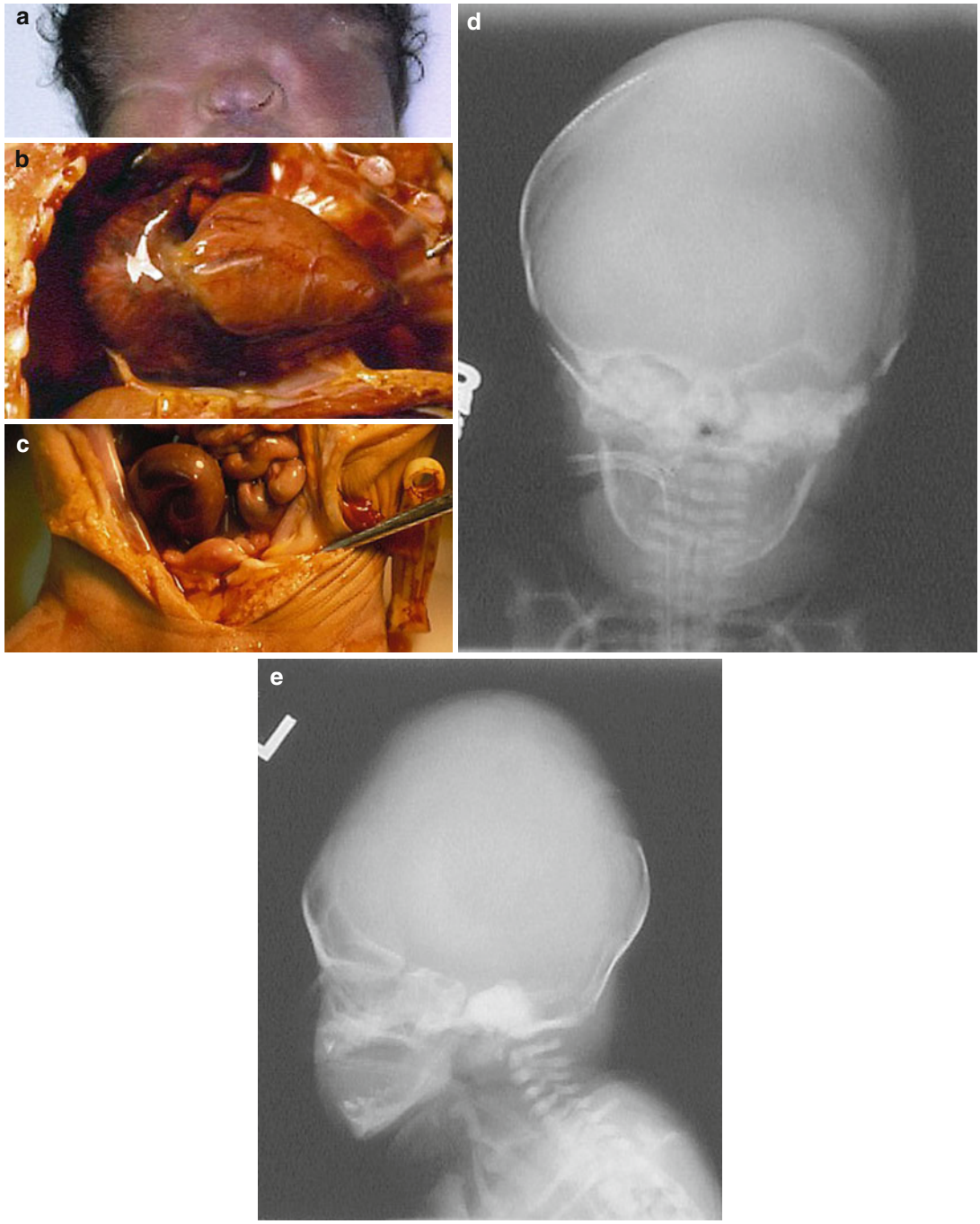

Fig. 1 (**a**–**e**) An infant with Fraser cryptophthalmos showing fused eyelids, lateral hair extending to lateral eyebrows, ocular hypertelorism, notched nares, and a tracheostomy site for management of laryngeal stenosis. Postmortem photos show lung hypoplasia, a small uterus, and clitoral hypertrophy. The skull radiographs show poorly ossified calvarium

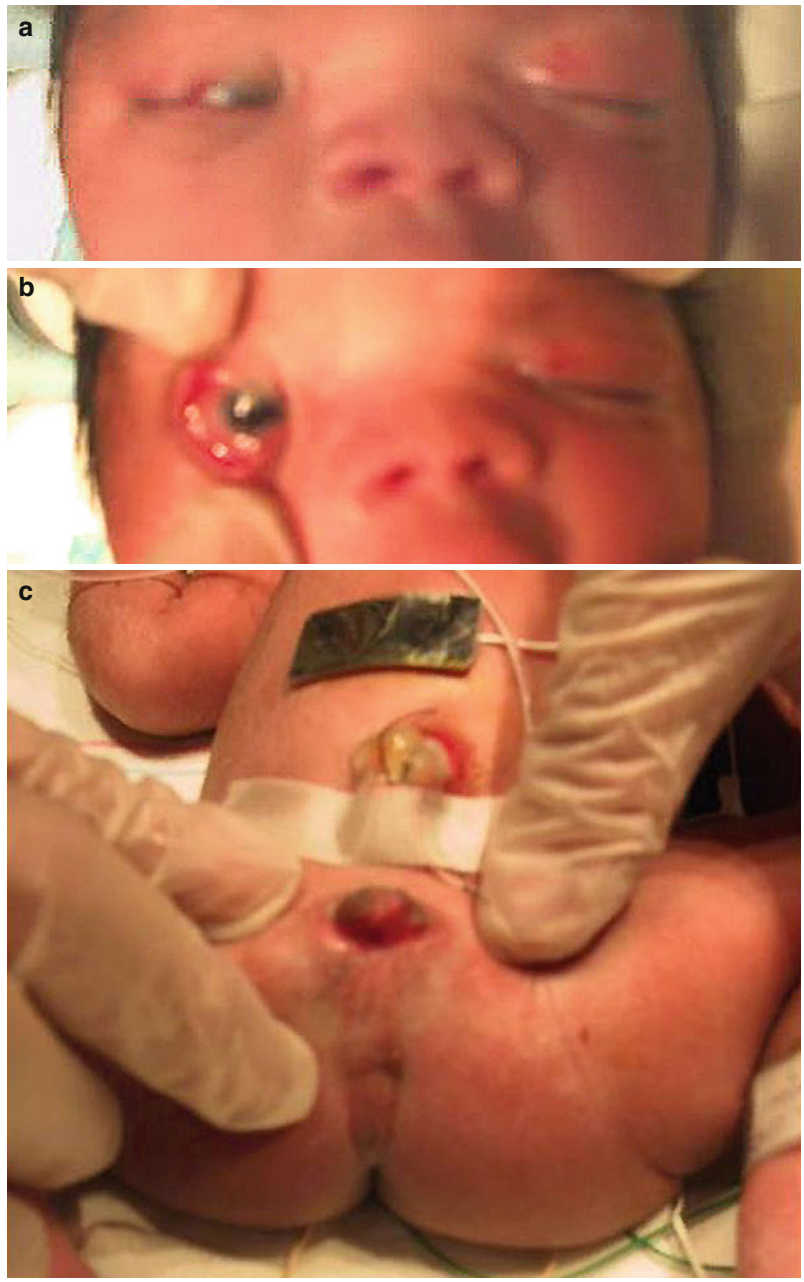

Fig. 2 (**a–c**) The sibling of the previous infant with Fraser syndrome showing microphthalmia, partial fusions of eyelids, ocular hypertelorism, genitourinary anomalies, and partial syndactyly of the toes. Variability of expression is illustrated in these two sibs

Freeman–Sheldon Syndrome

In 1938, Freeman and Sheldon described a syndrome characterized by a whistling face with a long philtrum, a puckered mouth, microstomia, H-shaped cutaneous dimpling on the chin, multiple joint contractures with camptodactyly, ulnar deviation of the fingers, bilateral talipes equinovarus, and kyphoscoliosis. Freeman–Sheldon syndrome (FSS) is the most severe of the distal arthrogryposes with the striking contractures of the orofacial muscles. The syndrome is also known as distal arthrogryposis (DA) type 2A, craniocarpotarsal dysplasia, or "whistling face" syndrome (Lev et al. 2000).

Synonyms and Related Disorders

Craniocarpotarsal dysplasia; "Whistling Face" syndrome

Genetics/Basic Defects

1. Caused by mutations in embryonic myosin heavy chain gene (*MYH3*) (Toydemir et al. 2006). Sheldon–Hall syndrome (SHS) is known to be caused by mutations in either *MYH3*, *TNNT2*, or *TNNT3* (Toydemir and Bamshad 2009)
2. Genetic heterogeneity (Lev et al. 2000)
   a. Autosomal dominant inheritance
      i. Usually with normal psychomotor development, although mild motor delay attributable to joint anomalies might be present
      ii. A variant of autosomal dominant inheritance, mapped to chromosome 11p15.5-pter (Krakowiak 1997)
   b. Autosomal recessive inheritance: severe developmental retardation reported in a few patients
3. Pathogenesis
   a. Considered a form of distal arthrogryposis
      i. Closely related to distal arthrogryposis type 1
         a) Similar limb phenotypes but distinguished only by differences in facial morphology
         b) Reports of families in which different individuals were diagnosed with distal arthrogryposis type 1 or Freeman–Sheldon syndrome
      ii. Proposed to classify Freeman–Sheldon syndrome as distal arthrogryposis type 2 (a distinct disorder from distal arthrogryposis type 1 with overlapping phenotypes) in a revised classification of distal arthrogryposis
   b. Primary brain anomalies suggested to explain many manifestations of the syndrome
   c. Also considered possibly a nonprogressive or slowly progressive myopathy (Vaněk et al. 1986)
4. Overlap of clinical characteristics of FSS with other DA syndromes suggests a shared etiology and/or pathogenesis (Stevenson et al. 2006)
   a. Several DAs can be caused by mutations in four genes that encode proteins of the troponin-tropomyosin complex of fast-twitch myofibers.
   b. Specifically, mutations in *TPM2*, *TNNT2* or *TNNT3*, and *MYH8* cause DA1, SHS, and trismus-pseudocamptodactyly (i.e., DA7), respectively.

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Clinical Features

1. Variable clinical severity and phenotypic abnormalities (Marasovich et al. 1989)
2. Normal intelligence
3. "Whistling face" appearance
   a. Long philtrum
   b. Microstomia
   c. Puckered mouth
   d. Pursed lips
   e. H-shaped cutaneous dimpling on the chin
4. Musculoskeletal anomalies
   a. Multiple joint contractures
   b. Camptodactyly
   c. Ulnar deviation of fingers
   d. Windmill vane hand (bilateral ulnar deviation and contracture of fingers two to five at the metacarpophalangeal joints with adduction of thumbs)
   e. Normal hands in a few reports
   f. Bilateral talipes equinovarus
   g. Kyphoscoliosis
5. Growth retardation
6. Other craniofacial features
   a. Masklike rigid face
   b. Flat midface
   c. Deep-sunken eyes with hypertelorism
   d. Antimongoloid slant of the palpebral fissures
   e. Blepharophimosis
   f. Convergent strabismus
   g. Full cheeks
   h. Small nose
   i. Coloboma alae of the nose
   j. Micrognathia
   k. Cleft palate or high-arched palate
   l. Choanal atresia
   m. Low-set and malformed ears
   n. Hearing loss
7. Other features
   a. Nasal speech
   b. Short neck
   c. Inguinal hernia
   d. Cryptorchidism
   e. Spina bifida occulta
8. Complications
   a. Difficulty in swallowing attributed to the mouth deformity
   b. Pulmonary problems due to decreased thoracic expansion
9. Diagnostic criteria of Freeman–Sheldon syndrome (Stevenson et al. 2006)
   a. Presence of $\geq$2 of the major clinical manifestations of distal arthrogryposis (DA) plus the presence of a small pinched mouth, prominent nasolabial folds, and H-shaped dimpling of the chin
   b. Major manifestations of DA of the upper limbs
      i. Ulnar deviation of the wrists and fingers
      ii. Camptodactyly
      iii. Hypoplastic, and/or absent flexion creases, and/or overriding fingers at birth
   c. Major manifestations of DA of the lower limbs
      i. Talipes equinovarus
      ii. Calcaneovalgus deformities
      iii. A vertical talus
      iv. Metatarsus varus
10. Differential diagnosis of Sheldon–Hall syndrome (SHS) (Stevenson et al. 2006): Diagnostic criteria of SHS include:
    a. $\geq$2 of the major clinical manifestations of DA
    b. Deep nasolabial folds
    c. A small oral opening (but a larger oral opening than that of FSS)
    d. A small but protuberant chin (but lack an H-shaped dimpling of the chin)
    e. Webbing of the neck

Diagnostic Investigations

1. Radiography
   a. Skull
      i. Shallow anterior cranial fossa
      ii. Hypoplastic mandible
      iii. Small malar bones
   b. Ulnar deviation and flexion contractures of the fingers
   c. Talipes equinovarus
   d. Kyphoscoliosis
2. Polysomnography for sleep-disordered breathing
3. Muscle biopsy findings: structural changes predominantly involving type I fibers suggesting that the muscle lesion is a form of congenital fiber type disproportion (Duggar et al. 1989)
4. Molecular genetic testing of *MHY3* mutations

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal dominant inheritance: low unless a parent is affected
      ii. Autosomal recessive inheritance: 25%
      iii. Empirical risks for sibs of sporadic cases: 7%
   b. Patient's offspring
      i. Autosomal dominant inheritance: 50%
      ii. Autosomal recessive inheritance: low unless the spouse is affected
      iii. Empirical risk for children of sporadic case: 37%
2. Prenatal diagnosis
   a. Ultrasonography at 20 weeks of gestation in a fetus with a positive family history (Robbins-Furman et al. 1995)
      i. Bilateral equinovarus and abnormally positioned toes
      ii. Clenched hands with overlapping thumbs
      iii. An abnormally appearing mouth with pursing of the lips
   b. Molecular genetic diagnosis: If the family history is positive and the mutation is known in the family, prenatal molecular genetic diagnosis is possible by direct molecular testing of fetal DNA sample obtained from chorionic villus or amniotic fluid.
3. Management
   a. Tracheostomy required for severe upper airway narrowing (Robinson 1997)
   b. Management of anesthetic risks (Duggar et al. 1989)
      i. Risks primarily related to severe microstomia
      ii. Combinations of myopathic and skeletal abnormalities predisposing affected patients to significant postoperative respiratory difficulty
      iii. Awake endotracheal intubation or fiberoptic nasotracheal intubation in infants before induction of general anesthesia
   c. Functional and cosmetic correction of microstomia (Neumann and Coetzee 2009)
   d. Functional hand reconstruction for hand deformities
   e. Orthopedic correction of clubfeet and scoliosis

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Fig. 1 (**a**–**f**) Freeman–Sheldon syndrome in a father and son showing whistling face appearance of the face and ulnar deviation of fingers and fixed position of the thumbs illustrated by radiographs

Fig. 2 (**a**, **b**) Freeman–Sheldon syndrome in a neonate showing characteristic "whistling face," ulnar deviation of the fingers with contractures, and talipes equinovarus

Fig. 3 (**a**, **b**) Another neonate showing characteristic "whistling face" with H-shaped cutaneous dimpling on the chin and ulnar deviation and contractures of the fingers

Fig. 4 A newborn with Freeman–Sheldon syndrome showing whistling appearance of the face, tight mouth opening, hypoplastic nasal alae, arthrogryposis of the hands and fingers with contractures and ulnar deviation of the wrists, and metatarsus adductus. Intrauterine growth retardation and Dandy–Walker malformation were detected prenatally by ultrasound

Friedreich Ataxia

During the period 1863–1877, Friedreich described the condition, now called Friedreich ataxia (FRDA), in nine members of three families. His initial report noted the following characteristics: age of onset around puberty and ataxia, dysarthria, sensory loss, muscle weakness, scoliosis, foot deformity, and cardiac symptoms.

FRDA is the commonest inherited ataxia (Harding 1984). Recent study based on molecular data suggests a carrier rate of 1 in 85 with a disease prevalence of 1 in 29,000 (Cossee et al. 1997).

Genetics/Basic Defects

1. An autosomal recessive disorder
2. The gene mutated in FRDA (FXN), mapped to 9q13-21.1, was initially called *X25* and later changed to *FRDA*
   a. FRDA: unique among trinucleotide repeat disorders in that it is autosomal recessive
   b. The repeat is intronic
   c. It is the only disease known to be the result of expansion of a GAA trinucleotide repeat
3. Frataxin, the encoded protein, is predicted to contain 210 amino acids. Frataxin has an N-terminal leader peptide that directs its subcellular localization to mitochondria
4. Intergenerational instability, premutations, and origin of mutations
   a. GAA repeat underlying FRDA: unstable in its transmission from parent to offspring as in other trinucleotide repeat disorders (Timchenko and Caskey 1996).
   b. Maternal transmission may result in a larger or smaller allele in offspring while paternal transmission always results in smaller allele (Monros et al. 1997; Pianese et al. 1997; Delatycki et al. 1998; De Michele et al. 1998). The size of the triplet repeat influences the direction of instability with smaller alleles more prone to increase in size and larger ones to decrease.
   c. Premutation alleles are prone to large expansion in one generation.
   d. Normal-sized alleles have a bimodal distribution.
      i. Small normal alleles (about 83%): between 6 and 12 repeats
      ii. Large normal alleles (about 17%): between 14 and 34 repeats
5. Genotype-phenotype correlation: not possible to predict the specific clinical outcome in any individual based on genotype (Bidichandani and Delatycki 2009)
   a. Variability in individuals with FRDA may be caused by:
      i. Genetic background (e.g., Acadian individuals)
      ii. Somatic heterogeneity of the GAA expansion
      iii. Other unidentified factors
   b. GAA repeat size in homozygotes for pathogenic GAA repeat expansions
      i. Statistically significant correlations with:
         a) Age of onset
         b) Presence of leg muscle weakness and/or wasting
         c) Duration until wheelchair use
         d) Prevalence of cardiomyopathy, pes cavus, and scoliosis

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ii. Individuals with late-onset FRDA (LOFA): frequently exhibit fewer than 500 GAA repeats in at least one of the expanded alleles
iii. Individuals with very-late-onset FRDA (VLOFA): usually have fewer than 300 GAA repeats in at least one of the expanded alleles
iv. Cardiomyopathy: more frequently seen with longer GAA repeat alleles
v. Diabetes mellitus or abnormal glucose tolerance: does not show a clear-cut correlation with the size of the GAA expansion

c. Spastic paraparesis without ataxia: may be seen in those with smaller expanded alleles or in association with the G130V missense mutation
d. Compound heterozygotes for an expansion and a point mutation
i. Most compound heterozygotes are clinically indistinguishable from typical individuals with FRDA with homozygous GAA expansions.
ii. Compound heterozygotes for an expansion and a borderline "mutable" allele. Individuals with somatically unstable borderline alleles present with LOFA/VLOFA, mild and gradually progressive disease, and normal reflexes/hyperreflexia.

6. Pathophysiology (Chawla 2008)
a. Major pathophysiologic finding: "dying back phenomena" of axons, beginning in the periphery with ultimate loss of neurons and a secondary gliosis
b. Primary sites of changes in spinal cord and spinal roots resulting in loss of large myelinated axons in peripheral nerves, which increases with age and disease duration
c. Unmyelinated fibers in sensory roots and peripheral sensory nerves are spared

Clinical Features

1. Diagnostic criteria for FRDA (Geoffroy et al. 1976)
a. Primary (essential for diagnosis)
i. Onset before the end of puberty (never after the age of 20 years)
ii. Progressive ataxia of gait
iii. Dysarthria
iv. Loss of joint position or vibration sense
v. Absent tendon reflexes in the legs
vi. Muscle weakness
b. Secondary
i. Extensor plantar responses
ii. Pes cavus
iii. Scoliosis
iv. Cardiomyopathy

2. Diagnostic criteria for FRDA (Harding 1981)
a. Primary (essential for diagnosis)
i. Age of onset of symptoms before the age of 25 years
ii. Progressive unremitting ataxia of limbs and of gait
iii. Absence of knee and ankle jerks
b. Secondary
i. Dysarthria
ii. Extensor plantar responses
c. Additional: If secondary criteria are absent, the following have to be present:
i. An affected sib fulfilling primary and secondary criteria
ii. Median motor nerve conduction velocities of greater than 40 m/s thus excluding cases of type I hereditary motor and sensory neuropathy

3. Typical and atypical FRDA (Harding 1981)
a. Typical: cases meeting above criteria
b. Atypical: cases not meeting above criteria

4. Cardinal features
a. Progressive gait and limb ataxia
b. Absent lower limb reflexes
c. Extensor plantar responses
d. Dysarthria
e. Reduction in or loss of vibration sense and proprioception (sensory modalities mediated by posterior column neurons)

5. Common but nonessential features
a. Cardiomyopathy
b. Scoliosis
c. Foot deformity

Diagnostic Investigations

1. Molecular genetic testing (Chawla 2008; Bidichandani and Delatycki 2009)
a. GAA triplet repeat expansion in intron 1 of the *FXN* gene with four classes of alleles (Sharma et al. 2004)

i. Normal alleles: 5–33 GAA repeats
   a) Short normal: <12 GAA repeats (>80%)
   b) Long normal: 12–33 GAA repeats (approximately 15%)
ii. Premutation (mutable normal) alleles: 34–65 pure, uninterrupted, GAA repeats
   a) Not associated with FRDA but may expand during parental transmission, resulting in disease-causing alleles.
   b) Expansion of premutation alleles, sometimes more than tenfold the original size, has been observed in both paternal and maternal transmission.
iii. Disease-causing expanded (full penetrance) alleles: 66–1,700 GAA repeats
iv. Borderline alleles: 44–66 uninterrupted GAA repeats

2. Clinical laboratory testing
   i. Targeted mutation analysis
      a) Homozygous GAA expansion in *FXN* (96%)
      b) Heterozygous GAA expansion in *FXN*
   ii. Sequence analysis: heterozygous point mutation in *FXN*
      a) Approximately 4% of patients are compound heterozygotes for a GAA expansion in the disease-causing range in one *FXN* allele and another inactivating *FXN* gene mutation in the other allele.
      b) No affected individuals with inactivating point mutations in both *FXN* alleles reported to date
3. Echocardiography: reveals symmetric, concentric ventricular hypertrophy, although asymmetric septal hypertrophy may be present
4. Brainstem auditory evoked responses: typically displaying absent waves III and IV with preservation of wave I, suggestive of involvement of central auditory pathways
5. Visual evoked potentials: absent or delayed latency and reduced amplitude of the p100 wave in two thirds of patients
6. Somatosensory evoked potentials
   a. Delayed central conduction time (N13a/N20, N13b/N20)
   b. Dispersed potentials at the sensory cortex
   c. Abnormal central motor conduction
7. Magnetic resonance imaging of the brain and spinal cord: consistently shows atrophy of the cervical spinal cord with minimal evidence of cerebellar atrophy
8. Nerve conduction studies
   a. Absent sensory nerve action potentials
   b. Absent spinal somatosensory evoked potentials, although these may be reduced or even normal early in the disease course (Harding 1984)
   c. Motor nerve conduction velocities are reduced to a lesser extent than sensory nerve action potentials.
9. Histological studies
   a. Loss of myelinated fibers of the dorsal columns and the corticospinal tracts in lower cervical cord (Weil stain)
   b. Milder involvement of spinocerebellar tracts
   c. Compact fibrillary gliosis in the affected tract on hematoxylin and eosin (H&E) stain but no breakdown products or macrophages, reflecting the very slow rate of degeneration and death of fibers
   d. Shrinkage and eventual disappearance of neurons associated with proliferation of capsular cells in the dorsal spinal ganglia (H&E)
   e. Nearly devoid of large myelinated fibers in the posterior roots
   f. Degeneration and loss of cells of the Clarke column within the thoracic spinal cord

Genetic Counseling

1. Ability to diagnose FRDA by molecular means with a high sensitivity and specificity
   a. Clinically typical patients
      i. A specific and rapid diagnosis can be made in most patients and in the 4% compound heterozygous for a point mutation.
      ii. The presence of one expanded allele indicates that the diagnosis is likely.
   b. Clinically atypical patients can be diagnosed to have or not to have FRDA by:
      i. GAA repeat study
      ii. Mutation analysis for point mutations
   c. Carrier testing
      i. Available for relatives of affected and their partners
      ii. There is a small possibility that a point mutation may be present.

d. For a subject with FRDA who has a carrier partner, there is a 1:2 risk of having an affected child. The a priori risk for a person with FRDA having a child with the condition is approximately 1:200 unless there is consanguinity.
e. If the partner of a carrier does not have an expanded allele, the chance that they carry a point mutation is about 1:5,000 (taking a FRDA carrier rate of 1:100 and that 2% of mutations are point mutations). Therefore, the risk of this couple having a child with FRDA is about 1:20,000 which is only about twice the background risk of the general population.

2. Recurrence risk (Bidichandani and Delatycki 2009)
   a. Patient's sib
      i. Both parents carry a full penetrance allele, or one parent carries a full penetrance allele, and the other parent carries another deleterious *FXN* gene mutation.
         a) At conception: each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
         b) Once an at-risk sib is known to be clinically unaffected, the risk of his/her being a carrier is 2/3.
         c) The wide range in age of onset and variable intergenerational instability of the GAA expansion dictate the use of caution in diagnosing an at-risk sib as unaffected.
      ii. One parent carries a full penetrance allele or another deleterious *FXN* gene mutation, and the other parent carries a mutable normal (premutation) allele.
         a) At conception: each sib of a proband whose parent is a carrier of a mutable normal (premutation) allele has a 25% chance of inheriting both parental mutations.
         b) Since the mutable normal (premutation) allele may remain unchanged or undergo minimal change (i.e., not expand to produce a full penetrance allele), the sibs have less than 25% chance of being affected.
         c) Each sib also has a 50% chance of being an asymptomatic carrier of one of the parental alleles and a 25% chance of being unaffected and having two normal alleles.
   b. Patient's offspring
      i. All offspring inherit one mutant allele from the affected parent.
      ii. Offspring have a 50% chance of being affected only if the reproductive partner of the proband is a carrier of a full penetrance allele or another deleterious *FXN* gene mutation.
      iii. If the reproductive partner of the proband carries a mutable normal (premutation) allele, the risk to each offspring of developing FRDA is less than 50%.
3. Prenatal diagnosis (Bidichandani and Delatycki 2009)
   a. Possible for pregnancies at 25% risk provided both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed
      i. Amniocentesis
      ii. Chorionic villus sampling
   b. Preimplantation genetic diagnosis: available for families in which the disease-causing mutations have been identified in an affected family member
4. Management
   a. Supporting measures (Bidichandani and Delatycki 2009)
      i. Prostheses, walking aids, and wheelchairs for mobility
      ii. Orthopedic interventions for scoliosis and foot deformities
      iii. Speech, occupational, and physical therapy
      iv. Hearing aids
      v. Pharmacologic agents for spasticity
      vi. Dietary modifications and placement of a nasogastric tube or gastrostomy for dysphagia
      vii. Antiarrhythmic agents
      viii. Anti–cardiac failure medications
      ix. Anticoagulants and pacemaker insertion for cardiac disease
      x. Oral hypoglycemic agents or insulin for diabetes mellitus
      xi. Antispasmodics for bladder dysfunction
      xii. Psychological support
   b. Currently, no treatments have been proven to delay, prevent, or reverse the inexorable decline that occurs in this condition. However, several

pharmaceutical agents are undergoing clinical assessment (Delatycki 2009).

c. Treatment with intermediate- and high-dose idebenone had beneficial effects on neurological symptoms (Schulz et al. 2009).
d. Improvement in both cardiac hypertrophy and neurological symptoms among patients with FRDA treated with idebenone (Meier and Buyse 2009)

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Fig. 1 This 22-year-old man was seen for progressive muscle weakness and progressive ataxia. The patient began noticing the problem while running during football practice in high school. In the last 6 months, he has had trouble swallowing, especially liquids, and trouble speaking. At present, he walks with a cane with ataxic gait. There was a significant thigh muscle mass loss. His deep tendon reflexes are absent. Friedreich ataxia DNA test showed that the patient is homozygous for the GAA repeat expansion mutation which confirms the clinical diagnosis of Friedreich ataxia type I (FRDA1) with X25 allele 1 of 400 GAA repeats and X25 allele 2 of 400 GAA repeats

Fig. 2 The patient stands with a cane and need to support standing with hand support on the wall

Frontonasal Dysplasia

Frontonasal dysplasia is a developmental field defect of craniofacial region characterized by hypertelorism and varying degrees of median nasal clefting. In 1967, DeMeyer first described the malformation complex "median cleft face syndrome" to emphasize the key midface defects. Since then, several terms have been introduced: frontonasal dysplasia, frontonasal syndrome, frontonasal dysostosis, and craniofrontonasal dysplasia (currently recognized as a syndrome distinct from frontonasal dysplasia) (Dubey and Garap 2000).

Synonyms and Related Disorders

Frontonasal malformation; Frontorhiny; Median facial cleft syndrome

Genetics/Basic Defects

1. Inheritance
   a. Sporadic in most cases.
   b. Rare autosomal dominant inheritance with variable expression.
   c. Recessive mutations in the homeobox gene *ALX3* cause a recurrent pattern of frontonasal malformation (Twigg et al. 2009).
   d. Rare autosomal recessive inheritance: disruption of *ALX1* causes autosomal-recessive *ALX*-related frontonasal dysplasia (Uz et al. 2010).
   e. Rare X-linked dominant inheritance.
2. Rare association with chromosome anomalies
   a. Partial trisomy 2q and partial monosomy 7q from a balanced maternal t(2;7)(q31;q36) (Chen et al. 1992)
   b. 22q11 microdeletion (Stratton and Payne 1997)
   c. Reciprocal translocation t(15;22)(q22;q13) (Fryns et al. 1993)
   d. Complex translocation involving chromosomes 3, 7, and 11 (Stevens and Qumsiyeh 1995)
3. Rare variants of frontonasal dysplasia/malformation with variable inheritance patterns
4. Embryologically classified as a developmental field defect (Sedano and Gorlin 1986)
5. Extreme variable phenotypic expression
6. Pathogenesis (Twigg et al. 2009)
   a. Formation of the human face is an exquisitely orchestrated developmental process involving multiple tissue swellings (the frontonasal, medial and lateral nasal, and maxillary and mandibular prominences) derived from the neural crest (Moore and Persaud 2007).
   b. During a critical period between 4 and 8 weeks of human fetal development, these processes must undergo cell proliferation and tissue fusion to form the orbital, nasal, and oral structures (Yoon et al. 2000; Moore and Persaud 2007).
   c. Disturbance to this developmental sequence causes frontonasal malformation, a very heterogeneous group of disorders characterized by combinations of hypertelorism, abnormal nasal configuration, and oral, palatal, or facial clefting, sometimes associated with facial asymmetry, skin tags, ocular or cerebral malformations, widow's peak, and anterior cranium bifidum (DeMeyer 1967; Sedano et al. 1970; Sedano and Gorlin 1986; van der Meulen and Vaandrager 1989; Guinon-Almeida et al. 1996; Tan and Mulliken 1997; Losee et al. 2004).

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Clinical Features

1. Pure frontonasal dysplasia (Dubey and Garap 2000)
   a. Variable mental retardation
   b. Inheritance pattern
      i. Sporadic in majority of cases
      ii. Familial transmission in few cases
   c. Cranium bifidum occultum
   d. CNS anomalies
      i. Frontal cephalocele
      ii. Meningocele/meningoencephalocele
      iii. Agenesis of the corpus callosum
      iv. Mild holoprosencephaly
      v. Hydrocephalus
   e. Nasal anomalies
      i. Mild colobomas of the nostril
      ii. Flattening of the nose with widely separated nares
      iii. A broad nasal root
      iv. Broad nasal tip
      v. Notching or clefting of alae nasi (cleft nose)
      vi. Nasal tag
   f. Ocular anomalies
      i. Hypertelorism
      ii. Epicanthal folds
      iii. Narrowing of the palpebral fissures
      iv. Accessory nasal eyelid tissue with secondary displacement of inferior puncti colobomas
      v. Epibulbar dermoids
      vi. Upper eyelid colobomas
      vii. Microphthalmia
      viii. Vitreoretinal degeneration with retinal detachment
      ix. Congenital cataracts
   g. Facial anomalies
      i. Widow's peak configuration of the anterior hairline in the forehead
      ii. Median cleft of upper lip
      iii. Median cleft palate
      iv. Preauricular tag
      v. Absent tragus
      vi. Low-set ears
   h. Other anomalies
      i. Conductive deafness
      ii. Hypoplastic frontal sinuses
      iii. Cardiac anomalies, especially tetralogy of Fallot
      iv. Limb anomalies
         a) Clinodactyly
         b) Polydactyly
         c) Syndactyly
         d) Tibial hypoplasia
      v. Umbilical hernia
      vi. Cryptorchidism
2. Autosomal-recessive frontonasal dysplasia in two distinct families (Uz et al. 2010)
   a. Bilateral extreme microphthalmia
   b. Bilateral oblique facial cleft
   c. Complete cleft palate
   d. Hypertelorism
   e. Wide nasal bridge with hypoplasia of the ala nasi
   f. Low-set, posteriorly rotated ears
3. Other syndromes associated with frontonasal dysplasia or frontonasal malformation (Martinelli et al. 2002)
   a. Autosomal dominant form of frontonasal dysplasia with vertebral anomalies
   b. Acromelic frontonasal dysplasia
      i. Autosomal recessive disorder
      ii. Similar frontonasal "dysplasia"
      iii. Rare agenesis of the corpus callosum
      iv. Tibial hypoplasia
      v. Polydactyly (duplicated hallux)
   c. Craniofrontonasal dysplasia
      i. Possible X-linked disorder
      ii. Rare mental retardation
      iii. Hypertelorism
      iv. Craniosynostosis
      v. Facial asymmetry
      vi. Broad nasal root
      vii. Bifid nasal tip
      viii. Syndactyly of toes and fingers
      ix. Split nails
      x. Broad first toe
   d. Acrocallosal syndrome
      i. Autosomal dominant or autosomal recessive disorder
      ii. Severe mental retardation
      iii. Hypertelorism
      iv. Hypoplastic or absent corpus callosum
      v. Prominent forehead
      vi. Small nose
      vii. Broad nasal bridge
      viii. Normal nasal tip
      ix. Cardiac defects
      x. Postaxial polydactyly of hands and feet

xi. Preaxial polydactyly of feet
xii. Syndactyly of toes
xiii. Clinodactyly
e. Oral-facial-digital syndrome
i. X-linked disorder
ii. Variable mental retardation
iii. Agenesis of the corpus callosum
iv. Median cleft lip and palate
v. Lobated/bifid tongue
vi. Clinodactyly
vii. Syndactyly
viii. Polydactyly
f. Oculo-auriculo-frontonasal dysplasia
i. Frontonasal dysplasia
ii. Ocular dermoids
iii. Eyelid colobomata
iv. Preauricular tags
g. Fronto-facio-nasal dysplasia
i. Autosomal recessive disorder
ii. Frontonasal dysplasia
iii. Ocular dermoids
iv. Preauricular tags
v. Cerebral lipoma
h. Acro-fronto-facio-nasal dysplasia I
i. Autosomal recessive disorder
ii. Frontonasal dysplasia
iii. Macrostomia
iv. Broad and notched nasal tip
v. Fibular hypoplasia
vi. Polydactyly
vii. Short stature
i. Acro-fronto-facio-nasal dysplasia II
i. Autosomal recessive disorder
ii. Frontonasal dysplasia
iii. Microcephaly
iv. Nasal midline groove with blind dimples
v. Broad thumbs
vi. Syndactyly
j. Greig acrocephalopolysyndactyly
i. Autosomal dominant disorder
ii. Mild mental retardation
iii. Mild features of frontonasal dysplasia
iv. Macrocephaly
v. Broad nasal root
vi. Normal nasal tip
vii. Postaxial polydactyly of hands
viii. Preaxial polysyndactyly of feet
ix. Broad thumbs and halluces
x. Syndactyly
k. Meinecke frontonasal dysplasia-cardiac defects
i. Frontonasal dysplasia
ii. Microcephaly
iii. Cardiac defects, especially tetralogy of Fallot
4. Prognosis depending on severity of defects
a. Normal intelligence in most patients
b. Mental retardation affecting 12% of cases without CNS abnormalities
c. Up to 50% of cases with mental retardation complicated by agenesis of the corpus callosum

Diagnostic Investigations

1. Radiography, CT, and MRI of the brain
a. Anterior cranium bifidum
b. Agenesis of the corpus callosum
c. Lipoma of the corpus callosum
d. Arhinencephaly
e. Hydrocephalus
2. Chromosome analysis for chromosome etiology
3. Molecular genetic diagnosis of *ALX1* and *ALX3* mutations: not available clinically

Genetic Counseling

1. Recurrence risk
a. Patient's sib
i. Autosomal dominant disorder: not increased in de novo case unless a parent is affected
ii. Autosomal recessive disorder: 25%
iii. X-linked dominant disorder: 50% when the mother is a carrier
iv. Chromosome disorder: not increased in a de novo case; risk of unbalanced segregation from a carrier parent
b. Patient's offspring
i. Autosomal dominant disorder: 50%
ii. Autosomal recessive disorder: not increased unless the spouse is a carrier
iii. X-linked dominant disorder: 50%
iv. Chromosome disorder: not surviving to reproductive age
2. Prenatal diagnosis
a. Ultrasonography (Martinelli et al. 2002)
i. Hypertelorism
ii. Frontonasal cephalocele

iii. Agenesis of the corpus callosum
iv. Median cleft lip

b. 3-D ultrasonography: increasingly helpful in identifying facial features (Johnstone et al. 2008)
c. Amniocentesis for associated chromosome anomaly

3. Management
   a. Speech therapy
   b. Maxillofacial surgeries for functional and cosmetic improvement
      i. Cleft lip/palate
      ii. Hypertelorism
      iii. Nose
   c. Psychosocial and/or psychiatric support

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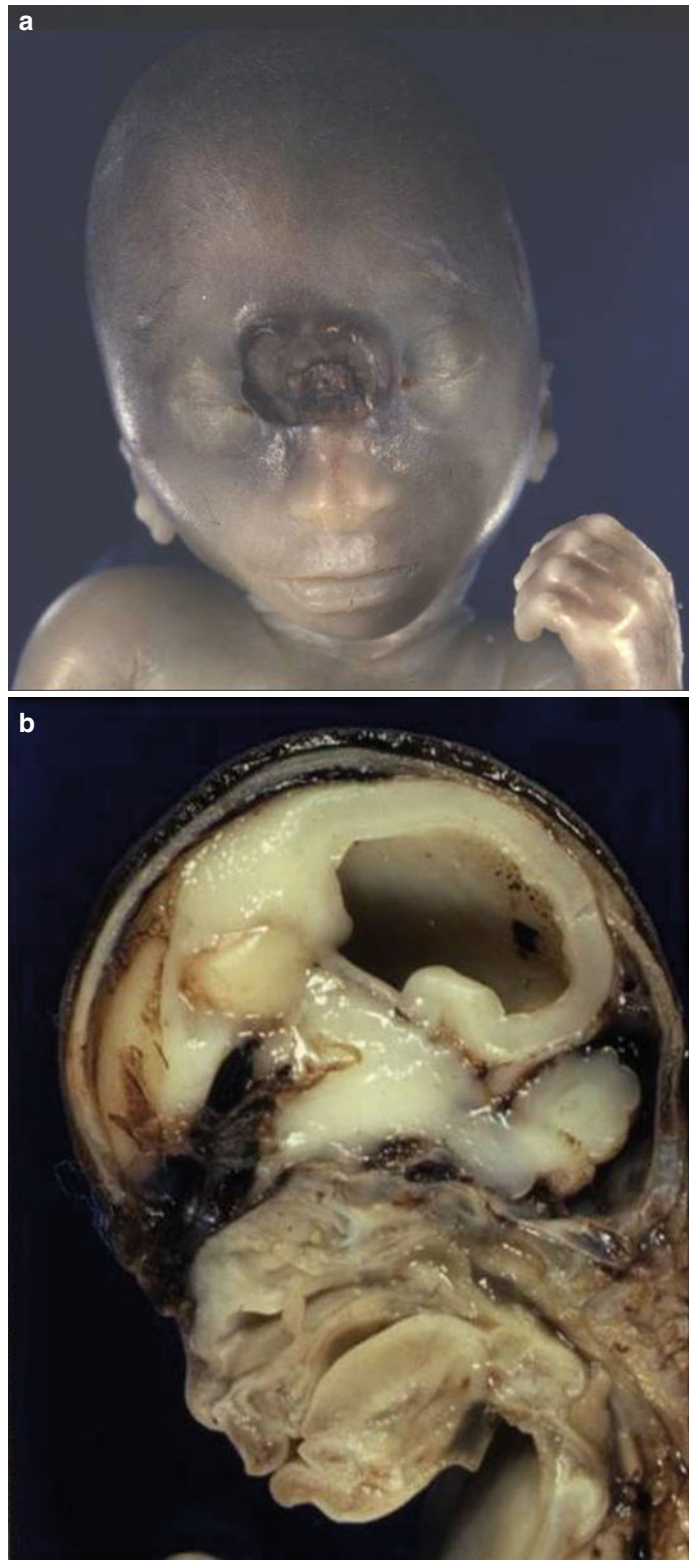

Fig. 1 (**a**, **b**) A newborn with frontonasal dysplasia showing ocular hypertelorism, cephalocele, hydrocephalus, and cranium bifidum

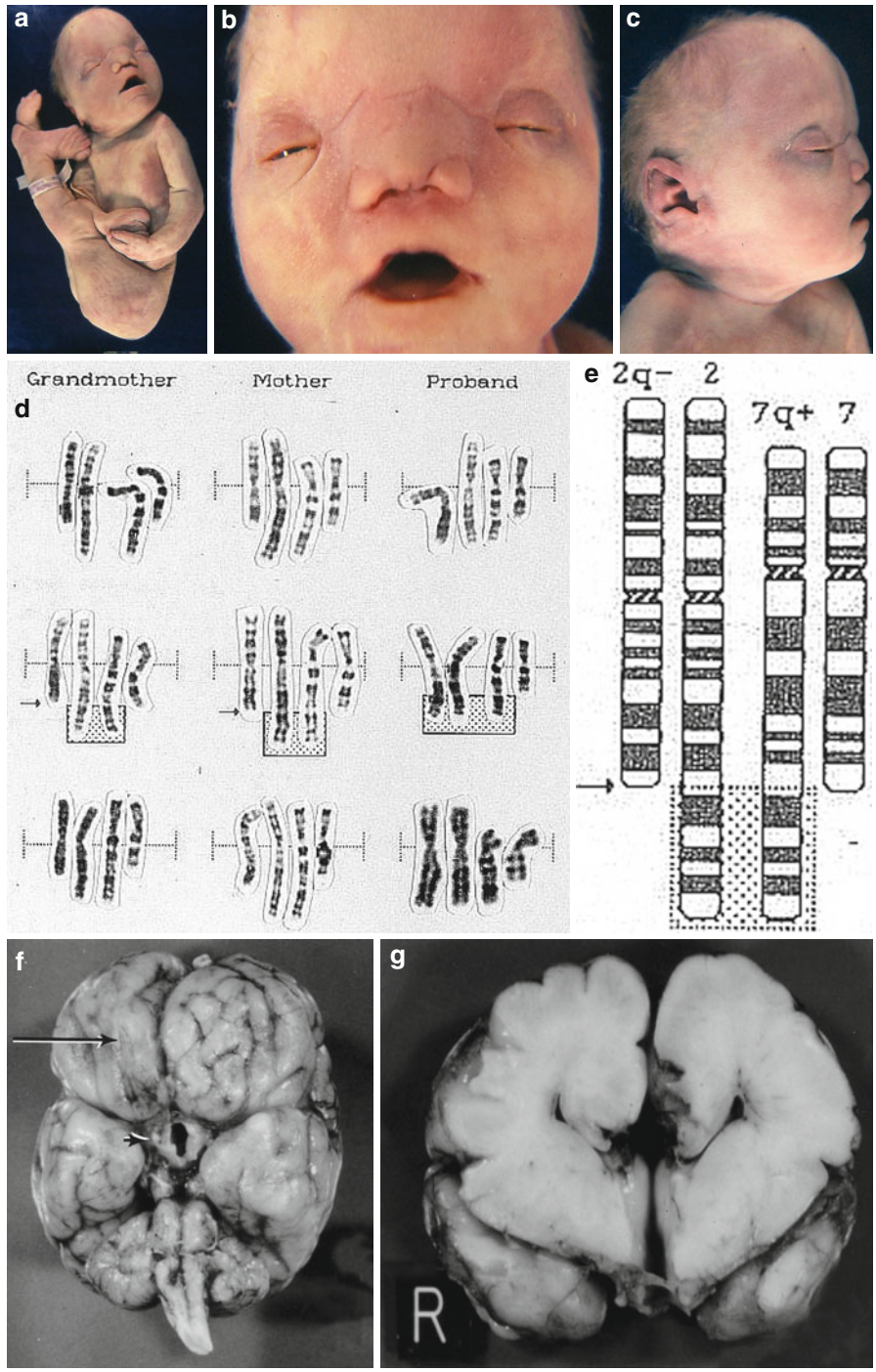

Fig. 2 (**a**–**g**) A newborn with frontonasal dysplasia and arrhinencephaly resulting from unbalanced segregation of a maternal t(2;7)(q31;q36). The patient had partial trisomy 2q and partial monosomy 7q, iris coloboma, tetralogy of Fallot, and limb anomalies

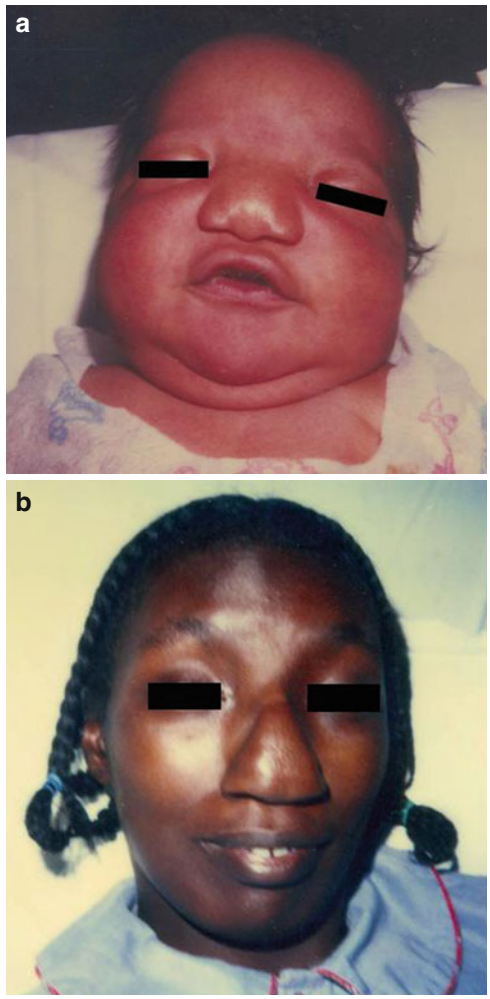

Fig. 3 (**a**, **b**) A mother and a child with frontonasal dysplasia showing hypertelorism and broad and notched nasal tip

Fig. 4 A 2-year-old girl with frontonasal dysplasia

Galactosemia

Classic galactosemia (G/G) is an autosomal recessive disorder of galactose metabolism, caused by a deficiency of galactose-1-phosphate uridyl transferase. The incidence is estimated to be 1 in 30,000–1 in 60,000 births, based on the results of newborn screening programs.

Synonyms and Related Disorders

Classic galactosemia; Galactose-1-phosphate uridyltransferase deficiency

Genetics/Basic Defects

1. Inheritance: autosomal recessive. (Leslie 2003)
2. Cause: deficiency of galactose-1-phosphate uridyl transferase (GALT)
3. Galactose metabolism (Arn 2003)
   a. D-galactose
      i. Galactose: an important sugar in human nutrition, especially during childhood.
      ii. Milk: major source of galactose, which contains lactose, a disaccharide of glucose and galactose.
      iii. Liver: the primary site of galactose metabolism.
      iv. Individuals have the capacity to metabolize large quantities of galactose under normal circumstances.
   b. Normal individuals
      i. Lactase (present in the small intestine): metabolizes galactose to glucose and galactose.
      ii. The resulting glucose and galactose is then absorbed via the portal system to the liver.
      iii. In the liver, a series of four reactions converts galactose to glucose-1-phosphate.
      iv. Glucose-1-phosphate can be metabolized to glucose, CO_2, pyruvate, or glycogen depending on prevailing metabolic conditions.
      v. Inborn errors have been described in all of the enzymes of the pathway.
   c. Affected individuals: Deficiency of the enzyme galactose-1-phosphate uridyl transferase (GALT) causes classic galactosemia.
4. Galactose-1-phosphate uridyl transferase
   a. The gene for GALT is mapped on chromosome 9p13.
   b. GALT is second enzyme in the Leloir pathway, catalyzing conversion of galactose-1-phosphate and UDP glucose to UDP galactose and glucose-1-phosphate.
   c. Essential in human infants who consume lactose as their primary carbohydrate source.
   d. Near total absence of GALT activity in infants with classical galactosemia.
   e. A deficiency causes elevated levels of galactose-1-phosphate and galactitol in body tissues.
5. Endogenous production of galactose may be responsible for the long-term effects, such as cognitive dysfunction and gonadal dysfunction in female patients
6. Duarte (D) allele (Beutler 1991)
   a. Very common
   b. Defined biochemically by:
      i. Reduced enzyme activity
      ii. An isoform distinguishable by gel electrophoresis and isoelectric focusing
   c. Heterozygous Duarte variants (D/N)
      i. Observed in about 11% of Caucasian subjects
      ii. Have about 75% of normal GALT activity

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d. Homozygotes for the Duarte variant (D/D)
   i. Have approximately one half (50%) of normal transferase activity
   ii. Mimic carriers for galactosemia
e. Infants with a galactosemia allele and a Duarte allele (D/G)
   i. Have 1 quarter (25%) of normal enzyme activity
   ii. Have reduced capacity to metabolize galactose with abnormal accumulation of galactose-1-phsphate in the red cells
   iii. Phenotypically normal with no ill effect

7. Genotype–phenotype correlations (Elsas II 2003).
   a. Q188R mutations (prevalent in 70% of Caucasians): a poorer outcome in homozygous state associated with essentially no enzyme activity (Elsas et al. 1995)
   b. Duarte variant (N314D)
      i. Homozygous state (D/D or N314D/N314D) with erythrocyte GALT enzyme activity reduced by only 50%
      ii. Compound heterozygotes (D/G or N314D/Q188R)
         a) Relatively benign in most infants
         b) May or may not require dietary intervention
   c. Los Angels (LA) variant with identical N314D missense mutation but has normal erythrocyte GALT activity
   d. S135L allele
      i. Prevalent in Africa
      ii. A good prognosis if therapy is initiated in the neonatal period without neonatal hepatotoxicity and chronic problems
   e. K285N allele
      i. Prevalent in Southern Germany, Austria, and Croatia
      ii. A poor prognosis for neurological and cognitive dysfunction in either the homozygous state or compound heterozygous state with Q188R

Clinical Features

1. Onset of symptoms
   a. May present by the end of the first week of life
   b. May die or develop cataracts, hepatomegaly, cirrhosis, and mental retardation in late-detected cases
2. Neonatal toxicity syndrome
   a. Exposure to dietary galactose in infants with classical galactosemia results in acute deterioration of multiple organ systems, including the following:
      i. Liver dysfunction
         a) Jaundice
         b) Hepatomegaly
      ii. Coagulopathy
      iii. Poor feeding and weight loss
      iv. Vomiting and diarrhea
      v. Lethargy and hypotonia
      vi. Renal tubular dysfunction
      vii. Cerebral edema (encephalopathy)
      viii. Vitreous hemorrhage
      ix. *Escherichia coli* (or other gram-negative) sepsis: consider diagnosis of galactosemia since a high frequency of neonatal death appears to be caused by *E. coli* sepsis (Levy et al. 1977)
   b. Withdrawal of dietary galactose results in reversal of neonatal toxicity syndrome and reducing mortality and morbidity in the early weeks of life.
3. Cataracts
   a. Resulting from accumulation of galactitol within the lens
   b. Seen in infants with classical GALT-deficient galactosemia (and also in galactokinase deficiency)
      i. The ocular hallmark of untreated or late-detected patients
      ii. Severity of lens involvement dependent on the severity of galactosemia and the age at commencement of therapy
   c. Reoccur in older patients who have poor dietary compliance
   d. May be prevented by dietary restriction of galactose
4. Premature ovarian failure
   a. Despite the high prevalence of premature ovarian failure and subsequent infertility in galactosemic women, spontaneous pregnancies occur and may not be as rare as is generally assumed (Gubbels et al. 2008)
   b. Hypergonadotropic hypogonadism occurring almost universally (>90%) in females with classical GALT deficiency
   c. The rapidity and severity of the ovarian failure vary widely among individuals

d. Clinical manifestations
   i. Delayed puberty
   ii. Primary amenorrhea
   iii. Secondary amenorrhea
   iv. Oligomenorrhea
5. Chronic brain effects
   a. Specific deficits
      i. Developmental speech dyspraxia and tremor
      ii. Globally decreased IQ and/or learning disability
   b. Uncertainty as to:
      i. Whether these deficits are initiated in early development, perhaps even prenatally, and unmasked, as more complex brain function is required
      ii. Whether these deficits represent true neurodegenerative processes compounded by dietary exposure and endogenous production of "intoxicants"
      iii. Longitudinal assessment of intellectual achievement in patients with classic galactosemia (Schadewaldt et al. 2010):
         a) Confirms the presence of reduced cognitive ability in classical galactosemia
         b) Presents evidence for an absence of substantial galactosemia-induced aggravation of this impairment with increasing age, at least in patients from 4 to 40 years of age
         c) Remains to be clarified whether a reduction of cognitive function in galactosemia may be initiated by an in utero toxicity of endogenously formed galactose and which role such a process may play in the development of intellectual deficiencies that are later maintained throughout life
6. Prognosis
   a. A life-threatening disorder if untreated.
   b. Currently, affected infants are treated before becoming ill because of newborn screening in most states.
7. Differential diagnosis (Elsas II 2003)
   a. Galactokinase (GALK) deficiency
      i. An autosomal recessive disorder
      ii. Considered in patients with cataracts and galactosemia but otherwise healthy
      iii. Cataracts
         a) The main clinical feature
         b) Due to accumulation of galactitol
      iv. Pseudotumor cerebri
         a) Described in several cases
         b) Considered to be a true consequence of the disorder
      v. These features resolve when a galactose-restricted diet is introduced
      vi. Diagnosis made by detection of reduced galactokinase activity
      vii. Caused by mutations in the *GALK1* gene
   b. UDP-galactose 4-epimerase (GALE) deficiency
      i. An autosomal recessive disorder
      ii. Considered in patients with liver disease, sensorineural deafness, failure to thrive, and elevated galactose-1-phosphate but normal GALT activity
      iii. Response to the removal of galactose from their diets
      iv. Diagnosis made by detection of reduced UDP-galactose 4-epimerase activity
      v. Caused by mutations in the *GALE* gene
   c. Neonatal hepatotoxicity
      i. Infectious diseases (sepsis)
      ii. Obstructive biliary disease
         a) Progressive familial intrahepatic cholestasis (Byler disease)
         b) Metabolic diseases such as Niemann–Pick disease, type C and Wilson disease

Diagnostic Investigations

1. Newborn screening programs in most states (Leslie 2003)
   a. An almost 100% detection of affected infants in states that include testing for galactosemia in their newborn screening programs
   b. Prevention of needless deaths associated with galactosemia, resulting from limiting diagnostic measures to infants who develop symptoms
   c. A positive (i.e., abnormal) screening, followed by a quantitative erythrocyte GALT analysis
2. Liver dysfunction
   a. Bilirubin determination.
      i. Initial unconjugated hyperbilirubinemia
      ii. Later conjugated hyperbilirubinemia
   b. Abnormal liver function tests.
   c. Abnormal clotting.
   d. Raised plasma amino acids, particularly phenylalanine, tyrosine, and methionine. Raised

phenylalanine may result in a false positive neonatal screening test for phenylketonuria.

3. Renal tubular dysfunction
   a. Metabolic acidosis
   b. Urinalysis
      i. Galactosuria
         a) The presence of reducing substances or galactose in the urine is neither sensitive nor specific.
         b) Small quantities of galactose commonly found in the urine of any patient with liver disease.
      ii. Albuminuria
         a) Present in the initial stage
         b) Quick disappearance of albuminuria after eliminating lactose-containing formula from the diet
      iii. Aminoaciduria in the later stage
4. Abnormal carbohydrate metabolism
   a. Increased plasma galactose
   b. Increased red cell galactose-1-phosphate
   c. Increased urine and blood galactitol
5. Testing for hemolytic anemia
6. Study for septicemia, especially *Escherichia coli*
7. Slit lamp examination for cataract assessment
8. Computerized tomography and magnetic resonance imaging
   a. Abnormalities on brain imaging: common in classical galactosemia
   b. Patients with late neurologic disease
      i. Abnormal white matter
      ii. Ventricular enlargement
      iii. Diffuse cortical atrophy with basal ganglia and brainstem involvement
      iv. Cerebellar atrophy
      v. Failure of normal myelination
9. Endocrine investigations for hypergonadotropic hypogonadism
   a. Raised follicle-stimulating hormone
   b. Raised luteinizing hormone
   c. Initially normal estradiol concentration with high gonadotropin levels, indicating continued follicular development, but fall as ovarian failure progresses
10. Increased urinary galactitol excretion
11. Beutler test
    a. A fluorescent spot test for galactose-1-phosphate uridyl transferase activity
    b. Now widely used for the diagnosis of galactosemia
    c. False negative resulting from recent blood transfusions (within 3 months)
    d. False positive resulting from glucose-6-phosphate dehydrogenase deficiency
12. Red blood cell galactose-1-phosphate
    a. Concentration always raised in classical galactosemia
    b. Not significantly affected by blood transfusions
13. Biochemical confirmation of the diagnosis
    a. Red blood cell galactose-1-phosphate uridyl transferase assay
       i. A quantitative assay to confirm the diagnosis (virtual absence of the enzyme activity in classical (G/G) galactosemia)
       ii. Also identifies variants with residual enzyme activity
       iii. False negative results due to blood transfusion within 3 months
    b. A GALT isoelectric-focusing electrophoresis test to distinguish variant forms such as the Duarte defect
14. DNA analysis: *GALT* genotyping for providing specific molecular diagnosis
    a. Classic (G/G) galactosemia
       i. Mutation analysis for the six common *GALT* galactosemia (G) mutations
          a) Q188R mutation: the most common *GALT* allele in whites
          b) S135L: the most common allele in blacks
          c) K285N
          d) L195P
          e) Y209C
          f) F171S
       ii. *GALT* sequence analysis to detect private mutations under the following two conditions:
          a) Both disease-causing mutations not detected by mutation analysis
          b) Diagnosis of galactosemia confirmed by biochemical testing
    b. Mutation analysis for Duarte variant (D/G) galactosemia identified by biochemical testing of the patient and both parents
       i. Identification of Duarte allele (N314D) by mutation analysis
       ii. Identification of G allele by mutation analysis or sequence analysis

15. Carrier testing
    a. Measuring GALT activity: about 50% of control values in carriers
    b. Molecular genetic testing for carriers available to family members, provided *GALT* mutation(s) has/have been identified in the proband

Genetic Counseling

1. Recurrence risk
    a. Patient's sib
        i. A proband with G/G galactosemia
            a) Given the parents are G/N and G/N: a 25% chance of being affected with G/G galactosemia for each sib
            b) Given the parents are D/G and G/N: a 25% chance of being affected with G/G galactosemia and a 25% chance of being affected with D/G galactosemia for each sib
        ii. A proband with D/G galactosemia, given the parents are D/N and G/N: a 25% chance of being affected with D/G galactosemia for each sib
    b. Patient's offspring:
        i. Patient with G/G galactosemia and the normal spouse with N/N: All offspring are carriers.
        ii. Patient with G/G galactosemia and the carrier spouse for a G allele (N/G): a 50% chance of having G/G galactosemia.
        iii. Patient with G/G galactosemia and the carrier spouse for a G allele (D/G): a 50% chance of having G/G galactosemia and a 50% chance of having D/G galactosemia.
2. Prenatal diagnosis possible for fetuses at a 25% risk for classical galactosemia
    a. Galactose-1-phosphate uridyl transferase assay in cultured amniotic fluid cells or in chorionic villus biopsies.
    b. Galactitol estimation in amniotic fluid supernatant.
    c. Mutation analysis of DNA extracted from amniocytes or chorionic villus samples if the genotype of the index case has been characterized.
    d. Prenatal diagnosis of a treatable condition, such as classic galactosemia, may be controversial if the prenatal testing is being considered for the purpose of pregnancy termination rather than early diagnosis.
    e. Preimplantation genetic diagnosis: may be available for families in which the disease-causing mutations have been identified.
3. Management (Arn 2003; Elsas II 2003)
    a. Dietary intervention.
        i. Lactose-galactose-restricted diet
            a) Restrict milk, the principal source of lactose, and products made from milk
            b) Breast milk and cows' milk contraindicated
        ii. Milk substitutes
            a) Use a formula free of bioavailable lactose (e.g., Isomil or Prosobee)
            b) Casein hydrolysate (Alimentum, Nutramigen, and Pregestimil): not recommended because they contain small amounts of bioavailable lactose
        iii. Difficult to totally eliminate galactose since it is present in a wide variety of food, such as infant foods, fruits, and vegetables
        iv. Older patients tolerating lactose much better than children, but recommend restrict milk intake throughout life
        v. Calcium supplements if calcium intake does not meet the recommended daily allowance
        vi. May prevent cataracts, hepatomegaly, liver cirrhosis, mental retardation, and other symptoms
        vii. Effect of dietary restrictions during pregnancy on the long-term complications of an affected fetus: unknown
        viii. Individuals with homozygous Duarte variant without symptoms: do not require treatment (Ficicioglu et al. 2008)
        ix. Management of D/G or N344D/Q188R compound heterozygotes
            a) Decision to treat should be based on the demonstration of abnormal biochemical indices.
            b) No dietary therapy is instituted if the blood galactose and/or galactose-1-phosphate do not rise above 12 mg/dL within 4 h following such ingestion, and there are no clinical signs associated with galactosemia.

c) Dietary therapy should probably be given if there is a greater accumulation of galactose or of galactose-1-phosphate.
d) There is possible benefit of dietary intervention to individuals with variant forms of galactosemia with residual GALT activity in the range of 5–20%: for prevention of cataracts, ataxia, dyspraxic speech, and cognitive deficits.

b. Vitamin K and fresh-frozen plasma to correct clotting abnormalities.
c. Pharmacologic treatment.
   i. An appropriate intravenous antibiotic for gram-negative sepsis.
   ii. Many medications, particularly tablets, contain lactose, and this should be considered when prescribing; however, the amount of galactose is often insignificant when given over a short period.
d. Treat unconjugated hyperbilirubinemia with phototherapy or exchange transfusion to infants who may be at an increased risk of kernicterus if albumin levels are particularly low secondary to liver disease.
e. Parental feeding if the infant is too sick to tolerate enteral feeding for more than 1 or 2 days, unless there is significant liver disease or thrombocytopenia.
f. Treat the following long-term problems in older children and adults with classical galactosemia, despite early and adequate therapy.
   i. Cataracts
   ii. Speech defects
   iii. Poor growth
   iv. Poor intellectual function
   v. Neurological deficits, predominantly extrapyramidal findings with ataxia
   vi. Ovarian failure
g. Physical/speech therapy.
   i. Speech therapy for speech delay or verbal dyspraxia (Nelson 1995)
   ii. Regular assessment of development and cognitive function using standardized tests recommended (Walter et al. 1999)
h. Other therapies/evaluations.
   i. Monitoring of red cell galactose-1-phosphate available for assessing dietary compliance, though despite dietary adherence, these levels never decline to normal
   ii. Ophthalmologic examination for cataract assessment to be made at the time of diagnosis, every 6 months until age 3 years, and then annually (Walter et al. 1999)
   iii. Referral to a pediatric endocrinologist by the time a female patient is 10 years (Walter et al. 1999)
i. Emerging therapies.
   i. None with trial data.
   ii. Environment, GALT genotype, and epigenetic pathway of galactose metabolism probably all contribute to outcome.
   iii. In the absence of new therapies emerging from pathogenetic studies, attempts to enhance GALT activities may prove of value (Holton 1996; Elsas and Lai 1998).

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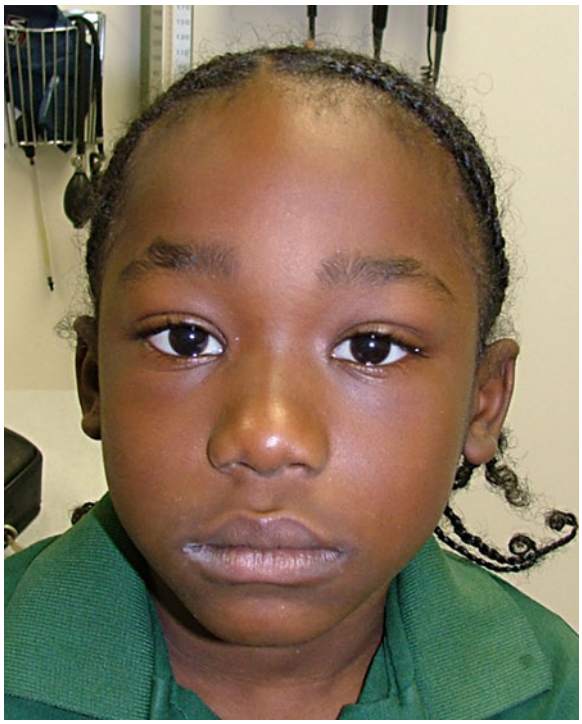

Fig. 1 A 5-year-old boy with classical galactosemia. The initial clinical presentation was at 12 days of age with unconjugated hyperbilirubinemia, presence of reducing substance in the urine, and *E. coli* sepsis. The patient was found to have posterior stellate lens opacities OU. He was found to have deficient galactose-1-phosphate uridyl transferase activity of 0.3 (normal range: 17–37 UMOL/HR/G HGB). Galactokinase was within normal limits. The patient was put on galactose-free diet and has been growing well

Fig. 2 A 2-month-old girl with D/G compound heterozygote. The newborn screening revealed total blood galactose (Gal + Gal-1-phosphate) level of 33.4 mg/dL (normal, <15.0) and blood galactose (without Gal-1-phosphate) level of 3.7 mg/dL. Enzyme assay for uridyl transferase was 41.3 μm (normal, >40.0). DNA analysis showed one copy of the N314D (Duarte galactosemia) variant and one copy of the Q188R (classical galactosemia) mutation. The patient is currently on Isomil and growing well

Gastroschisis

Gastroschisis (Greek for belly cleft) is a congenital paraumbilical wall defect characterized by the protrusion of the intestines uncovered by the peritoneum. It represents one of the most common congenital malformations requiring multidisciplinary neonatal intensive care, with an incidence of approximately 1 in 3,300 births that seems to be increasing (Alvarez and Burd 2007).

Genetics/Basic Defects

1. Precise etiology unknown
2. Inheritance
   a. Isolated occurrence in most cases
   b. Rare autosomal dominant inheritance
3. Pathogenesis and risk factors Sharp et al. (2000); Fillingham and Rankin 2008; Lammer et al. 2008; Rasmussen and Frias 2008)
   a. Pathogenesis
      i. Most commonly quoted: Hoyme's vascular disruption theory with disruption occurring in the omphalomesenteric artery (Hoyme et al. 1983)
      ii. More recent proposed pathogenesis
         a) Consequence of abnormal folding of the body wall (Feldkamp et al. 2007)
         b) Disruption of endothelial oxide synthase pathway (its relationship to vasculogenesis) by environmental exposures or by genetic variation may represent one pathogenetic model for gastroschisis (Lammer et al. 2008).
   b. Risk factors
      i. Vascular insult
         a) Association of maternal smoking and maternal cocaine use with an increased incidence of gastroschisis
         b) The association of intestinal atresia and gastroschisis
      ii. Premature atrophy or abnormal persistence of the right umbilical vein
      iii. In utero rupture of a hernia of the umbilical cord
      iv. Young maternal age (<20 years of age): the most striking epidemiological association with gastroschisis (20–25%)
      v. Primiparous mothers
      vi. Socially disadvantaged mothers
      vii. Use of vasoactive drugs (e.g., decongestant pseudoephedrine) early in pregnancy
      viii. Use of aspirin and decongestants
      ix. Recreational drug use (particularly the use of more than one drug)
      x. Low socioeconomic status
      xi. Maternal nutrition
      xii. Living in close proximity to landfill sites
      xiii. Other novel risk factors
         a) Prior history of gynecological infection/disease
         b) Change of paternity
         c) Paternal age
4. Rare syndrome association
   a. Omphalocele-exstrophy-imperforate anus-spinal defects (OEIS)
   b. Amniotic band syndrome
   c. Limb-body wall complex

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5. Rare association with chromosome abnormalities
   a. Trisomy 21
   b. Trisomy 13

Clinical Features

1. Herniation of abdominal contents
   a. Through a small abdominal wall defect
      i. Lateral to the insertion of the umbilical cord
      ii. Most often to the right side of the umbilical cord
   b. Without covering sac
   c. The herniated viscera floating freely in the amniotic cavity
   d. Rare extrusion of the liver
   e. Dilatation of bowel loops due to partial lymphatic and venous obstruction when they are mechanically compressed against the sidewall of the defect
   f. Massive dilatation of the bowel secondary to volvulus, atresia, and ischemia
2. The incidence of associated anomalies relatively infrequent except associated gastrointestinal anomalies (10–20%)
   a. Intestinal stenosis/atresia, often related to:
      i. Intrauterine volvulus
      ii. Strangulation of the blood supply to the extruded segment of intestine at the extremely tight abdominal wall defect
   b. Adhesions
   c. Malabsorption
   d. Meckel diverticulum
   e. Protein-loosing enteropathy
   f. Midgut volvulus
   g. Necrosis
   h. Severe short gut syndrome
   i. Hypoperistalsis
3. Prognosis and complications
   a. Oligohydramnios
      i. Associated with a high incidence of intrauterine growth retardation which occurs in up to 60% of affected fetuses
      ii. Possible secondary effects of severe oligohydramnios
         a) Pulmonary hypoplasia
         b) Limb compression
         c) Cord compression
   b. Polyhydramnios probably associated with reduced bowel motility or bowel obstruction
   c. Fetal distress during labor
   d. IUGR
   e. Small for gestational age
   f. Prematurity
   g. Sepsis
   h. Bowel damage
   i. Cardiac anomalies
   j. Non-gastrointestinal-associated anomalies including occasional occurrence of amyoplasia and arthrogryposis
   k. Problems with absorptive and motility functions
   l. Intraoperative complications
   m. Greater than 90% survival rate (Baerg et al. 2003)
   n. Higher mortality rate (50%) associated with herniation of the liver
   o. Rare reports of spontaneous resolution of gastroschisis and closure of the anterior abdominal wall defect
4. Outcomes in neonates with gastroschisis in US children's hospitals (Lao et al. 2010)
   a. Critical comorbidities and procedures
      i. Cardiovascular defects (15%)
      ii. Pulmonary conditions (5%)
      iii. Intestinal atresia (11%)
      iv. Intestinal resection (12.5%)
      v. Ostomy formation (8.3%)
   b. Factors associated with mortality
      i. Large bowel resection (odds ratio 8.26)
      ii. Congenital circulatory disease (odds ratio 5.62)
      iii. Pulmonary disease (odds ratio 8.22)
      iv. Sepsis (odds ratio 3.87)
   c. Factors associated with sepsis
      i. Intestinal ostomy (odds ratio 2.94)
      ii. Respiratory failure (odds ratio 2.48)
      iii. Congenital circulatory anomalies (odds ratio 1.58)
      iv. Necrotizing enterocolitis (odds ratio 4.38)
5. Differential diagnosis (Nichol et al. 2008)
   a. Omphalocele
      i. Characterized by its involvement of the cord insertion and surrounding membrane.
      ii. The distinction is important given the higher risk for chromosomal and other anomalies in omphalocele.
      iii. The rare finding of a ruptured omphalocele may be very difficult to distinguish from a gastroschisis in utero.

b. Limb-body wall and body-wall complex
   i. Both may involve defects of the ventral body wall, often large and asymmetric, and often involving multiple organs including the liver.
   ii. The lack of a free-floating umbilical cord and scoliosis, with or without limb defects, will suggest this diagnosis.
c. Amniotic band syndrome
   i. Amniotic band syndrome is often difficult to distinguish from body-wall complex.
   ii. Frequently, will also involve severe anomalies of the craniofacial area.
   iii. Like limb-body wall complex, may involve adhesion to the placenta.

Diagnostic Investigations

1. Routine blood work
2. Chromosome analysis rarely indicated (incidence of chromosomal anomalies <5%)
3. Abdominal radiography
4. Abdominal ultrasound
5. Gastrointestinal investigations to rule out gastroesophageal reflux, abnormal intestinal absorption and motility, and Hirschsprung disease
6. Echocardiography

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: The sibling recurrence risk is estimated to be 3.5% (familial occurrence of gastroschisis has been reported) (Torfs and Curry 1993) unless a parent is affected with an autosomal dominant disorder.
   b. Patient's offspring: The offspring recurrence risk is not increased unless the patient is affected with an autosomal dominant disorder.
2. Prenatal diagnosis
   a. Elevated maternal serum alpha-fetoprotein (MSAFP): MSAFP levels are greater in gastroschisis than in omphalocele.
   b. Prenatal ultrasonography
      i. Demonstration of a mass adjacent to the anterior ventral wall representing the herniated viscera
      ii. Herniation almost always exits through the right rather than the left lower quadrant.
      iii. Cord vessels observed to the left of the exiting bowel
      iv. Dilated bowel loops within or outside the abdomen observed when the abdominal wall defect is small
      v. Possible evisceration of stomach
      vi. Possible evisceration of the urinary bladder with secondary hydronephrosis
      vii. Polyhydramnios associated with bowel obstruction
   c. Amniocentesis
      i. Elevated amniotic fluid alpha-fetoprotein
      ii. Positive acetylcholinesterase
      iii. Chromosome analysis
3. Management
   a. Counseling of parents (Hunter and Soothill 2002)
      i. Inform 5–10% incidence of fetal or neonatal death
      ii. Inform long-term digestion problems associated with short gut syndrome
   b. No clear evidence indicating early cesarean section improves the outcome
   c. Endotracheal intubation for respiratory distress in neonates
   d. Avoid hypothermia, hypovolemia, and sepsis
   e. Fluid and electrolyte balance to prevent metabolic acidosis commonly observed as a result of poor perfusion related to hypovolemia
   f. Insertion of an orogastric tube
      i. To prevent air swallowing
      ii. To aspirate intestinal contents
   g. Parenteral antibiotics
   h. Surgical repair: primary repair versus staged repair with silastic silo
   i. Total parenteral nutritional support for prolonged adynamic ileus
   j. Potential need for organ transplantation (Mian et al. 2008)

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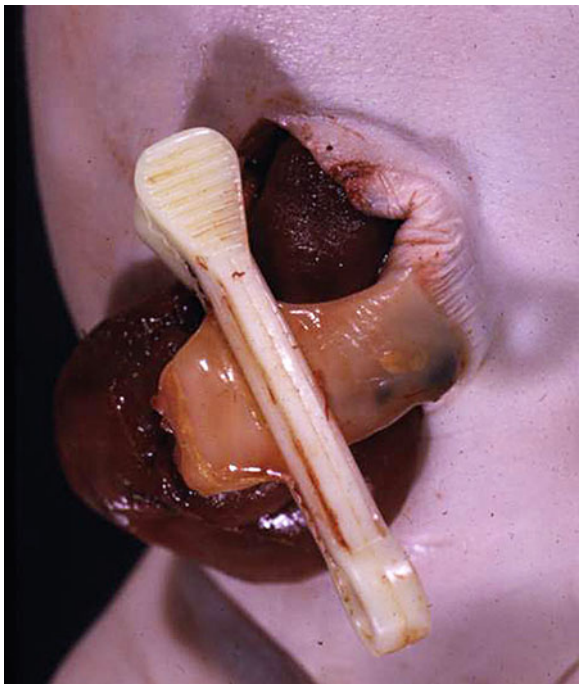

Fig. 1 A premature neonate had herniation of gastric antrum, small intestine, and colon through the gastroschisis, right of intact umbilicus. There was malrotation of the intestine

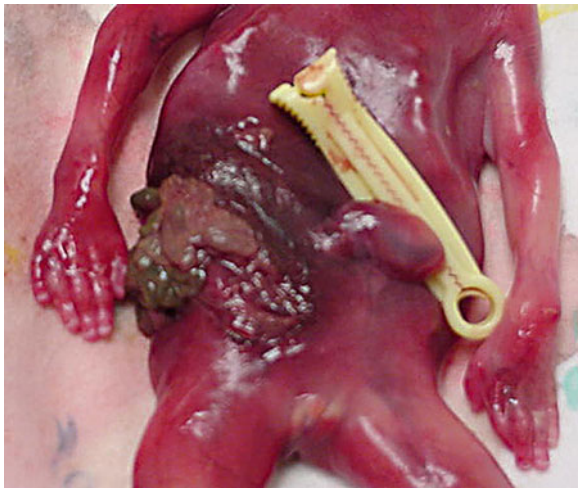

Fig. 2 A stillborn with gastroschisis showing herniation of abdominal contents

Gaucher Disease

Gaucherdisease is the most common lysosomal storage disease and the most common genetic disorder among Ashkenazi Jews. The disease incidence in the Ashkenazi population in Israel is 1 in 7,750 to 1 in 10,000. The disease frequency in the Caucasian population is approximately 1 in 50,000 live births (Grabowski 2000).

Synonyms and Related Disorders

Acid beta-glucocerebrosidase deficiency; Gaucher disease type 1 (non-neuropathic type); Gaucher disease type 2 (acute neuropathic type); Gaucher disease type 3 (chronic neuropathic type); Gaucher disease type 4 (cardiovascular type); Glucocerebrosidase deficiency; Perinatal lethal Gaucher disease (collodion type)

Genetics/Basic Defects

1. Inheritance
   a. Autosomal recessive
   b. The gene encoding β-glucocerebrosidase (acid β-glucosidase) mapped to 1q21
2. Caused by mutation in the glucocerebrosidase (*GBA*) gene that results in deficiency of β-glucocerebrosidase activity
   a. Over 200 different mutations reported.
   b. Four common mutations (N370S, L444P, 84GG, IVS2 + 1).
      i. Account for about 90% of the disease-causing alleles in the Ashkenazi Jewish population.
      ii. Account for 50–60% of the disease-causing alleles in the non-Jewish population.
      iii. Presence of the common N370S precludes neuronopathic involvement, also in combination with severe L444P.
   c. Other rare mutations and unique mutations: worldwide differences in genetic mutations.
   d. Genetic heterogeneity results in phenotypic heterogeneity: phenotypic presentation of the same mutation may vary in a wide spectrum: this difference is most possibly related with ethnicity, genetic background, and environmental and nutritional factors (Harmanci and Bayraktar 2008).
3. Consequences of deficient β-glucocerebrosidase activity (Charrow et al. 1998)
   a. Accumulation of glucocerebroside in the lysosomes of monocyte-derived macrophages in the reticuloendothelial system.
   b. Resulting hypersplenism produces progressive anemia and thrombocytopenia.
   c. Accumulation of glucocerebroside in bone marrow resulting in:
      i. Osteopenia
      ii. Lytic bone lesions
      iii. Pathologic fractures
      iv. Chronic bone pain
      v. Acute episodes of excruciating "bone crisis"
      vi. Bone infarct
      vii. Osteonecrosis

Clinical Features

1. Notable for marked phenotypic variability
2. Type 1 (non-neuronopathic type)
   a. Adult or chronic form: the most common form

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b. Representing about 85% of cases with Gaucher disease
c. Wide range of age of onset and rate of progression
   i. Ranging from disability in toddlers to asymptomatic disease in octogenarians
   ii. The mean age at diagnosis: 21 years
d. Skeletal involvement (Charrow et al. 1998)
   i. Clinical or radiographic evidence of bone disease in 70–100% of patients with type 1 Gaucher disease.
   ii. May be the most debilitating and disabling aspect of type 1 Gaucher disease, leading to:
      a) Bone marrow infiltration by Gaucher cells
      b) Failure of remodeling
      c) Osteopenia
      d) Focal lytic or sclerotic lesions
      e) Osteonecrosis
      f) Osteomyelitis and bone crisis
      g) Chronic bone pain
      h) Pathologic fractures
e. Hepatosplenomegaly
   i. Enlarged spleen with resultant hypersplenism associated with pancytopenia.
   ii. Infarction of the spleen resulting in acute abdominal pain.
   iii. Rare acute surgical emergencies because of splenic rupture.
   iv. Hepatomegaly common but cirrhosis and hepatic failure rare.
f. Pancytopenia
   i. Anemia secondary to the following cause:
      a) Hemolysis secondary to hypersplenism
      b) Hemodilution such as pregnancy
      c) Splenic sequestration
      d) Depressed erythropoiesis due to bone marrow failure from Gaucher cell infiltration or medullary infarction (in advanced cases, particularly postsplenectomy)
   ii. Leukopenia
      a) Commonly noted
      b) Rarely severe enough to contribute to recurrent infections
      c) Risk of infection compounded by chemotactic defects in leukopenic patients
   iii. Thrombocytopenia
      a) Resulting from hypersplenism, splenic pooling of platelets, or marrow infiltration of Gaucher cells or infarction.
      b) Associated with easy bruising or overt bleeding, particularly with trauma, surgery, or pregnancy.
      c) The risk of bleeding increases when there are concomitant clotting abnormalities.
g. Pulmonary disease
   i. Interstitial lung disease
   ii. Alveolar/lobar consolidation
   iii. Pulmonary hypertension
   iv. Hepatopulmonary syndrome
      a) Dyspnea
      b) Cyanosis with digital clubbing
      c) Liver dysfunction
h. Cholelithiasis in adult patients (32%)
i. Cardiac and renal complications rarely encountered
j. Neurological complications secondary to bone disease
   i. Severe osteopenia with vertebral compression.
   ii. Emboli following long bone fracture.
   iii. Coagulopathy secondary to hematomyelia.
   iv. Parkinsonian features in a few patients: uncertain cause-and-effect relationship or just a coincidence.
k. Absence of primary central nervous system disease

3. Type 2 (acute neuronopathic type)
   a. Infantile form: the rarest and most severe form of the disease
   b. Representing about 10% of cases with Gaucher disease
   c. Onset before age 2 years, mostly symptomatic by age 6 months
   d. Normal at birth
   e. Development of hepatosplenomegaly
   f. Regression of developmental milestones
   g. Arrest of growth
   h. Bulbar signs
      i. Stridor
      ii. Squint
      iii. Swallowing difficulty
   i. Pyramidal signs
      i. Opisthotonus
      ii. Head retroflexion
      iii. Spasticity
      iv. Trismus
   j. Oculomotor abnormalities
      i. Oculomotor apraxia
      ii. Saccadic initiation failure

iii. Opticokinetic nystagmus
iv. Strabismus

k. Collodion baby phenotype (congenital ichthyosis) in some neonates
l. Perinatal lethal Gaucher disease: a subset of type 2 or a specific clinical entity (Mignot et al. 2003)
i. Lethality of a homozygous null mutation reported
ii. Non-neurological involvement
a) Nonimmune hydrops fetalis
b) Prematurity
c) Fetal demise or death usually occurring within 2 days to 3 months
d) Hepatosplenomegaly (92%)
e) Thrombocytopenia (38%) associated with purpura (22%)
f) Anemia (10%)
g) Neonatal ichthyosis/collodion baby phenotype (41%)
h) Bone marrow invasion by Gaucher cells, a constant finding at autopsy
iii. Neurological involvement
a) Neurologic signs overlapping with classical type 2 Gaucher disease.
b) Hypokinesia (43%) with facial dysmorphology.
c) Contractures of distal joints (club foot, camptodactyly) (30%).
m. Universally progressive and fatal, succumb to apnea or aspiration by age 2–4 years

4. Type 3 (chronic neuronopathic type)
a. Juvenile form: presenting in childhood or early adulthood
b. Observed primarily in a cluster of cases from Sweden (Norrbottenian type) but may occur in other ethnic groups
c. Hepatosplenomegaly
d. Anemia
e. Thrombocytopenia
f. Bony involvement
g. Pulmonary infiltrates and esophageal varices associated with liver cirrhosis
h. Neurologic disease
i. Supranuclear gaze palsy
ii. Seizures in some patients
a) Generalized tonic-clonic seizures
b) Progressive myoclonic epilepsy
iii. Advanced stage
a) Dementia
b) Ataxia
i. Lifespan extending into the third to fourth decade

5. Type 4 (cardiovascular type)
a. Calcification of the aortic and mitral valves
b. Mild splenomegaly
c. Corneal opacities
d. Supranuclear ophthalmoplegia

Diagnostic Investigations

1. General clinical laboratory blood tests (Charrow et al. 1998)
a. Hemoglobin concentration for anemia.
b. Platelet count for thrombocytopenia.
c. Liver enzymes for liver disease.
d. Iron, ferritin, and total iron-binding capacity for coexistent iron deficiency or iron overload.
e. Prothrombin time and activated partial thromboplastin time for:
i. Clotting defects associated with liver disease.
ii. Factors IX and Factor X deficiency with Gaucher disease.
iii. Factor XI deficiency that may cosegregate with Gaucher disease among Ashkenazi Jewish population.
f. Alkaline phosphatase, serum calcium, phosphorous, and 24-h urinary calcium for markers of bone involvement and defects in calcium absorption and metabolism.
g. Total and direct bilirubin, and total protein and albumin for monitoring liver function.
h. Serum protein electrophoresis and serum immunoelectrophoresis for detecting monoclonal gammopathies that may be more common in adult patients with Gaucher disease than in the general population.
i. Plasma chitotriosidase (markedly elevated in plasma).

2. Abdominal ultrasound
a. Assessing organ volume and parenchymal abnormalities
b. Gallstone detection

3. Brainstem auditory evoked response (BAER) for abnormal wave form in type 2 and type 3
4. Bone densitometry for quantitative assessment of osteopenia

5. Radiography (Wenstrup et al. 2002)
   a. Erlenmeyer flask deformity
      i. Common but not pathognomonic finding.
      ii. Deformity resulting from the impairment of remodeling of the metaphyseal region of tubular bones.
      iii. Manifesting as a flaring of the distal lateral aspects of the femur and proximal tibia.
   b. Lytic lesions
   c. Osteosclerosis due to aberrant remodeling after bone infarction with deposition of calcium
   d. Generalized osteopenia
      i. Nearly universal in children and adults with Gaucher disease.
      ii. Associated with increased risk of bone fractures.
   e. Osteonecrosis (avascular necrosis)
      i. Believed to be secondary to chronic infarction.
      ii. Affecting primarily the femoral head, proximal humerus, and vertebral bodies.
      iii. Resulting in fracture and joint collapse.
   f. Fractures
   g. Bone marrow infiltration
6. MRI
   a. Extent of marrow involvement
   b. Fibrosis and/or infarction
   c. Cerebral atrophy
7. Bone marrow aspiration (Pastores and Hughes 2011)
   a. Presence of lipid-engorged macrophages ("Gaucher cells").
      i. Fibrillary, "crumpled silk" appearance to the cytoplasm.
      ii. Eccentrically placed nucleus.
      iii. Stained positively with periodic acid-Schiff (PAS) reagent.
   b. Not a mandatory test since the bone marrow findings are nonspecific changes and not reliable.
8. Assay of acid β-glucocerebrosidase enzyme activity in peripheral blood leukocytes, lymphoblasts, cultured fibroblasts, amniocytes, and chorionic villi samples (Pastores and Hughes 2011)
   a. The most efficient and confirmatory diagnostic test.
   b. Affected individuals: 0–15% of normal activity.
   c. Individuals with type 1 Gaucher disease: 10–15% of normal activity.
   d. Individuals with type 2 Gaucher disease: $\leq$10% of normal value.
   e. Unreliable for carrier detection since the values overlap in carriers and noncarriers.
9. Molecular genetic testing to identify two disease-causing alleles providing additional confirmation of the diagnosis (Pastores and Hughes 2011)
   a. Targeted mutation analysis
   b. Sequence analysis

Genetic Counseling

1. Recurrence risk (Pastores and Hughes 2011)
   a. Patient's parents
      i. Heterozygotes (carrying a single copy of a disease-causing mutation in the *GBA* gene) in most instances
      ii. Asymptomatic
      iii. A homozygous parent possible.
         a) High carrier frequency in certain population (approximately 1 in 18 in Ashkenazi Jews population)
         b) Variable phenotype with the N370S/N370S genotype
   b. Patient's sib
      i. 25% affected, given the parents are carriers.
      ii. 50% affected when one of the parents is a homozygote and the other a heterozygote.
   c. Patient's offspring
      i. When the spouse is not a carrier: all offspring obligate heterozygotes.
      ii. When the spouse is a carrier: 50% of offspring affected and 50% of offspring carriers.
2. Prenatal diagnosis
   a. Prenatal ultrasound findings in perinatal lethal Gaucher disease (Rowlands and Murray 1997)
      i. Nonimmune hydrops fetalis
      ii. Hepatosplenomegaly
      iii. Abnormal fetal movements, posture, and tone
   b. Available to pregnancies at increased risk
      i. Highly useful to predict non-neuronopathic disease with assurance.
      ii. Overall difficulty in predicting disease progression adding complexity.

c. Analysis of β-glucocerebrosidase enzymatic activity (0–15% of normal), performed on fetal cells obtained by:
   i. CVS cells
   ii. Amniocytes
d. Mutation analysis of the *GBA* gene when the disease-causing *GBA* mutations have been identified in both parents or a prior affected sibling, performed on fetal cells obtained by:
   i. CVS cells
   ii. Amniocytes
e. Preimplantation genetic diagnosis (PGD) (Altarescu et al. 2010)
   i. In the case of type 1 Gaucher disease, PGD might be considered because it obviates the ethical dilemma of pregnancy termination should the fetus be affected.
   ii. PGD is possible for at-risk pregnancies provided the disease-causing mutations have been previously identified in the family.

3. Management (Pastores and Barnett 2003)
   a. Symptomatic care
      i. Partial or total splenectomy
         a) For patients who have massive splenomegaly with significant infarction and persistent severe thrombocytopenia with high risk of bleeding.
         b) Enzyme replacement therapy alleviates hypersplenism and eliminates the need for splenectomy.
      ii. Transfusion of blood products for severe anemia and bleeding
      iii. Analgesics for bone pain
      iv. Joint replacement surgery to relieve bone pain and restore joint function
      v. Oral bisphosphonates suggested in patients with Gaucher disease and low bone density
   b. Therapy to reduce glucosylceramide accumulation
      i. Bone marrow transplantation
      ii. Enzyme replacement therapy
      iii. Substrate reduction therapy
      iv. Gene therapy
   c. Bone marrow transplantation
      i. Corrects metabolic defect
      ii. Improves blood counts
      iii. Reduces increased liver volume
      iv. Stabilizes bone disease and neurologic disease in a few patients
      v. Limited use in patients with type 1 and type 3 Gaucher disease because of the morbidity and mortality associated with the bone marrow transplantation
      vi. Useful concomitant therapy for patients with chronic neurological Gaucher disease and progressive disease on enzyme replacement therapy
   d. Enzyme replacement therapy (ERT) (Charrow 2009)
      i. Efficacy using alglucerase and imiglucerase (Bembi et al. 2002).
         a) For treating the visceral and hematological aspects of Gaucher disease: improvement in hematologic parameters, normalization of bone marrow fat content, and improved bone mineral content and quality of life.
         b) Treatment responses seen within months.
         c) Effective for halting or reversing the skeletal pathology of Gaucher disease.
         d) The optimal dosage and the response time of ERT for treating the skeletal system, particularly for pediatric patients, are not well defined.
      ii. Intravenous infusions of purified macrophage-targeted human β-glucocerebrosidase.
         a) Alglucerase (Ceredase, Genzyme Corporation), derived from human placenta
         b) Imiglucerase (Cerezyme, Genzyme Corporation), derived from recombinant DNA production methods
      iii. Treatment results (visceral aspects of type 1 and type 3 Gaucher disease).
         a) Breakdown of stored glucocerebroside.
         b) Reduction in liver and spleen size.
         c) Amelioration or resolution of anemia and thrombocytopenia.
         d) Decreased bone pain.
         e) Increased bone mineralization.
         f) Remodeling over a period of several years.
         g) Improved health-related quality of life.

h) IgG antibodies to alglucerase reported to develop in approximately 13% of patients. These antibodies have little clinical effect and diminish with continued therapy in most circumstances. However, the presence of antibodies could be associated with an increased risk of hypersensitivity reactions (Charrow et al. 1998).

iv. Treatment in patients with type 2 Gaucher disease (Charrow et al. 1998).
   a) Limited and disappointing: unaltered ultimate fatal course.
   b) Therapy at birth given to an infant, identified prenatally, failed to alter the inevitable neurologic outcome.
   c) Currently not recommended to treat patients with type 2 Gaucher disease.

v. Currently, no hard data available to show the efficacy of enzyme therapy for reversing existing or rapidly progressing CNS disease in type 3 patients with Gaucher disease.

vi. Effect of enzyme therapy on the cardiac, valvular, and hydrocephalic manifestations of type 4 patients remains unknown.

vii. ERT is a lifelong treatment since withdrawal of therapy inevitably leads to progression of Gaucher disease and the (sometimes rapid) loss of the progress made with ERT.

e. Substrate reduction therapy
   i. Miglustat, a formulation aimed at restoring metabolic homeostasis by limiting the amount of substrate precursor synthesized to a level that can be effectively cleared by the mutant enzyme with residual hydrolytic activity.
   ii. Additional controlled longitudinal studies needed to be undertaken with a larger number of patients not only to determine the biochemical but also clinical long-term outcomes of patients with type 1 Gaucher disease on miglustat therapy (Ficicioglu 2008).

f. The future of Gaucher disease therapy (Harmanci and Bayraktar 2008)
   i. Gene therapy
      a) Neither ERT nor SRT has achieved excellent results in terms of neurological and pulmonary involvement due to problems such as inability to pass through the blood–brain barrier.
      b) Possibility of administration and incorporation of a healthy genome replacing a deficient genome.
      c) In early animal models of gene therapy, the vectors responsible for "infecting" a healthy genome were viruses (adeno-associated virus, leutivirus, and retrovirus). These studies showed promising results for the future (Kim et al. 2004; Enquist et al. 2006; McEachern et al. 2006).
      d) The advantage of gene therapy: its widespread infection of specific targeted cells in the body substantially increasing the enzyme levels to a considerable level.
   ii. Chaperone treatment
      a) Imino sugars: ability to increase the strength of the target enzyme (glucocerebrosidase) (Sawkar et al. 2002).
      b) These chemicals increase the half-life of the enzyme by inhibiting its degradation and by providing stabilization.
      c) Although this option currently does not seem to offer a monotherapy option, chaperones might be an option for combination treatment strategies.

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Fig. 1 A 3-year-old African-American female with Gaucher disease showing hepatosplenomegaly. She had history of "large belly" since she was 6–12 months of age, anemia (hemoglobin of 8.7 g%), and thrombocytopenia (73,000). She had an elevated total acid phosphatase of 29 U/L (2.3–5.0), a very low leukocyte beta-glucocerebrosidase of 0.01 U (0.08–0.35), and "Gaucher cells" in the bone marrow

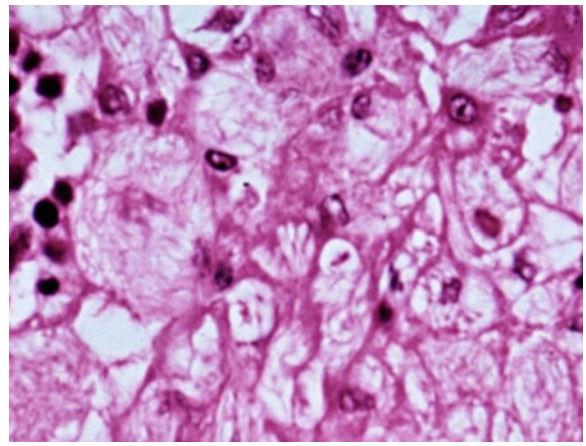

Fig. 2 Bone marrow smear from another patient with Gaucher disease showing extensive infiltration by Gaucher cells (H&E stain)

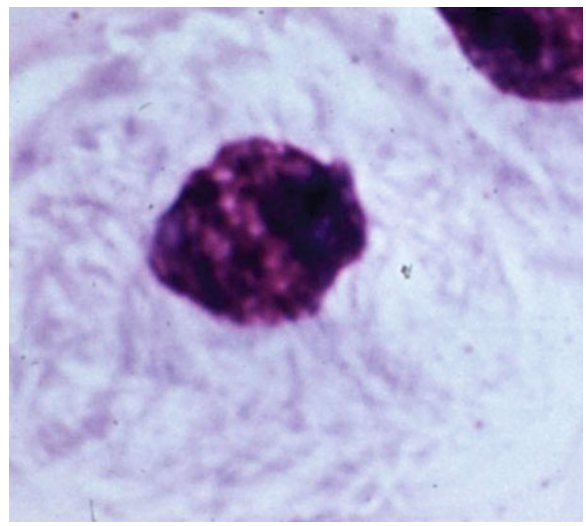

Fig. 3 Higher magnification of bone marrow smear showing a Gaucher cell (Wright-Giemsa stains)

Generalized Arterial Calcification of Infancy

General arterial calcification of infancy is a rare and usually fatal disease. The condition is also called idiopathic arterial calcification of infancy.

Synonyms and Related Disorders

Idiopathic infantile arterial calcification; Infantile occlusive arteriopathy

Genetics/Basic Defects

1. Inheritance: autosomal recessive.
2. Cause (Rutsch et al. 2008).
   a. Loss-of-function mutations in *ENPP1* gene (located on chromosome 6q22–q23) that inactivate ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*).
      i. This cell-surface enzyme generates inorganic pyrophosphate, a solute that regulates cell differentiation and serves as an essential physiologic inhibitor of calcification.
      ii. *ENPP1* coding region mutations are associated with generalized arterial calcification of infancy in ≈75% of subjects.
      iii. This mutation was recently found to also cause autosomal-recessive hypophosphatemic rickets (Lorenz-Depiereux et al. 2010).
   b. Plasma cell membrane glycoprotein-1 (PC-1) deficiency.
      i. Associated with human infantile arterial calcification, especially with periarticular calcification.
      ii. May explain the sharing of certain phenotypic features between some infantile arterial calcification patients and PC-1-deficient mice.
3. Basic defects.
   a. Possibly a defect of elastic fiber.
      i. Occurrence of calcification particularly in the internal elastic lamina.
      ii. Material with the staining properties of mucopolysaccharide accumulates around the elastic fibers.
   b. Fundamental lesions.
      i. A remarkable predilection for mineralization around the internal elastica laminae of medium- to large-sized arteries.
      ii. Narrowing of the arterial lumen due to a marked intimal proliferation.
   c. Pathogenesis.
      i. Incompletely understood.
      ii. Involves calcification (calcium hydroxyapatite deposition) in the internal elastic lamina of large- and medium-sized arteries, associated with a stenosing, fibroproliferative medial smooth muscle cell-mediated process, maximal in the area of the internal elastic lamina.
      iii. Relates to decreased levels of plasma and urinary inorganic pyrophosphate whose role is to inhibit hydroxyapatite crystal deposition in bone and cartilage.

Clinical Features

1. Stormy clinical course.
2. Infant usually thrive normally right after birth.

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3. Thereafter, following symptoms develop rapidly.
   a. Poor feeding.
   b. Vomiting.
   c. Respiratory distress.
      i. Tachypnea.
      ii. Tachycardia.
      iii. Cyanosis.
   d. Hypertension (Van Dyck et al. 1989).
   e. Myocardial infarctions.
   f. Progressive congestive cardiac failure.
4. Prognosis.
   a. Death (sudden death or unexpected infant death).
      i. Usually occurring during early infancy secondary to coronary insufficiency.
      ii. 85% of cases dying before 6 months of age (Byard 1996).
      iii. Causes of death.
         a) Vascular occlusion due to extensive calcification of the arterial media associated with intimal proliferation.
         b) Other complications of obstructive arteriopathy including renal artery stenosis.
         c) Ischemic myocardial ischemia/cardiomyopathy resulting in refractory heart failure.
   b. Rare regression of calcification and prolonged survival (Ciana et al. 2006): Once the severe circulatory problems of infancy are overcome, disease prognosis may be better than previously thought.

Diagnostic Investigations

1. Blood workup.
   a. Normal calcium levels.
   b. Normal phosphate levels.
2. Radiography.
   a. Demonstration of the calcified arteries, leading to possible diagnosis of the condition during life.
   b. Extensive vascular calcification.
      i. Upper and lower limbs.
      ii. Neck.
      iii. Subclavicular fossae.
      iv. Axillae.
   c. Periarticular calcification and stippled calcification of the epiphyseal cartilage.
   d. Cardiac enlargement.
3. ECG changes suggesting.
   a. Coronary occlusion.
   b. Myocardial infarct.
4. Echocardiography to demonstrate coronary calcification.
5. Aortogram showing striking obliterations of the peripheral vessels.
6. Biopsies of peripheral arteries showing extensive intimal mineralization.
7. Postmortem gross pathological findings usually limited to the cardiovascular system.
   a. An enlarged heart.
   b. Focal calcifications of coronary arteries and other peripheral arteries.
   c. Pale or mottled areas of the myocardium or other viscera indicative of infarction.
8. Histopathology.
   a. Extensive mineralization (calcium hydroxyapatite deposition) of arteries.
      i. Usually noted around the internal elastic lamina of the medium-sized arteries.
      ii. Often accompanied by a marked intimal hyperplasia causing luminal narrowing.
      iii. Tends to be most severe in the coronary arteries.
         a) Resulting in myocardial ischemia and infarction.
         b) Death usually attributable to myocardial infarction or heart failure.
   b. Involvement of a variety of arteries.
      i. Aorta.
      ii. Pulmonary arteries.
      iii. Carotid arteries.
      iv. Iliac arteries.
      v. Femoral arteries.
      vi. Visceral arteries.
      vii. Limb arteries.
      viii. Vessels of the brain usually not affected.
   c. Cardiac abnormalities.
      i. Left or biventricular hypertrophy.
      ii. Fibrointimal thickening.
      iii. Calcification of the coronary arteries.
      iv. Endocardial fibroelastosis.
      v. Widespread ischemic myocardial damage.

   d. Generalized arterial calcification of infancy generally indistinguishable from the following conditions.
      i. Metastatic calcification of arteries secondary to advanced renal disease.
      ii. Arterial lesions in hypervitaminosis D or secondary to other toxic agents.
      iii. Hyperparathyroidism of pregnancy.
9. Molecular genetic diagnosis: not yet available clinically (only available in a few research laboratories) (Cheng et al. 2005; Dlamini et al. 2009).

Genetic Counseling

1. Recurrence risk.
   a. Patient's sib: 25%.
   b. Patient's offspring.
      i. Not surviving to reproductive age in majority of patients.
      ii. Low recurrence risk for those who survive.
2. Prenatal diagnosis.
   a. Fetal ultrasonography and radiography to detect calcium hydroxyapatite deposits (echogenic walls of arterial vessels).
      i. Presence of mitralic echogenic foci in the 14th week of gestation (Ciana et al. 2006).
      ii. Echogenic great arteries at 29 weeks of gestation (Reitter et al. 2009).
   b. Fetal echocardiography (Nagar et al. 2003).
      i. Fetal nonimmune hydrops.
      ii. Increased echo (calcific type) density of walls of the fetal aorta, pulmonary arteries, coronary arteries, within the lumen of the heart, and other arterial walls.
      iii. Poor focal contraction of the heart, as a result of the expected accompanying cardiac ischemia due to coronary artery narrowing.
      iv. Dilated cardiac chambers.
      v. Pericardial effusion.
      vi. Hypertrophic cardiomyopathy.
   c. Prenatal diagnosis.
      i. Reference ranges for the disease-related enzymes in amniocytes or fibroblast cultures from CVS have not been established.
      ii. Molecular genetic diagnosis: Prenatal diagnosis may be possible in at-risk families, provided disease-causing mutations have been identified previously.
3. Management.
   a. Therapy with diphosphonates (nonhydrolyzable analogs of inorganic pyrophosphate) (Van Dyck et al. 1989).
      i. Function of diphosphonates.
         a) Simple chemical compounds containing phosphate-carbon-phosphate bonds.
         b) Inhibit the precipitation of several calcium salts in vitro.
         c) Block the conversion of amorphous calcium phosphate into crystalline hydroxyapatite.
         d) Partially converting apatite crystals into a colloidal state with treatment of large amounts of certain diphosphonates.
      ii. Effective in some patients.
         a) Some apparent reduction of calcification.
         b) Usually with persistence of ischemic effects of intimal fibroproliferation.
         c) Except for the p.P305T mutation, which was universally lethal when present on both alleles, the identified *ENPP1* mutations per se have no discernable effect on survival. However, survival seems to be associated with hypophosphatemia linked with hyperphosphaturia and also with bisphosphonate treatment (Rutsch et al. 2008).
         d) Case report by Ramjan et al. 2009: Low-dose disodium pamidronate (0.1 mg/kg per week for 4 weeks), which commenced on the seventh day after birth and was changed to oral risedronate sodium (1 mg/kg per week as a single dose) at 4 weeks of age. Complete resolution of arterial calcification was seen by 3 months of age. Treatment with bisphosphonates is ongoing but is planned to be discontinued at 3 years of age. The child has remained healthy and developmentally normal.
   b. Management of arterial hypertension.
      i. May be refractory to conventional medical therapy.
      ii. Prostaglandin E_1 infusion.

c. Management of myocardial infarctions.
d. In utero diphosphonate etidronate therapy (Stuart et al. 1990; Bellah et al. 1992).
   i. Apparent radiographic and ultrasonographic improvement in the degree of vascular calcification.
   ii. Unable to prevent the lethal progression of intimal vascular occlusive disease.

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Fig. 1 Postmortem picture of a neonate (twin B) with generalized arterial calcification showing ischemic changes of the right arm. The pregnancy was complicated by polyhydramnios. At 2 weeks of age, he was noted to have intercostal retraction and tachypnea with distended abdomen and hepatomegaly

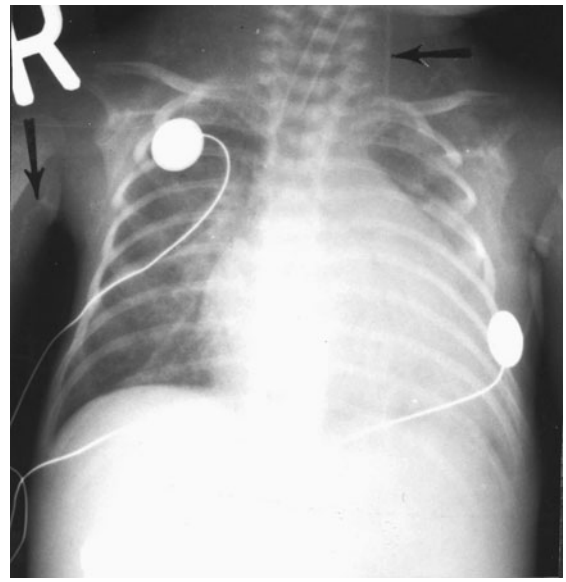

Fig. 2 Radiograph examinations showed extensive vascular calcification extending down the upper and lower limbs, neck, supraclavicular fossae, and axillae. Radiograph here shows an enlarged heart and linear calcification (*arrows*) of the carotid and brachial arteries

Fig. 3 Gross view of vessels, especially the renal arteries, intercostalis, and iliacs, which were hard with mineralization of vessel walls

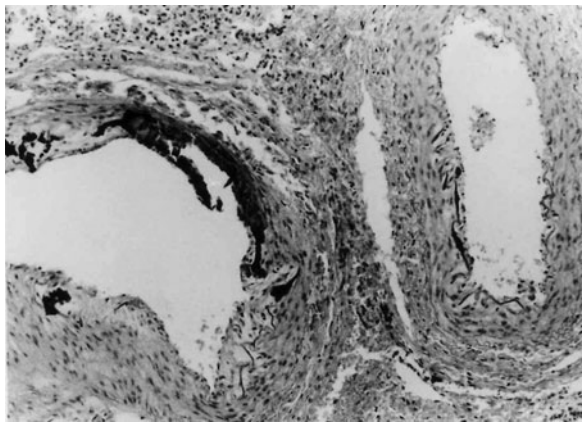

Fig. 4 Artery on the right shows the earliest type of lesion with mild intimal hyperplasia, mild fragmentation, and early mineralization of internal elastic lamina. Artery on the left shows a more advanced lesion with moderate intimal proliferation, moderate fragmentation of internal elastica lamina, and heavy mineralization in and around elastic fibers

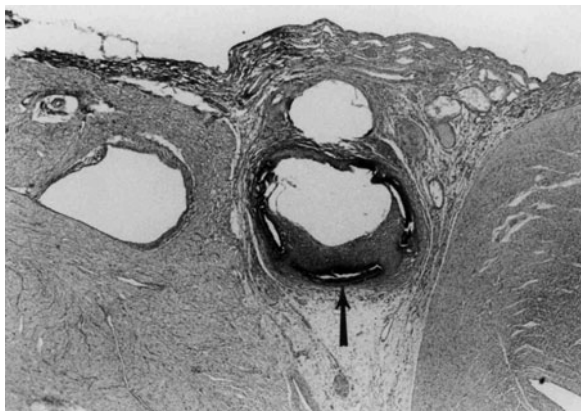

Fig. 5 Advanced mineralization in and around internal elastica lamina (coronary artery)

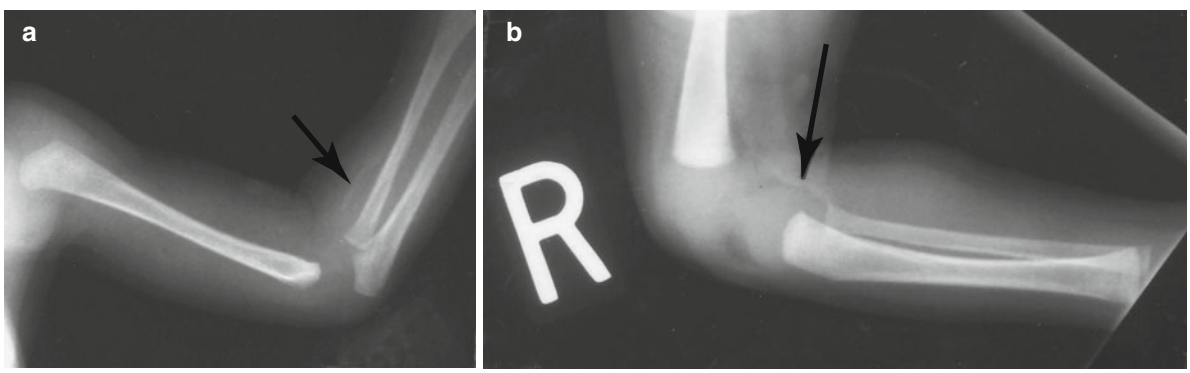

Fig. 6 (**a, b**) Radiographs of twin B show linear calcification (*arrow*) of the radial artery (*upper*) and popliteal artery (*lower*). At 35 days of age, the twin suffered a cardiac arrest and expired shortly thereafter. No autopsy was performed

Genitopatellar Syndrome

In 1988, Goldblatt et al. first reported a 4-year-old boy with hypoplastic patellae, mental retardation, scrotal hypoplasia, skeletal deformities, renal anomalies, flattened nasal bridge, and short stature. Later in 2000, Cormier-Daire et al. reported seven patients with genital anomalies (scrotal hypoplasia and cryptorchidism in the boys and clitoral hypertrophy in the girls), facial dysmorphism, renal anomalies, absent patella, and severe mental retardation in the two survivors. The condition is now known as genitopatellar syndrome.

Synonyms and Related Disorders

Absent patellar, facial dysmorphism, mental retardation, renal anomalies, and scrotal hypoplasia

Genetics/Basic Defects

1. An autosomal recessive inheritance of this condition was proposed (Cormier-Daire et al. 2000).
2. Normal karyotypes and normal array based comparative genome hybridization (aCGH) in all except one case of ovotestes and XY sex reversal in a female with an interstitial 9q33.3–q34.1 deletion encompassing *NR5A1* and *LMX1B* causing features of genitopatellar syndrome (Schlaubitz et al. 2007).
3. No molecular etiology has been identified (Abdul-Rahman et al. 2006; Schlaubitz et al. 2007): Mutations of *LMX1B*, *TBX4*, *WNT4*, and *WNT7A* genes, consistent with nail–patella syndrome, small patella syndrome, and defects in Müllerian ducts and limb development, respectively, were excluded.

Clinical Features

1. Genital anomalies
   a. Males
      i. Scrotal hypoplasia
      ii. Cryptorchidism
      iii. Small penis
   b. Females
      i. Prominent clitoris and labia minora
      ii. Hypoplastic clitoris and labia minora
2. Absent/hypoplastic patella
3. Arthrogryposis
   a. Knees
      i. Flexion contractures
      ii. Skin dimples at the knee
   b. Flexion contractures or dislocation/subluxation of the hips
4. Other skeletal anomalies
   a. Brachydactyly of the upper limbs
   b. Clubfeet
   c. Hypoplasia of pelvic bones
5. Distinctive craniofacial features
   a. Microcephaly
   b. Abnormal skull shape
   c. Hypertelorism
   d. Midfacial hypoplasia
   e. A large, broad nose with a high nasal bridge
   f. Micrognathia

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6. CNS anomalies
   a. Severe psychomotor retardation
   b. Hypotonia
   c. Swallowing and feeding difficulties during neonatal period
   d. Absence of corpus callosum
   e. Colpocephaly
7. Congenital heart defects
   a. VSD
   b. ASD
   c. PDA
   d. PFO
   e. Abnormal aortic arch
8. Renal anomalies
   a. Multicystic kidneys
   b. Hydronephrosis
   c. Large fused kidney
   d. Vesicoureteral reflux
9. Anal atresia or ventral displacement of the anus
10. Mild manifestations of ectodermal dysplasia
    a. Sparse scalp hair
    b. Delayed tooth eruption
11. Severe respiratory problems
    a. Apnea
    b. Pulmonary hypoplasia
12. Hearing loss
13. Differential diagnosis (Lam et al. 2009)
    a. Nail–patella syndrome
       i. Nail dysplasia
       ii. Absent/hypoplastic patella
       iii. Elbow synostosis
       iv. Presence of iliac horns
       v. Nephropathy (glomerular basement membrane)
       vi. Open-angle glaucoma
    b. Short patella syndrome
       i. Caused by *TBX4* gene mutations
       ii. Absent/hypoplastic patella
       iii. Knee contractures
    c. Subtelomeric 1q deletion syndrome causing patellar hypoplasia and limb deformities, features overlapping with genitopatellar syndrome.

Diagnostic Investigations

1. Cranial ultrasound and MRI to detect CNS malformations
2. Radiography for skeletal anomalies and absent patella (for older child)
3. Renal ultrasound for renal anomalies
4. MRI of the patella to ascertain absence of the patella

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: a 25% recurrence risk
   b. Patient's offspring: recurrence risk not increased unless the spouse is a carrier
2. Prenatal diagnosis: has not been accomplished
3. Management: supportive

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Fig. 1 The neonate was a twin A of dizygotic twins, delivered at 29 weeks via emergency C section secondary to suspected chorioamnionitis. The baby was noted to have no scrotal sac with nonpalpable testes. He was noted to have abnormal positioning of the legs with contractures of the hips and the knees and clubfeet. He was also noted to have an imperforate anus with intestinal malrotation which were repaired. Renal ultrasound showed bilateral hydronephrosis

Fig. 2 Craniofacial features were characterized by coarse face, flat occiput, bitemporal narrowing, and a deep crease across the nasal bridge. The neck was short. There were proximal interphalangeal contractures of the digits two to four on both hands, a single flexion crease on the fifth digit. Transverse palmar creases were present bilaterally. MRI of the brain showed absence of the corpus callosum with delayed myelination, prominent DSF spaces in the frontal region, and mega cisterna magna. Chromosome analysis and microarray analysis were normal

Fig. 3 Showed knee dimples with flexion contractures, popliteal webbing, and talipes equinovarus

Fig. 4 Dimples on both knees shown by *black arrows*

Fig. 5 External genitalia showed scrotal hypoplasia and bilateral cryptorchidism

Fig. 6 This photo showed scrotal hypoplasia and imperforate anus

Fig. 7 MRI of the knee showed absence of the patella

Giant Congenital Melanocytic Nevi

Giant congenital melanocytic nevi (GCMN) or giant congenital nevi are rare, congenital, disfiguring lesions present at birth with a risk of degeneration to malignant melanoma (Watt et al. 2004) and may be associated with neurocutaneous melanosis (HCM) (Hale et al. 2005; Ka et al. 2005). The incidence of giant-sized congenital melanocytic nevi greater than 20 cm in diameter was estimated as approximately 1 in 20,000 live births. The larger bathing-trunk variety occurs approximately 1 in 500,000 live births (Castilla et al. 1981).

Synonyms and Related Disorders

Giant congenital nevi

Genetics/Basic Defects

1. GCMN generally occurs in isolation, but rare familial occurrence (Voigtländer and Jung 1974; Hecht et al. 1981; De Wijn et al. 2009) points to a genetic background.
2. Genetic basis of giant nevi.
   a. Concept of paradominant inheritance.
      i. Heterozygous individuals carrying the mutation are phenotypically normal, and the trait would only manifest itself when heterozygosity was lost at an early developmental stage.
      ii. Would explain why lesions occur in a mosaic pattern, occur sporadically, and do not show any consistent pattern of Mendelian inheritance.
      iii. Discordance for giant pigmented nevi in monozygotic twins was reported.
   b. Nevi harboring the BRAFE600 mutation undergo cell cycle arrest and senescence, thus preventing the development of malignancy in these lesions.
   c. Using single-strand conformational polymorphism and sequencing analysis, BRAF and N-ras oncogene mutations were found to be extremely common in individuals with congenital nevi, which could explain the higher risk of developing cutaneous melanoma.
   d. Reports on chromosome abnormalities in GCMNs: infrequent.
      i. Two balanced translocations involving the BRAF gene and one deletion of the long arm of chromosome 6 out of 27 GCMNs (Dessars et al. 2008).
      ii. 22% of mitoses with polyploid and 4% with chromosome rearrangements involving 1p, 12q, and 19p from a single GCMN (Heimann et al. 1993).
   e. The pattern of inheritance (De Wijn et al. 2009).
      i. Likely not Mendelian.
      ii. Discordance in identical twins and the segmental distribution of lesions suggest a postzygotic mutation.
      iii. A polygenic paradominant inheritance best explains the clinically observed transmission pattern.
      iv. Candidate genes include those influencing neural crest development and melanocyte proliferation.
3. Embryological origin of congenital melanocytic nevus.
   a. Not well understood

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b. Hypothesis
   i. Giant congenital nevi develop between the 5th and 25th weeks of gestation.
   ii. Dysregulated growth of melanoblasts occurs secondary to morphogenic errors in neuroectodermal development, resulting in dysregulated migration of melanoblasts from the neural crest to the skin and leptomeninges.

Clinical Features

1. Congenital melanocytic nevi
   a. Definition: benign proliferation of cutaneous melanocytes, clinically apparent at birth or becomes so within the first postnatal weeks.
   b. Incidence: affects approximately 1% of all newborns
   c. Characteristics: vary in size, macroscopic appearance, and histology as a group
   d. Classification of congenital melanocytic nevi based on final size of the nevi:
      i. Small: less than 1.5 cm in diameter
      ii. Intermediate: 1.5–20 cm in diameter
      iii. Giant or large (also called garment or bathing trunk nevi: measuring more than 20 cm in diameter).
2. Giant congenital nevi: classified based on the percentage of body area affected (a congenital nevi covering 1% body surface area in the face and neck and 2% elsewhere on the body)
3. Clinical manifestations of giant congenital nevi
   a. Onset: flat, brown, or brownish-black patches but with increasing age may become elevated and develop a mottled appearance and nodular surface.
   b. Appear darker at birth than a few weeks later.
   c. Found most commonly on the trunk, followed by the limbs and the head.
   d. Giant nevi: almost always confined to the skin but, rarely, invade underlying fascia and muscle.
   e. Most giant CMN involve the trunk and have a predominant bathing suit distribution.
   f. Associated abnormalities (De Wijn et al. 2009).
      i. Neurocutaneous melanosis (Arneja and Gosain 2005)
         a) Characterized by presence of benign or malignant melanocytic proliferations in the CNS in association with a giant CMN or three or more smaller melanocytic nevi (Kadonaga and Frieden 1991).
         b) Signs and symptoms of symptomatic neurocutaneous melanosis (hydrocephalus, seizures, developmental delay, cranial nerve palsies, or a tethered spinal cord) (Foster et al. 2001).
         c) Almost all children with neurocutaneous melanosis have giant nevi on the head, neck, or dorsal spine.
      ii. Structural brain abnormalities
         a) Dandy-Walker malformation
         b) Hemimegalencephalopathy
         c) Meningohydroencephalocele
         d) Lissencephaly
         e) Microcephaly
         f) Spina bifida oculta
      iii. Polydactyly
      iv. Linear epidermal nevus syndrome
      v. Segmental neurofibromatosis
      vi. Encephalocraniocutaneous lipomatosis
      vii. General lipomatosis
      viii. Placental nevomelanocytosis
      ix. Hirschsprung disease
      x. Hypotrophy of the underlying bone or subcutaneous fat (limb hypoplasia)
      xi. Ear deformities
      xii. Angiomas
4. Prognosis
   a. Usually disfiguring.
   b. The lifetime risk for development of malignant melanoma in giant congenital nevi: approximately 4–42% (about a 14-fold increased risk of developing cutaneous and extracutaneous melanoma) (Trozak et al. 1975; Baader et al. 1992).
   c. Giant nevi on the scalp in a posterior axial location and those with surrounding satellite nevi are at greatest risk of malignant transformation.
5. Neonatal malignant melanoma (Leech et al. 2004)
   a. Extremely rare
   b. Develops within a giant congenital nevus or preexisting nevus
   c. Can occur de novo on apparently normal skin
   d. Arises from maternal malignant melanoma via placental metastases
   e. May metastasize or spread locally

f. Notoriously difficult to diagnose in children, especially neonates
   i. Clinical indicators such as changes in color, size, shape, rapid growth rate, nodularity, and even ulceration may occur in benignly evolving GCNs.
   ii. Histologic features accepted as evidence of malignancy in an adult, such as mitotic activity, nuclear pleomorphism, and pagetoid melanocytic proliferation, may also be present in benign lesions in infants.
   iii. Morphologic findings of melanocytic lesions from frozen tissue specimen cannot be confidently interpreted.

Diagnostic Investigations

1. Biopsies
   a. Probably only useful in clarifying the nature of pathological changes that occur in discrete areas of these nevi.
   b. Sampling of multiple areas required when there is a question of malignant change.
2. Magnetic resonance imaging (MRI)
   a. Highly sensitive in detecting melanin, which produces short T1 and T2 relaxation times due to interactions of unpaired electrons in the stable free radicals of melanin with the protons of free water.
   b. Can delineate the extent of underlying soft tissue involvement and assist in preoperative planning.
   c. Neither the location nor the size of the nevus appears to correlate completely with the presence or absence of MRI abnormalities suggestive of CNS melanosis.
   d. Foci of melanosis generally became more difficult to detect on follow-up images, which may be related to changes in the signal intensity of the brain that accompany myelination.
   e. Recommend MR imaging in addition to ongoing developmental and neurological evaluations to help identify individuals who are at greater risk for CNS disease, as well as encourage MR imaging for those with giant nevi in the lumbosacral region.
3. Positron emission tomography (Makosz et al. 2004)
   a. To detect occult primary melanoma as well as melanoma metastases within the nevi
   b. May play an important role in long-term monitoring and management of these patients
4. Dermoscopy (episcopy, dermatoscopy, skin surface microscopy, epiluminescence microscopy): allows in vivo visualization of anatomical pigmented structures in the epidermis, dermoepidermal junction, and superficial papillary dermis not usually seen by the naked eye (Lodha et al. 2003).

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: increased but exact risk not known
   b. Patient's offspring: increased but exact risk not known
2. Prenatal diagnosis: not reported but possible by fetoscopy (an invasive procedure)
3. Management
   a. Early and complete surgical excision is recommended because of an increased lifetime risk of malignancy.
   b. The surgical and reconstructive options for congenital melanocytic nevus are varied depending on the size and location of the nevus (Pearson et al. 2005).
      i. Laser treatment: the results for congenital nevus have been unsuccessful because the deeper portions of the nevi are unaffected by the laser.
      ii. Dermabrasion.
         a) Plagued by recurrence if performed too superficially and hypertrophic scar if performed too deep.
         b) Produces uneven changes in the pigmentation of the skin because the melanocytic cells are found at varying depths in the dermis; dermabrasion produces uneven changes in the pigmentation of the skin.
         c) Dermabrasion has been abandoned for the treatment of nevi.
      iii. Excision.
         a) Excision followed by primary closure: a frequently used technique
         b) Caution not to distort important structures such as oral commissure, eyelids, and eyebrows

iv. Stage excision.
   a) Consider when the resultant wound is too large to close or places excessive tension along the closure, increasing the risk of wound dehiscence
   b) An outpatient procedure involving less postoperative care and expense

v. Skin grafting.
   a) A useful tool in the management of medium to large congenital nevi.
   b) Avoid split-thickness skin grafting because of the potential for an unsightly donor site and a greater need for inpatient care or a more complicated outpatient experience.
   c) Consider full-thickness grafts to allow for an acceptable donor site and less postoperative care.
   d) Considered in areas of the body of lesser esthetic importance.

vi. Tissue expansion.
   a) Commonly used when a nevus is too large for primary closure: serial excision will produce residual deformity on the adjacent structures, or skin grafting will produce an undesirable esthetic result.
   b) The ability to replace tissue with like tissue, such as hair-bearing scalp with hair-bearing scalp, typically allows an acceptable esthetic result.
   c) The drawbacks include multiple operations (placement followed by removal and advancement), difficulty in expanding axial portions of the body, the weekly clinical visits for expansion, discomfort for the child during the expansion process, and the esthetic deformity produced during the expansion process.

vii. Cultured epithelial autograft.
   a) Represents another reconstructive option
   b) Requires a tissue sample from the patient, several weeks for cellular production, and final placement
   c) Cultured epithelia autograft's application to giant congenital nevi: natural as in the burn treatment of large total body surface area burn
   d) Can be used for giant nevi that preclude the use of tissue expansion or skin grafting secondary to lack of donor site availability
   e) Definite shortcomings: including expense, time required for manufacturing of the graft (less of a limiting factor in children with nevi), and durability
   f) Preferred procedure to split-thickness skin grafting because no donor site morbidity exists, decreased blood loss occurs, a greater area of excision with resultant faster removal of a nevus can be accomplished, and the durability of the cultured epithelia autograft compares favorably with a split-thickness graft

viii. Enzymatically separated epidermal grafting (Kishi et al. 2009).
   a) A useful method for the treatment of GCMN
   b) Easy to perform
   c) Cosmetically satisfactory results

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Fig. 1 (**a**–**c**) A newborn with multiple congenital nevi scattered throughout the body including a giant one on the right anterior chest

Fig. 2 (**a**–**d**) A neonate with a bathing-trunk nevus, extending from mid-trunk to knees, with a large unevenly pigmented lesion of the back, buttocks, and upper extremities as well as several nodules and a large hypertrophic area over the sacrum

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme defect, affecting more than 400 million people worldwide, especially in tropical Africa, the Middle East, tropical and subtropical Asia, some areas of the Mediterranean, and Papua New Guinea. The gene frequencies are estimated to be as high as 5–25% in these areas (Luzzatto et al. 2001).

Genetics/Basic Defects

1. Caused by mutations in the G6PD gene (mapped to Xq28 region) (Luzzatto 2006).
   a. About 140 mutations have been described.
   b. Most mutations are single missense point mutations, entailing single amino acid replacements in the G6PD protein.
   c. Few exceptions
      i. Small deletions (of one to eight amino acids)
      ii. Presence of two mutations (rather than one)
2. Inheritance
   a. X-linked recessive in terms of clinical expression
      i. Not truly recessive since heterozygous females can even develop severe hemolytic attacks
      ii. Coexistence in female heterozygotes of two-cell populations, G6PD(+) and G6PD(−), secondary to X-chromosome inactivation
      iii. Homozygous females not rare in many populations with high frequency of G6PD deficiency
   b. Codominant in terms of biochemical characteristics of electrophoretic variants segregating in a pedigree
3. Genetic heterogeneity (Luzzatto et al. 2001)
   a. Diverse biochemical characteristics
      i. Presence of about 400 different variants
      ii. Many allelic mutations in the G6PD gene causing these variants
      iii. Presence of several structural mutants without enzyme deficiency
   b. Heterogeneous molecular characteristics
      i. Some variants with different names proved to be identical.
      ii. Some variants thought to be homogeneous proved to be heterogeneous.
   c. Different mutations responsible for:
      i. Chronic hemolytic anemia: less common
      ii. Episodic hemolysis: more frequently seen
   d. Diverse clinical manifestations, to a large extent, explainable by the genetic heterogeneity
4. Pathogenesis
   a. G6PD
      i. A central enzyme in the pentose phosphate shunt of glucose metabolism
      ii. Catalyzes glucose-6-phosphate (G6P) to 6-phosphogluconic acid (6PG)
      iii. Reduces nicotinamide adenine dinucleotide phosphate (NADP) to the reduced form of NADP (NADPH)
   b. NADPH: converts glutathione disulfide (GSSG) to reduced glutathione (GSH)
   c. Reduced glutathione GSH
      i. Inactivates hydrogen peroxides (H_2O_2)
      ii. Protects protein sulfhydryl groups from oxidation
      iii. Neutralizes agents that threaten to oxidize either hemoglobin or components of the red cell membrane.

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   d. In the absence of G6PD
      i. Red cell membrane and hemoglobin damaged by oxidant exposure
      ii. Leading to rapid hemolysis
5. Hemolysis secondary to inability of G6PD-deficient red cells to withstand the oxidative damage produced, directly or indirectly, by the triggering agents (Luzzatto et al. 2001).
   a. Drugs
   b. Infections
   c. Ingestion of fava beans with life-threatening manifestations especially favism in children
6. G6PD deficiency conferring resistance against *Plasmodium falciparum* malaria based on (Luzzatto et al. 2001)
   a. Prevalence of G6PD deficiency and the past and present endemicity of *Plasmodium falciparum* malaria
   b. The high prevalence in malaria-endemic areas of G6PD mutants
   c. Heterozygote advantage

Clinical Features

1. History
   a. Asymptomatic in the vast majority of G6PD-deficient individuals without being aware of their genetic abnormality
   b. No positive history of acute intravascular hemolytic crises without exposure to oxidant stress
   c. Neonatal jaundice
   d. Chronic hemolytic anemia
      i. An insidious decrease in hemoglobin
      ii. Observed in certain variant enzymes
   e. Required a careful investigation to establish the history of exposure to inciting agents
2. Common clinical manifestations
   a. Neonatal jaundice: may cause permanent neurologic damage or death in some severe cases
   b. Episodes of acute hemolytic anemia
      i. Drug-induced hemolysis
      ii. Infection-induced hemolysis
      iii. Favism: occurrence of acute hemolysis after ingestion of broad beans (*Vicia faba*)
      iv. Chronic nonspherocytic hemolytic anemia
      v. Associated with hemoglobinuria since red cell destruction in these acute hemolytic events is largely intravascular
      vi. Concomitance with a variety of clinical situations, including diabetic ketoacidosis, hypoglycemia, myocardial infarction with pericardial tamponade, and strenuous exercise
   c. Symptoms and signs of acute hemolytic crisis
      i. Headache
      ii. Lethargy
      iii. Pallor
      iv. Jaundice
      v. Red, clear urine
3. Symptoms and signs of chronic hemolytic crisis
   a. Pallor
   b. Jaundice
   c. Severe chronic hemolysis observed in a rare subset of G6PD-deficient patients
4. Drugs responsible for hemolysis (Cappellini and Fiorelli 2008)
   a. Antimalarials
      i. Definite association (primaquine, pamaquine)
      ii. Possible association (chloroquine)
      iii. Doubtful association (quinacrine, quinine)
   b. Sulfonamides
      i. Definite association (sulfanilamide, sulfacetamide, sulfapyridine, sulfamethoxazole)
      ii. Possible association (sulfadimidine, sulfasalazine, glyburide)
      iii. Doubtful association (sulfoxone, sulfadiazine, sulfisoxazole)
   c. Sulfones: definite association (dapsone)
   d. Nitrofurantoin: definite association (nitrofurantoin)
   e. Antipyretic/analgesic
      i. Definite association (acetanilid)
      ii. Possible association (aspirin)
      iii. Doubtful association (acetaminophen, phenacetin)
   f. Other drugs
      i. Definite association (nalidixic acid, niridazole, methylene blue, phenazopyridine, sepirin)
      ii. Possible association (ciprofloxacin, chloramphenicol, vitamin K analogs, ascorbic acid, p-aminosalicylic acid)
      iii. Doubtful association (PAS, doxorbicin, probenecid, dimercaprol)
   g. Other chemicals
      i. Definite association (naphthalene, trinitrotoluene)

a) Development of kernicterus after exposure to naphthalene in the glucose-6-phosphate dehydrogenase Mediterranean polymorphic variant (revealed by mutation analysis) (de Gurrola et al. 2008).
b) As the use of naphthalene in stored clothes is a common practice, glucose-6-phosphate dehydrogenase testing in neonatal screening could prevent severe clinical consequences.

ii. Possible association (*Acalypha indica*)

5. Types of G6PD deficiency (Segel et al. 2002)
   a. X-minus variety
      i. Most common type seen in the USA
      ii. An X-linked condition primarily affecting African-American males
      iii. Females affected if homozygous for G6PD deficiency or if unfavorable random X-chromosome inactivation resulting in a large proportion of deficient red cells.
   b. Mediterranean variety
      i. Develops severe hemolysis when exposed to oxidant drugs
      ii. Characterized by enzyme deficiency in red cells of all ages, including reticulocytes, and shows no evidence of spontaneous recovery.
   c. Other varieties
      i. Develops chronic hemolytic anemia without external oxidant exposure
      ii. Susceptible to develop cholelithiasis because of heightened bilirubin turnover
      iii. Complaints of abdominal pain or fatty food intolerance

Diagnostic Investigations

1. Acute hemolysis (Segel et al. 2002)
   a. Precipitous anemia
      i. A fall in hemoglobin
      ii. A fall in hematocrit
      iii. Subsequent rise in reticulocyte percentage
   b. Elevated bilirubin, particularly the indirect fraction
   c. Reduced haptoglobin as it binds free hemoglobin and is removed from the circulation
   d. Hemoglobinemia +/− hemoglobinuria
2. Diagnosis of G6PD deficiency (Frank 2005; Kaplan and Hammerman 2010)
   a. Rapid fluorescent screening spot test detecting the generation of NADPH (reduced NADP) from NADP
      i. The test is positive if the blood spot fails to fluoresce under ultraviolet light (NADPH fluoresces intensely when activated by long-wave UV light; fluorescence under UV light source is normal and indicates G6PD activity).
      ii. Useful in identifying totally deficient individuals with <20% residual activity
      iii. Could erroneously classify as normal males and females with partial deficiency (20–60% residual enzyme activity)
      iv. Not helpful in identifying most heterozygotes with intermediate levels of G6PD activity
   b. Quantitative analysis of G6PD activity by assessing NADPH formation spectrophotometrically
      i. G6PD-deficient male hemizygotes and female homozygotes: usually <50% normal activity, frequently <20%, and often undetectable (Luzzatto 2006).
      ii. Heterozygous females may have intermediate activity, but this may range from normal to deficient and many female heterozygotes with partial enzyme activity will not be detected.
      iii. Falsely obtaining normal test results during or immediately after an acute hemolytic event
   c. In field research, where quick screening of a large number of patients is needed, other tests have been used; however, they require definitive testing to confirm an abnormal result (Iwai et al. 2003; Jalloh et al. 2004).
   d. Tests based on polymerase chain reaction detect specific mutations and are used for
      i. Population screening
      ii. Family studies
      iii. Prenatal diagnosis
3. Direct DNA analysis
   a. Sequence analysis (analysis of the entire coding region)
   b. Targeted mutation analysis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib (if the mother is a carrier)
      i. 50% of male siblings affected

   ii. 50% of female siblings carriers (some female heterozygotes may be affected)
  b. Patient's offspring
   i. 100% of female offspring carriers (some female heterozygotes may be affected)
   ii. 50% of female offspring affected (homozygotes) if the spouse is a carrier
   iii. Male offspring not affected unless the spouse is a carrier
2. Prenatal diagnosis: may be possible in at-risk families, provided disease-causing mutations have been identified previously
3. Management
  a. Prevent or remove precipitating agents
  b. Phototherapy for neonatal hyperbilirubinemia
  c. Supportive transfusion
  d. Exchange transfusion to prevent kernicterus
  e. Hemodialysis may be necessary if there is acute renal failure.

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Fig. 1 (**a**, **b**) A 1-month-old and a 2-month-old boys with G6PD deficiency who are asymptomatic. The newborn screenings of both boys identified one (hemizygous) copy of the double mutations (G202A; A376G)

Fig. 2 An 8-week-old girl with G6PD deficiency who is asymptomatic. The newborn screening identified compound heterozygote consisting of one copy of the double mutation (G202A; A376G) and one copy of the A378G mutation. This phenotype is seen only in females since this is an X-linked disorder

Fig. 3 A 1-month-old boy with G6PD deficiency who is asymptomatic. The newborn screening revealed G6PD of 3.8 (10.8–16.2 U/g Hb). Molecular analysis showed one copy of A376G mutation

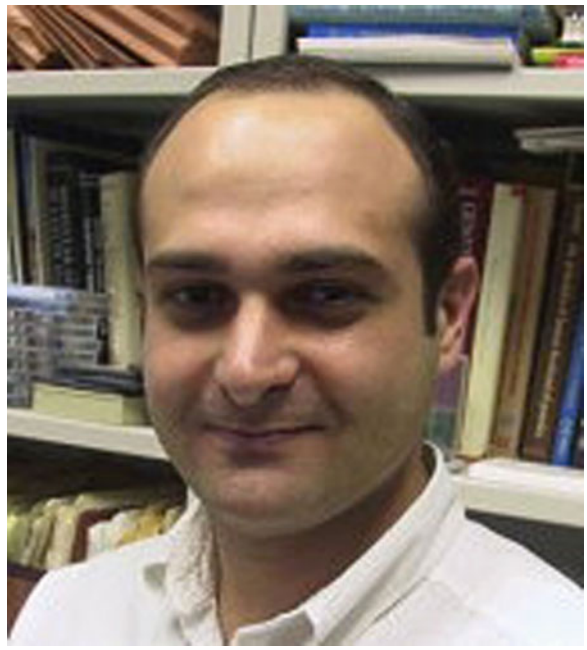

Fig. 4 A patient of Mediterranean ancestry with G6PD deficiency. He has had a history of hemolytic anemia crisis after ingestion of fava bean

Fig. 5 Fava beans

Glycogen Storage Disease, Type II

Type II glycogen storage disease (GSD), also known as Pompe disease, is an autosomal recessive disorder caused by deficiency of the lysosomal enzyme acid α-glucosidase (acid maltase). Incidence is estimated at 1 in 50,000 in most populations, implying a carrier frequency of 1 in 100 (Kleijer et al. 1995).

Synonyms and Related Disorders

Acid maltase deficiency; Glycogenosis type II; Pompe disease

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Kleijer et al. 1995)
2. Caused by deficiency of acid maltase (acid α-glucosidase), leading to the pathological accumulation of glycogen in lysosomes, predominantly in the skeletal muscle, heart, and liver.
   a. Virtual absence of α-glucosidase activity in infantile form (Pompe disease)
   b. Considerable residual enzyme activity in the great majority of patients with the adolescent or adult form
3. Identification of various mutations in the α-glucosidase (*GAA*) gene (mapped on 17q23–25), leading to the disease
   a. Types of mutations
      i. Point mutations
      ii. Deletions
      iii. Insertions
   b. Compound heterozygotes in most patients
   c. Relatively common mutations among European patients
      i. The single base pair deletion ΔT525 causing premature termination at nucleotide 658–660
      ii. Deletion of exon 18
4. Genotype-phenotype correlation
   a. The nature of the mutation is generally considered a good predictor of a clinical phenotype.
   b. Homozygosity for either Δexon 18 or ΔT525 mutation or compound heterozygosity for these two mutations results in a severe infantile form of GSDII.
   c. Combination of either of these mutations with leaky IVS1t-13 g mutation results in the majority of cases in the adult phenotype.
   d. A splicing defect (IVS6 t-22 g) results in a removal of exon 6, and insertion of 21 nucleotides of the intronic sequence defined the juvenile phenotype in a compound heterozygote patient who carries a silent second allele. Homozygosity for the same splicing defect resulted in a milder adult phenotype.
   e. Growing number of cases in recent years where the genotype does not match the phenotype.
5. Pathophysiology (American Association of Neuromuscular and Electrodiagnostic Medicine 2009)
   a. Mutations in both copies of the GAA gene lead to varying degrees of GAA deficiency.
      i. Infantile-onset form: either totally or virtually absent acid α-glucosidase enzyme activity in skin fibroblasts
      ii. Late-onset form: some residual enzyme activity (1 ∼ 40%) in skin fibroblasts in most affected children and adults

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b. Primary defect.
   i. Progressive intralysosomal storage of glycogen
   ii. Recognition of the role of dysfunctional autophagy in the disease process

Clinical Features

1. Infantile form (Raben et al. 2002).
   a. Classical infantile form
      i. Onset within first weeks or months of life or even at birth.
      ii. Characterized by complete or near complete deficiency of α-glucosidase.
      iii. Poor feeding (difficulty sucking and swallowing) and failure to thrive, early complaints.
      iv. Cyanosis and attacks of dyspnea beginning early.
      v. Frequent respiratory infections.
      vi. Delayed motor milestones.
      vii. Cardiomyopathy (hypertrophic) (∼95%): the important finding suggesting diagnosis.
         a) Marked cardiomegaly
         b) Congestive heart failure
      viii. Striking hypotonia.
         a) Increasing generalized weakness
         b) Affecting bulbar musculature
         c) Without muscle atrophy
      ix. Macroglossia (∼62%).
      x. Moderate hepatomegaly (∼82%).
      xi. Calf hypertrophy.
      xii. Depressed or absent reflexes due to glycogen accumulation in spinal motor neurons.
      xiii. Impaired alertness.
      xiv. Accumulation of glycogen in the lysosomes rapidly disrupts cellular function in the most severe form.
         a) Rapidly disrupts cellular function.
         b) Leading to intractable cardiorespiratory failure.
         c) Most patients die by 1 year of age.
   b. Nonclassical infantile form
      i. Onset in infancy
      ii. Slower progression
      iii. Involving primarily skeletal muscle with minimal or no cardiac involvement (without cardiomegaly)
      iv. May present with delayed motor milestones if onset is in early preschool age
      v. May present with a decrease in motor skills if onset is later in childhood
      vi. Usually demonstrates progressive proximal weakness with different degrees of respiratory muscle involvement
      vii. Presence of respiratory complications often contributing to early death
2. Juvenile form.
   a. Juvenile onset (first decade)
   b. Characterized by presence of reduced but residual α-glucosidase activity
   c. Clinical boundaries between juvenile and adult forms not precisely defined
   d. Clinical manifestations
      i. Predominantly skeletal muscle weakness with respiratory muscle involvement and mild hepatomegaly.
      ii. Cardiac involvement: absent or mild.
         a) Arrhythmia
         b) Mild ventricular dysfunction
      iii. Death results from respiratory failure after a course lasting several years.
3. Adult form.
   a. Onset: second to sixth decades
   b. Characterized by higher levels of residual α-glucosidase activity
   c. Slower progression of the skeletal muscle weakness
      i. Upper arms
      ii. Pectoral muscles
      iii. Asymmetry of affected muscle groups
      iv. Limb-girdle weakness, a prominent finding
      v. Respiratory muscle involvement (weakness of the diaphragm) (about 33%): a hallmark of the disease
      vi. Little or no cardiac abnormality
   d. Acute respiratory failure
4. Differential diagnosis of infantile-onset Pompe disease (with respect to shared signs and symptoms) (Kishnani et al. 2006).
   a. Acute Werdnig-Hoffman disease (spinal muscular atrophy I)
      i. Hypotonia
      ii. Progressive proximal myopathy
      iii. Absent reflexes
   b. Hypothyroidism
      i. Hypotonia
      ii. Macroglossia

c. Endocardial fibroelastosis
   i. Breathlessness
   ii. Feeding difficulties
   iii. Cardiomegaly
   iv. Heart failure
d. Myocarditis: cardiomegaly
e. Congenital muscular dystrophy
   i. Severe hypotonia
   ii. Severe muscle weakness
f. Glycogen storage diseases: IIIa (Debrancher deficiency/Cori or Forbes disease) and IV (branching enzyme deficiency/Anderson disease)
   i. Cardiomegaly
   ii. Myopathy
   iii. Elevated creatine kinase (CK)
g. Mitochondrial/respiratory chain disorders
   i. Hepatomegaly
   ii. Muscle weakness
   iii. Cardiomegaly
   iv. Elevated creatine kinase (CK)
h. Danon disease
   i. Cardiomegaly
   ii. Cardiomyopathy
   iii. Myopathy
   iv. Vacuolar glycogen storage
i. Idiopathic hypertrophic cardiomyopathy: biventricular hypertrophy
j. Peroxisomal disorders
   i. Hypotonia
   ii. Hepatomegaly

5. Differential diagnosis of late-onset Pompe disease (Kishnani et al. 2006; American Association of Neuromuscular and Electrodiagnostic Medicine 2009): Heterogeneity of presentation can mimic other neuromuscular disorders, and the differential diagnosis includes a broad range of myopathies, as well as motor neuron and neuromuscular junction disorders (Kishnani et al. 2006).
   a. Dystrophies
      i. Limb-girdle muscular dystrophy: progressive muscle weakness in the pelvis, legs, and shoulders (shared signs and symptoms)
      ii. Dystrophinopathies (Duchenne and Becker muscular dystrophy): progressive proximal muscle weakness, respiratory impairment, difficulty walking, and elevated creatine kinase (CK) (shared signs and symptoms)
      iii. Myofibrillar myopathy
      iv. Myotonic dystrophy type 2
      v. Scapuloperoneal syndromes: progressive muscle weakness behind the knees and around the shoulder blades (shared signs and symptoms)
      vi. Danon disease: hypertrophic cardiomyopathy, skeletal muscle myopathy, and vacuolar glycogen storage (shared signs and symptoms)
      vii. X-linked myopathy with excessive autophagy
      viii. Facioscapulohumeral muscular dystrophy
      ix. Rigid spine syndrome: spinal rigidity and lower back pain (shared signs and symptoms)
   b. Inflammatory myopathies
      i. Polymyositis: unexplained muscle weakness (shared signs and symptoms)
      ii. Inclusion body myositis
   c. Congenital myopathies
      i. Nemaline rod myopathy
      ii. Central core and multiminicore myopathy
      iii. Centronuclear myopathy
      iv. Hyaline body myopathy
      v. Other congenital myopathies
   d. Other metabolic myopathies
      i. Glycogen storage diseases (debranching enzyme deficiency (IIIa), branching enzyme deficiency (IV), McArdle disease (V), and muscle phosphofructokinase deficiency (VII)): hypotonia, hepatomegaly, muscle weakness, and elevated creatine kinase (CK)
      ii. Mitochondrial myopathy: hypotonia, hyperreflexia, hepatomegaly, and some forms with hypertrophic cardiomyopathy, muscle weakness, and elevated creatine kinase (CK)
      iii. Lipid disorder myopathies
   e. Motor neuron disorders
      i. Spinal muscular atrophy types II and III: asymmetrical muscle weakness and atrophy of voluntary muscles (shared signs and symptoms)
      ii. Kennedy disease
      iii. Amyotrophic lateral sclerosis
   f. Neuromuscular junction disorders
      i. Myasthenia gravis: generalized muscle weakness (shared signs and symptoms)

ii. Congenital myasthenic syndromes
iii. Lambert-Eaton syndrome
g. Rheumatoid arthritis: stiffness/pain upon exertion (shared signs and symptoms)

Diagnostic Investigations

1. Elevated serum creatine kinase in most patients
2. Elevated serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic dehydrogenase (LDH)
3. Radiography: tremendous cardiomegaly
4. EKG: can readily observe the signs of cardiac glycogenosis (indicators of relative myocardial ischemia)
   a. Very large QRS complex in all leads
   b. Short P-R interval: pathognomonic of infantile Pompe disease
   c. Left axis deviation or absence of the normal right axis deviation (presence of biventricular hypertrophy)
   d. Inverted T wave
   e. ST segment depression
5. Echocardiography: biventricular hypertrophy without outflow obstruction
6. EMG
   a. Infantile form: nonspecific myopathic changes or normal finding
   b. Adult form
      i. Pseudomyotonia
      ii. High-frequency discharges
      iii. Fibrillations
7. Muscle biopsy
   a. Presence of vacuoles that stain positive for glycogen (PAS) as well as for the lysosomal enzyme acid phosphatase
   b. A typical lacework appearance of histologic sections from the myocardium resulting from deposition of stored material in the cardiac fibrils
   c. Electron microscopy
      i. Membrane-bound glycogen
      ii. Glycogen accumulation within the lysosome
8. Glycogen accumulation
   a. Infantile form
      i. Muscle
      ii. Liver
      iii. Motor nuclei in the brain stem
      iv. Anterior horn cells of the spinal cord
      v. Placenta
         a) Amniotic storage cells identified and shown histochemically to contain glycogen
         b) Pathognomonic accumulation of lysosomal glycogen in the placenta by electron microscopy in the second trimester
         c) Confirmation of the prenatal diagnosis made by enzyme assay
      vi. Other tissues
         a) Endothelial cells
         b) Kidneys
         c) Skin
   b. Adult form: not seen in the heart, liver, or brain
9. Diagnostic enzymatic test: deficient acid maltase in leukocytes, muscle, and skin fibroblasts
10. DNA analysis by targeted mutation analysis
11. Newborn screening by determining the total α-glucosidase in plasma or dried blood spots (Umapathysivam et al. 2001; Chien et al. 2009)
12. Heterozygote detection
    a. Reduced α-glucosidase activity: not reliable
    b. DNA-based detection more appropriate and definitive within families

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is a carrier in which cases 50% of offspring will be affected and 50% will be carriers
2. Prenatal diagnosis (Phupong et al. 2004)
   a. Rapid prenatal diagnosis by electron microscopy of uncultured amniocytes
   b. Deficient activity of lysosomal acid α-glucosidase in cultured amniocytes or CVS
   c. Electron microscopic study of chorionic villus biopsies for the pregnancy at risk: fibrocytes with typical vacuoles filled with glycogen
   d. Mutation analysis on amniocytes or CVS: 100% reliable prediction of the genetic status of the fetus, including heterozygosity (Kleijer et al. 1995)
3. Management
   a. Supportive therapy to manage symptoms and minimize complications whenever possible

i. Respiratory therapy
ii. Physical therapy (Case and Kishnani 2006)
iii. Dietary therapy
iv. Infection prevention
v. A high-protein diet to improve muscle function
vi. Ventilator support

b. Administration of purified α-glucosidase not effective
c. Bone marrow transplantation presumably to provide enzyme secreted by the normal cells continuously
   i. Results not promising
   ii. Transitory engraftment of the haploidentical transplant
   iii. No enzyme detected in muscle cells
   iv. Patient died of complications of the transplant
d. Enzyme replacement therapy (ERT)
   i. ERT with recombinant human α-glucosidase from rabbit milk in Pompe patients in an open-label study
      a) Intended to directly address the underlying metabolic defect via intravenous infusions of recombinant human GAA (rhGAA) enzyme
      b) The enzyme generally well tolerated
      c) Normalization of muscle α-glucosidase activity
      d) Improved tissue morphology and motor and cardiac function
      e) Significantly decreased left ventricular mass index
      f) Recommend early treatment (before irreversible damage) and follow-up of long-term effects
      g) Anti-rhGAA antibody may limit the efficacy of the treatment
      h) Extensive muscle damage may be unrefractive to therapy
   ii. Infantile-onset Pompe disease (Klinge et al. 2005; Kishnani et al. 2006, 2007): significantly prolongs survival, decreases cardiomegaly, and improves cardiac and skeletal muscle function
   iii. Late-onset Pompe disease (Bernstein et al. 2010): Gastrointestinal symptoms resolved within the first 6 months of ERT with recombinant human alglucosidase alpha (rhGAA). Patients gained weight and remain symptom free, two for over 4 years.
e. Gene therapy aiming at providing a permanent endogenous source of enzyme for the affected tissues: not available currently

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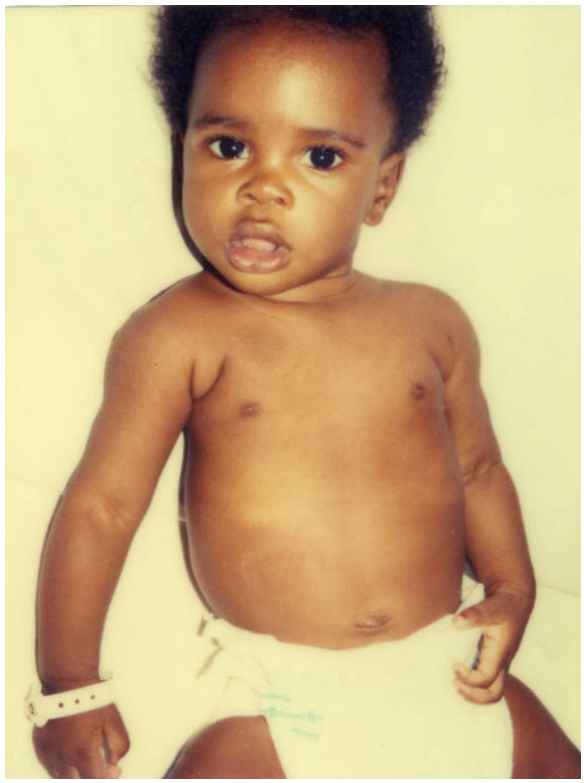

Fig. 1 An infant with massive cardiomegaly and hypotonia. Diagnosis of Pompe disease was confirmed by deficient acid maltase in the leukocytes

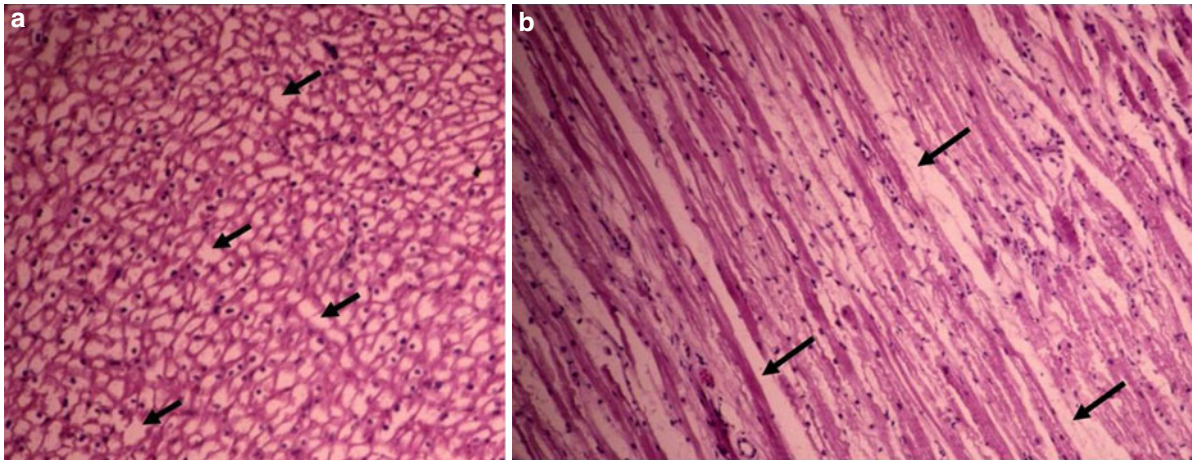

Fig. 2 Different patient with Pompe disease. (**a**) Myocardium. Note numerous vacuolated fibers (*arrows*) due to glycogen accumulation. HE, ×40. (**b**) Smooth muscle from GI tract. Note clear areas represent glycogen deposition (*arrows*)

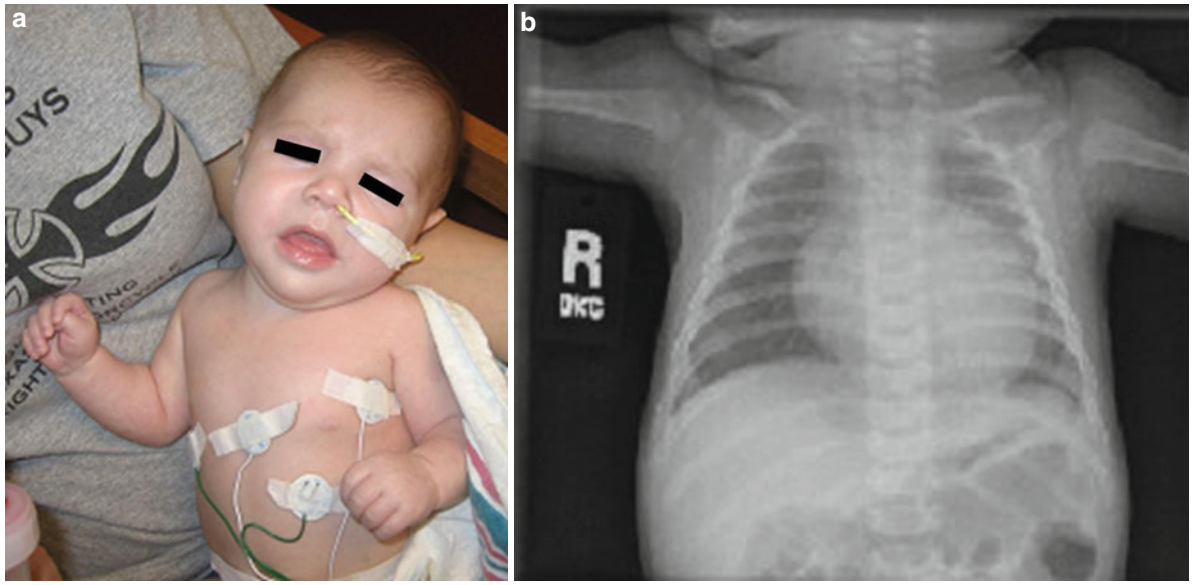

Fig. 3 (**a**, **b**) A 23-month-old boy was seen because of respiratory distress and heart failure. A chest X-ray showed a large globular-shaped heart. An echocardiogram showed a hypertrophic cardiomyopathy. He was noted to be hypotonic and had an enlarged liver. Muscle biopsy showed excessive glycogen storage with glycogen content 5.6% (control: 0.94 +/− 0.55% wet weight). Muscle α-glucosidase was deficient (0.01; control: 0.42 +/− 0.2 micromol/min/g of tissue). Muscle neutral α-glucosidase was 0.05 (control: 0.12 +/− 0.6 micromol/min/g of tissue). Blood acid α-glucosidase was 1.3 (control: 10.0–49.0 pmol/punch/h). Blood neutral α-glucosidase was 52.3 (control: 23.8–132.6 pmol/punch/h). Urine Hex4 was 34.1 (control for <6 month: <19 nmol/mol creatinine). Mutation analysis revealed c.1846 G > A (exon 13) and c.2608 C > A (exon 18). The c.2608CA mutation is a nonsense mutation that results in a premature termination codon, a reported disease causing mutation. The c.1846 G > A mutation has not been previously reported as a mutation causing Pompe disease or a known polymorphism, but has been seen once in the Duke University laboratory, in the homozygous state as the only mutation in a patient with Pompe disease. This patient received 1 dose of enzyme replacement therapy and tolerated his first dose of Myozyme well

Goldenhar Syndrome

In 1952, Goldenhar described a pair of monozygotic twins discordant for hemifacial microsomia, mandibular hypoplasia, auricular malformations, and epibulbar dermoids. Gorlin et al. later in 1963 coined the term "oculoauriculovertebral dysplasia" to describe patients with mandibular hypoplasia, microtia, epibulbar dermoids, and vertebral anomalies. The presence of vertebral anomalies and epibulbar dermoids delineates the so-called Goldenhar syndrome. Oculoauriculovertebral spectrum (OAVS) is a relatively common disorder affecting approximately 1 in 5,600 live births.

Synonyms and Related Disorders

Hemifacial microsomia; Oculoauriculovertebral spectrum

Genetics/Basic Defects

1. The term, "Oculoauriculovertebral dysplasia spectrum," suggested to represent an etiologically diverse spectrum of congenital anomalies
   a. Oculoauriculovertebral dysplasia
   b. Facioauriculovertebral syndrome (Goldenhar-Gorlin syndrome)
   c. Hemifacial microsomia (second most common facial anomaly, second only to cleft lip and palate) (Sze et al. 2002)
   d. Hemifacial microtia
   e. Otomandibular dysostosis
   f. Original Goldenhar syndrome
   g. Goldenhar-Gorlin syndrome
   h. Anomalies of the first and second branchial arches
2. Congenital anomalies
   a. Usually unilateral
   b. Primarily right sided
   c. More common in monozygous twins usually with one affected
3. Causes: unknown but likely heterogeneous
   a. Usually sporadic occurrence
   b. Maternal teratogenic exposures
      i. Retinoic acid
      ii. Thalidomide
      iii. Primidone
      iv. Cocaine
   c. Presumed vascular disruption
   d. Maternal diabetes
   e. Discordant occurrence in monozygotic twins: arising from a disturbance of blastogenesis leading to malformations
   f. Autosomal dominant inheritance (Guizar-Vazquez et al. 1978; Zankl and Zang 1979; Sanchez-Corona et al. 1982; Oliveira et al. 1989; Orstavik et al. 1990; Gupta and Patton 1995; Tasse et al. 2007; Vendramini-Pittoli and Kokitsu-Nakata 2009)
   g. Autosomal recessive inheritance (Ellwood et al. 1968; Konigsmark et al. 1972; Schmid et al. 1985; Strisciuglio et al. 1986)
   h. Associated chromosome abnormalities
      i. Del(5p)
      ii. Monosomy 6q
      iii. Trisomy 7
      iv. Dup(7q)

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v. Dup(8q)
vi. Trisomy 9 (mosaic)
vii. Del(18q)
viii. Der(18)
ix. R(21)
x. Del(22)(q13.31)
xi. Dup(22)(q11.2q13.1)
xii. Trisomy 22 (mosaic)
xiii. 47,XXY
xiv. 49,XXXXY

4. Pathogenesis: unknown but likely heterogeneous
   a. Interference with vascular supply and focal hemorrhage in the developing first and second branchial arch region
   b. Impaired interaction of cranial neural crest cells with branchial arch mesenchyme
   c. A disorder of blastogenesis
5. Hypothesis: candidate genes for OAVS, particularly in familial cases
   a. Homeobox genes, especially of the MSX class
      i. *Msx* critical for the differentiation of first branchial arch ectoderm-mesenchyme leading to various craniofacial structures
      ii. Strongly expressed in cephalic neural crest cells prior to migration of the cells that contribute extensively to craniofacial development
   b. Encompasses previous partial pathogenetic explanations for OAVS, including neurocristopathy and developmental field defects, and represents a unifying concept regarding the wide spectrum of involvement in OAVS
   c. Mutations that result in partial loss of function of these genes could explain incomplete penetrance and clinical variability occurring in individuals with different genetic backgrounds.

Clinical Features

1. Major clinical features
   a. Ocular manifestations
      i. Epibulbar dermoids or lipodermoid (Goldenhar syndrome)
      ii. Unilateral microphthalmia
      iii. Upper eyelid coloboma
      iv. Strabismus
      v. Diminished visual acuity
      vi. Tilted optic disc
      vii. Optic nerve hypoplasia
      viii. Tortuous retinal vessels
      ix. Macular hypoplasia and heterotropia
      x. Microphthalmia
      xi. Anophthalmia
   b. Ear anomalies
      i. Microtia
      ii. Preauricular tags and/or pits
      iii. Middle ear anomaly
      iv. Inner ear defects
      v. Variable deafness
   c. Vertebral defects
      i. Hemivertebrae
      ii. Hypoplasia of vertebrae, usually cervical
      iii. Abnormal ribs
   d. Hemifacial microsomia
      i. Unilateral microtia
      ii. Ipsilateral hypoplasia of malar, maxillary, and mandibular region, especially temporomandibular joint
      iii. Ipsilateral macrostomia
      iv. Ipsilateral hypoplasia of the facial musculature
2. Other associated features
   a. Craniofacial features
      i. Cranial nerve palsy
      ii. Cleft lip/palate
      iii. Malfunction of soft palate
      iv. Decreased parotid secretion
      v. Anomalies in function or structure of the tongue
      vi. Low scalp hairline
      vii. Branchial cleft remnants in anterior-lateral neck
   b. CNS anomalies
      i. Hydrocephaly
      ii. Microcephaly
      iii. Plagiocephaly
      iv. Frontal/occipital encephalocele
      v. Cranial bifidum
      vi. Lipoma
      vii. Dermoid cyst
      viii. Arnold-Chiari malformation
      ix. Lissencephaly
      x. Holoprosencephaly/arhinencephaly
      xi. Arachnoid cyst
   c. Congenital heart diseases (5–58% depending on ascertainment of cases)

i. Tetralogy of Fallot (with or without right aortic arch) and VSD (account for over half of the cases with congenital heart diseases)
ii. Pulmonary stenosis
iii. Patent ductus arteriosus
iv. Coarctation of aorta
v. Total atrioventricular canal defect
vi. ASD
vii. Transposition of great vessel
viii. Rare isolation of the left innominate artery infradiaphragmatic total anomalous pulmonary venous connection
ix. Wolf-Parkinson-White syndrome

d. Respiratory tract anomalies
i. Laryngeal anomaly
ii. Incomplete lobulation of the lung
iii. Pulmonary hypoplasia to aplasia
iv. Sequestration
v. Focal tracheomalacia due to extrinsic vascular compression
vi. Obstructive sleep apnea

e. Gastrointestinal anomalies
i. Esophageal atresia
ii. Tracheoesophageal fistula
iii. Diaphragmatic hernia
iv. Imperforate anus

f. Renal anomalies
i. Renal agenesis
ii. Hydronephrosis
iii. Ectopic kidney
iv. Double ureter
v. Hydroureter

g. Prenatal growth deficiency
h. Normal intelligence in most cases

Diagnostic Investigations

1. Radiography
a. Platybasia/occipitalization of atlas
b. Hypoplasia of the mandibular-maxillary bones
c. Fused vertebrae, especially cervical
d. Segmentation anomaly of the vertebra
e. Hemivertebrae
f. Klippel-Feil anomaly
g. Rib anomalies
h. Aplasia of radius/thumb
i. Spina bifida

2. Echocardiography: variable and nonspecific findings because cardiovascular abnormalities are complex in most cases

Genetic Counseling

1. Recurrence risk: depending on the etiology and the mode of inheritance
a. Patient's sib
i. Isolated: empiric recurrence risk of 2%
ii. Autosomal dominant inheritance: recurrence risk not increased unless a parent is affected, in which case the recurrence risk is 50%
iii. Autosomal recessive inheritance: 25% of siblings affected, 50% of siblings carriers, and 25% of siblings normal

b. Patient's offspring
i. Isolated: unknown
ii. Autosomal dominant inheritance: 50%
iii. Autosomal recessive inheritance: recurrence risk not increased unless the spouse is also a carrier, in which case the recurrence risk is 50%

2. Prenatal diagnosis by ultrasonography
a. Hemifacial microsomia
b. Microphthalmia or anophthalmia
c. Cleft lip/palate
d. Unilateral facial cleft with macrostomia
e. Unilateral ear hypoplasia
f. Unilateral preauricular tag
g. Hemiatrophy of the nose
h. Hyposegmentation of the unilateral lung
i. Single umbilical artery
j. Imperforate anus
k. Polyhydramnios

3. Management
a. Surgical removal of epibulbar dermoids, if needed.
b. Manage associated conductive hearing loss.
c. Cleft lip/palate repair.
d. Combined surgical-orthodontic approach for dental occlusion.
e. Traditional osteotomies, followed by acute orthopedic movement and osseous fixation for adult patients with maxillomandibular hypoplasia, facial asymmetry, congenital micrognathia, and hemifacial microsomia.
f. Alternative procedure: distraction osteogenesis.

g. Assess cervical spine for instability before undergoing any general surgery. C1–C2 fusion or occipitocervical fusion may be needed (Kaymak et al. 2002).
h. Anesthesia: anticipate airway obstruction and difficulty in tracheal incubation, resulting from a combination of micrognathia, unilateral mandibular hypoplasia, and vertebral anomalies including vertebral fusion and odontoid elongation.

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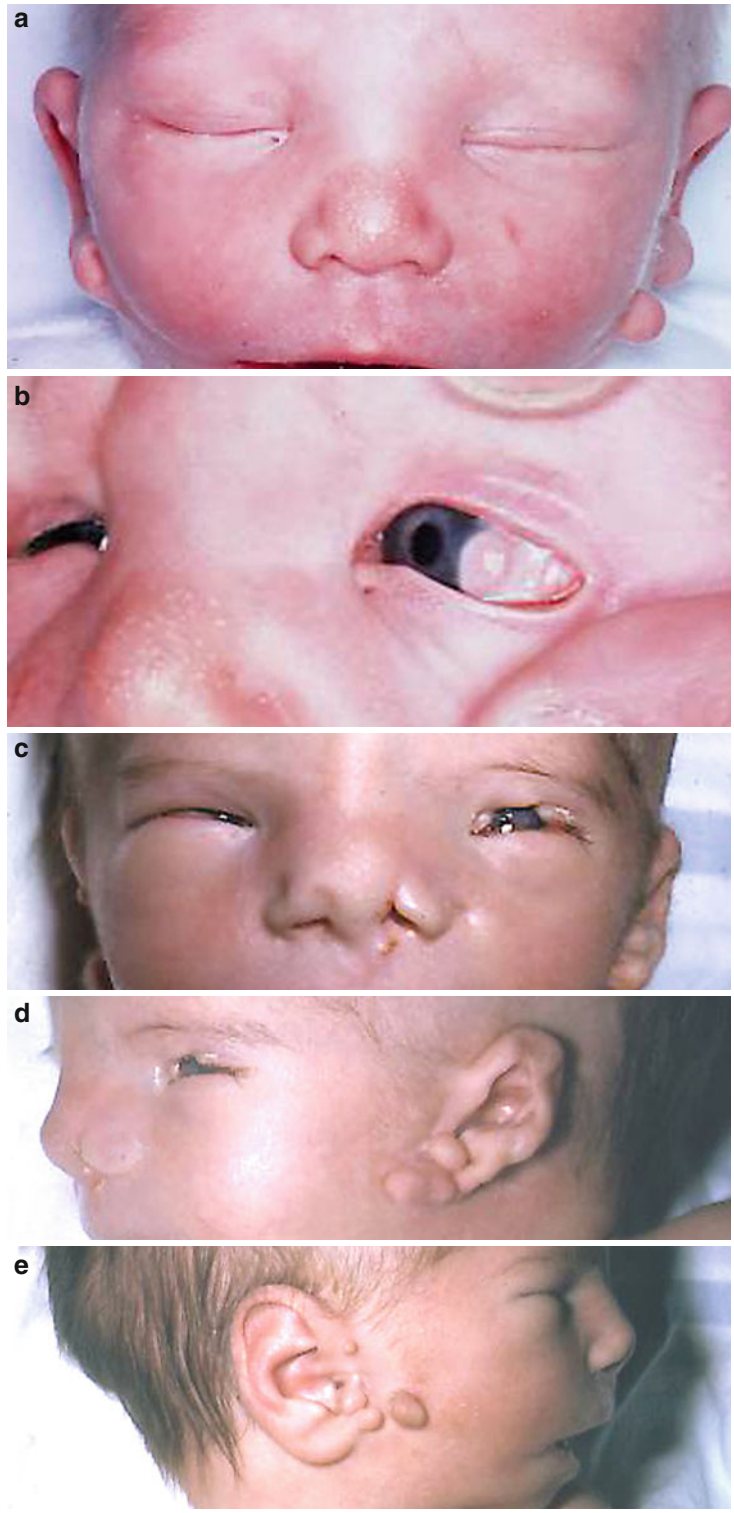

Fig. 1 Two infants (**a**–**e**) with Goldenhar syndrome showing hemifacial microsomia, epibulbar dermoids, upper eyelid coloboma, clefting nose, macrostomia, and unilateral microtia with preauricular tag

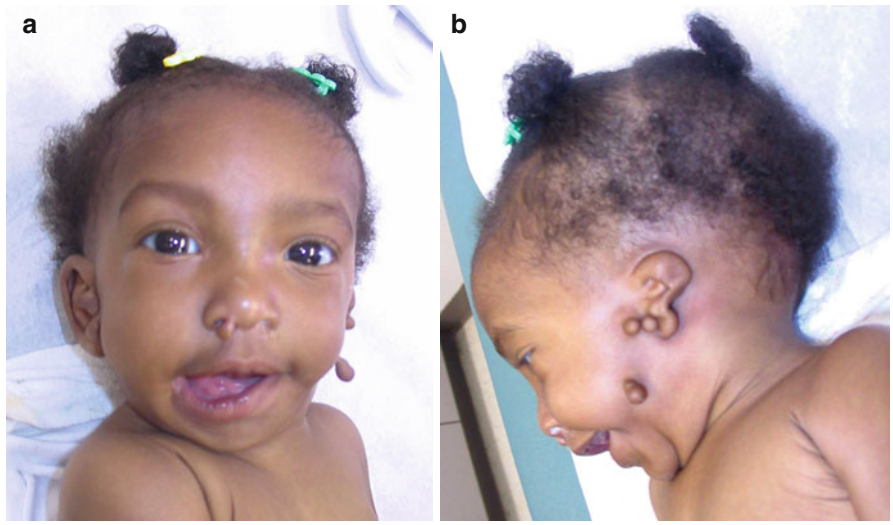

Fig. 2 (**a**, **b**) An 8-month-old child with hemifacial microsomia showing facial asymmetry, unilateral microtia, and preauricular tags

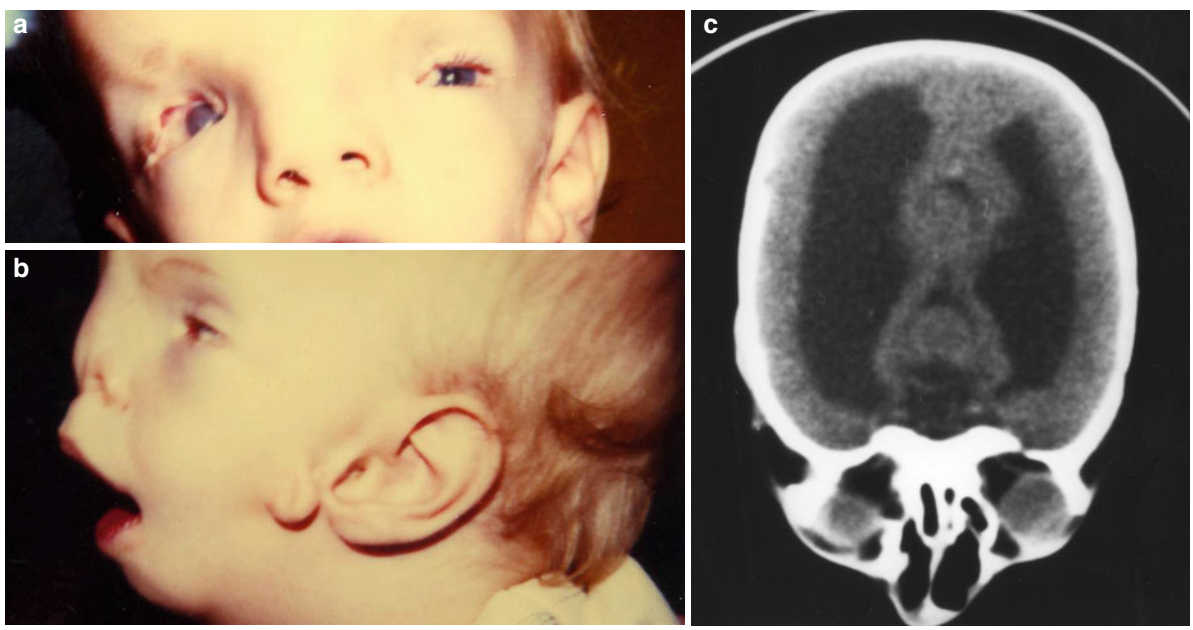

Fig. 3 (**a–c**) An infant with primidone embryopathy presenting as Goldenhar syndrome showing hemifacial microsomia, facial palsy, upper eyelid coloboma, epibulbar dermoid, and hydrocephaly by MRI

Gorlin Syndrome

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, was first reported by Jarisch and White in 1894 who described a patient with multiple basal cell carcinomas, scoliosis, and learning disability. Howell and Caro in 1959 were the first to associate the basal cell nevus with other multiple cutaneous cancer and associated developmental anomalies. The spectrum of disease associated with this syndrome, comprising the principal triad of multiple basal cell nevi, jaw keratocysts, and skeletal anomalies, was described in detail by Gorlin and Goltz in 1960. A spectrum of other neurological, ophthalmic, endocrine, and genital manifestations are now known to be variably associated with this triad (Manfredi et al. 2004). The prevalence is estimated to be 1 in 60,000 persons (Cohen 1999).

Synonyms and Related Disorders

Gorlin-Goltz syndrome; Multiple basal cell nevi; Nevoid basal cell carcinoma syndrome; Odontogenic keratocysts and skeletal anomales

Genetics/Basic Defects

1. An autosomal dominant disorder with complete penetrance and variable expressivity (Bare et al. 1992; Bonifas et al. 1994).
2. The gene responsible has been localized to chromosome 9q22.1-q31 (Farndon et al. 1992; Compton et al. 1994).
3. Causes:
   a. Between 50% and 85% of patients with GS harbor germ line mutations in the only susceptibility gene identified to date, *PTCH1*, a key component in the Sonic Hedgehog signaling pathway:
      i. Caused by mutations in the human homolog of the Drosophila patched gene, *PTCH* (Johnson et al. 1996)
      ii. *PTCH*: a tumor suppressor gene, encoding a transmembrane glycoprotein that acts as an antagonist in the Hedgehog signaling pathway (Bak et al. 2003)
   b. A microdeletion at 9q22.3 involving a deletion of *PTCH* gene in a few cases (Shimkets et al. 1996; Sasaki et al. 2000; Olivieri et al. 2003; Midro et al. 2004; Boonen et al. 2005; Yamamoto et al. 2009).
   c. SUFU, another component in this pathway, is known to be involved in susceptibility to medulloblastoma but has never been reported in Gorlin syndrome patients to date. A *SUFU* germ line splicing mutation (c.1022þ1G > A) has been identified for the first time in a family that was *PTCH1*-negative and who had signs and symptoms of Gorlin syndrome, including medulloblastoma (Pastorino et al. 2009).
4. Odontogenic keratocysts (Agaram et al. 2004).
   a. A distinctive odontogenic cyst with a potential for aggressive behavior, local recurrence, and an association with nevoid basal cell carcinoma syndrome
   b. A significant number of odontogenic keratocysts show clonal loss of heterozygosity of common tumor suppressor genes

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c. Presence of clonal deletion mutations of genomic DNA in these cysts supports the hypothesis that they are neoplastic rather than developmental in origin

Clinical Features

1. Clinical features
   a. An increasing number of basal cell nevi:
      i. Mostly appearing from the age of puberty onwards
      ii. Having tendency to develop into basal cell carcinomas of the skin
      iii. Most commonly in sun-exposed areas
   b. Dermal pits of the palms and soles:
      i. Particularly useful in diagnosis
      ii. Pits more pronounced when the hands and feet are soaked in warm water for up to 10 min, appearing as white "punched-out" or pink "pinpricked" lesions
   c. Keratocysts of the jaws
   d. Skeletal anomalies:
      i. Spine and rib anomalies:
         a) Bifid ribs
         b) Thoracic and cervical vertebral anomalies
         c) Scoliosis
         d) Spina bifida
         e) Osteoporosis
         f) Short fourth metacarpals
      ii. Abnormal craniofacial configurations:
         a) Macrocephaly
         b) Frontal, parietal, and temporal bossing
         c) Hypertelorism
         d) Broad nasal bridge
         e) Maxillary retrognathia
         f) Mandibular prognathism
         g) Increased gonion angle
         h) Increased facial height
   e. Intracranial calcifications (Dahl et al. 1976; Donatsky et al. 1976; Kimonis et al. 1997; Evans et al. 1993):
      i. Falx cerebri
      ii. Falx cerebelli
      iii. Petroclinoid ligament
      iv. Dura
      v. Pia
      vi. Choroid plexus
   f. Other features:
      i. Sensitive to ultraviolet and ionizing radiation
      ii. Occasional abnormalities (Evans et al. 1993; Kimonis et al. 1997)
         a) Dental agenesis
         b) Cleft palate and lip
         c) Mental deficiency
         d) Agenesis of corpus callosum
         e) Vermian dysgenesis
         f) Anosmia
         g) Hydrocephalus
         h) Cataract
         i) Coloboma of iris
         j) Retinal atrophy
         k) Glaucoma
         l) Strabismus
         m) Mandibular coronoid process hyperplasia
         n) Arachnodactyly
         o) Polydactyly
         p) Renal anomalies
         q) Other neoplasms such as medulloblastoma, meningioma, fibroma, lipomata, melanoma, neurofibromata of skin, cardiac fibromas, eyelid carcinomas, breast cancer, lung cancer, lymphoid leukemia, non-Hodgkin's lymphoma, ovarian dermoid, lymphomesenteric cysts, and hepatic mesenchymal tumors
2. Diagnostic criteria for nevoid basal cell carcinoma syndrome (Evans et al. 1993; Evans and Farndon 2010; Kimonis et al. 2004): A diagnosis can be made when two major, or one major and two minor criteria are fulfilled:
   a. Major criteria:
      i. Multiple (>2) basal cell carcinomas (BCC) or one BCC under the age of 20 years, or >10 basal cell nevi
      ii. Any odontogenic keratocyst histologically or observed on orthopantogram as an area of translucency or polyostotic bone cyst
      iii. Palmar or plantar pits (three or more)
      iv. Ectopic calcification: lamellar (sheetlike) falx calcification or evidence of early calcification in an individual younger than 20 years
      v. First degree relatives with NBCCS
   b. Minor criteria:
      i. Congenital skeletal anomaly: bifid, fused, splayed, or missing ribs, or bifid, wedged, or fused vertebra

ii. Occipital-frontal circumference >97 percentile (macrocephaly), with frontal bossing
iii. Cardiac or ovarian fibromas
iv. Childhood medulloblastoma (primitive neuroectodermal tumor)
v. Lymphomesenteric or pleural cysts
vi. Congenital malformation: cleft lip and/or palate, polydactyly, eye anomaly (cataract, coloboma, microphthalmia)

Diagnostic Investigations

1. Family history:
   a. Brain tumors
   b. Female organ tumors
2. Medical and dental history:
   a. Removal of jaw cysts
   b. Abscesses
   c. Skin lesions
3. Physical examination:
   a. Mandibular and maxillary swelling
   b. Head circumference
   c. Head shape
   d. Skin basal cell nevi
   e. Pits on the palms and soles
4. Radiographic studies:
   a. Skull radiography for detection of calcified cerebral falx
   b. Jaw radiography for detection of maxillary and mandibular cystic lesions
   c. Chest radiography for rib and vertebral anomalies
5. MRI of the brain to detect meningiomas or medulloblastomas at an early age
6. Ovarian ultrasonography for detection of ovarian cysts or fibromas
7. Echocardiograms to evaluate cardiac fibromas
8. Cytogenetic analysis to detect rare interstitial 9q deletion associated with clinical features of NBCCS and additional features such as severe developmental delay or short stature
9. Molecular genetic testing (Evans and Farndon 2010):
   a. Sequence analysis of exons 2-23 with intron-exon junctions and one of the splice forms of exon 1 to detect *PTCH1* gene mutation (Marsh et al. 2005; Klein et al. 2005)
   b. Deletion testing to detect exonic and whole *PTCH1* gene deletions

Genetic Counseling

1. Recurrence risk:
   a. Patient's sib:
      i. An affected parent: a 50% risk
      ii. Unaffected parents: a low risk
   b. Patient's offspring: a 50% risk
2. Prenatal diagnosis:
   a. Ultrasonography:
      i. Hydrocephalus
      ii. Macrocephaly
      iii. Cleft lip and palate
      iv. Intracardiac tumor
      v. Fetal hydrops
      vi. Fetal chylothorax
   b. Molecular genetic testing available, provided the disease-causing allele of an affected family member has been identified, by analyzing DNA extracted from fetal cells obtained by:
      i. CVS
      ii. Amniocentesis
3. Management:
   a. Surgical excision of keratocysts identified early in life
   b. Basal cell carcinomas:
      i. Complete eradication of aggressive BCCs; surgical excision supplemented by cryotherapy, laser treatment for early lesion, and photodynamic therapy
      ii. Preserve normal tissue to prevent disfigurement
   c. Surgical excision of ovarian fibromas

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Fig. 1 (**a**, **b**) An 11-year-old boy and his father both have Gorlin syndrome. The boy had multiple odontogenic cysts removed from his jaw. Craniofacial CT scan showed extensive dural and choroid plexus calcifications and abnormal enlargement of subarachnoid space in the left frontal and anterior temporal regions. He was noted to have macrocephaly, forehead bossing, and plantar pits. His father had his multiple odontogenic cysts removed at 16 years of age. In addition, he has several soft subcutaneous tissue masses in his fingers and his right foot. The patient is heterozygous for a duplication of a single "A" nucleotide in exon 2 of the *PTCH* gene. The normal sequence with the base that is duplicated in braces is "TTGTT(A)CATTCA." This mutation is denoted c.278dupA at the cDNA level or p Tyr93Stop (Y93X). The c.278DupA mutation results in the replacement of a Tyrosine codon with a Stop codon at position 93

Fig. 2 CT scan of jaw shows multiple odontogenic cysts

Fig. 4 A small subcutaneous nodule seen in the dorsal aspect of the foot of the father

Fig. 3 A small subcutaneous nodule seen in the index fingers of the father

Greig Cephalopolysyndactyly Syndrome

Greig cephalopolysyndactyly (GCPS) syndrome is named after David Middleton Greig for his 1926 description of a patient with unusual head shape, hypertelorism, and limb anomalies. It is a rare, pleiotropic, multiple congenital anomaly syndrome characterized by the primary clinical triad of polysyndactyly, macrocephaly, and hypertelorism.

Synonyms and Related Disorders

Cephalopolysyndactyly; Polysyndactyly with peculiar skull shape

Genetics/Basic Defects

1. Inheritance: Autosomal dominant with high penetrance in majority of cases.
2. Caused by mutations in the transcription factor *GLI3* on chromosome 7p13 resulting in functional haploinsufficiency of *GLI3*. The mutations include:
   a. Point mutations
   b. Frameshift mutations
   c. Translocation mutations
   d. Deletion mutations
   e. Insertion mutations
3. Allelic to the Pallister-Hall syndrome (PHS) and one form of the acrocallosal syndrome:
   a. Severe GCPS phenotype is likely caused by deletion of contiguous genes and substantially overlaps with the mild end of the acrocallosal syndrome (an autosomal recessive disorder characterized by pre- or postaxial polydactyly, syndactyly, agenesis corpus callosum, ocular hypertelorism, macrocephaly, moderate to severe mental retardation, intracerebral cysts, seizures, and umbilical and inguinal hernias).
   b. *GLI3* mutations can also cause PHS, postaxial polydactyly type A, and other *GLI3* morphopathies. GCPS and PHS are likely allelic with distinct modes of pathogenesis.
4. Phenotypes caused by mutations in GLI3 are diverse, discrete, variable, and pleiotropic. The mutations in GLI3 that cause PHS and GCPS correlate with the phenotypes on two levels:
   a. Many types of inactivating mutations cause GCPS.
   b. Whereas PHS is caused almost exclusively by truncation mutations in the middle third of the gene.
5. Mutations in genes other than *GLI*: possible in some patients with a GCPS phenotype.

Clinical Features

1. The primary clinical triad.
   a. Macrocephaly
   b. Hypertelorism
   c. Polysyndactyly
2. Variable clinical manifestations
3. Developmental history:
   a. Feeding problems/failure to thrive
   b. Developmental delay, seizures, and psychomotor retardation: more likely in a child with rare CNS malformations or uncommon hydrocephalus and more common in individuals with large (>300 kb) deletions that encompass *GLI3*

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4. Craniofacial features: highly variable
   a. Significant hypertelorism (increased interpupillary distance) with or without telecanthus (increased inner canthal distance) in some patients
   b. Macrocephaly, not typically associated with CNS anomalies, such as hydrocephalus and seizures
5. Digital anomalies:
   a. Polydactyly:
      i. Classically described as preaxial.
      ii. May occur in any limb.
      iii. Postaxial may be more common than preaxial.
      iv. Most common finding: postaxial polydactyly of the hands and preaxial polydactyly of the feet.
      v. Severity varies widely among individuals and among limbs in the same individual. This can vary from an apparently normal extremity, through subtle broadening of the thumb or hallux, tiny postaxial nubbins, to partially bifid digits, hypoplastic supernumerary digits, fully formed supernumerary digits, and higher order polydactyly.
   b. Cutaneous syndactyly: highly variable.
      i. Absent in many patients
      ii. Mild partial cutaneous syndactyly of a few digits in some patients
      iii. The spectrum continues through to complete cutaneous syndactyly of all digits, not unlike that seen in patients with Apert syndrome.
6. Less common anomalies:
   a. Craniosynostosis: very few patients.
   b. Mental retardation: not common.
   c. Agenesis of the corpus callosum.
   d. Umbilical and diaphragmatic hernias.
   e. Risk of cognitive impairment appears to be associated with the GCPS-contiguous gene syndrome.
7. Diagnostic criteria (Johnston et al. 2005):
   a. Presumptive diagnosis: a proband with:
      i. Preaxial polydactyly
      ii. Syndactyly of toes 1–3 or fingers 3–4
      iii. Ocular hypertelorism
      iv. Macrocephaly
   b. Firm diagnosis:
      i. Presence of an affected first-degree relative whom the diagnosis has been independently established
      ii. A proband who has features of GCPS and a mutation in *GLI3*
   c. Cautions in applying above diagnostic criteria:
      i. Clinical criteria: useful but not sufficiently specific to warrant a "firm" diagnosis on clinical grounds alone
      ii. A small but significant fraction of individuals with features of GCPS do not have mutations in *GLI3*.
      iii. Features of GCPS are seen in many other syndromes.
8. Diagnostic criteria (combined clinical-molecular definition for the syndrome) (Biesecker 2008)
   a. A presumptive diagnosis with the classic triad:
      i. Preaxial polydactyly with cutaneous syndactyly of at least one limb
      ii. Hypertelorism
      iii. Macrocephaly
   b. Definitive diagnosis:
      i. A phenotype consistent with GCPS but which may not manifest all three attributes listed above
      ii. Presence of a *GLI3* mutation
9. Additional definitive diagnostic criteria: persons with a GCPS-consistent phenotype who are related to a definitively diagnosed family member in a pattern consistent with autosomal dominant inheritance
10. Prognosis:
    a. A mild form: excellent general health and normal longevity reported in several large families
    b. Slight increase in the incidence of developmental delay or cognitive impairment
    c. Worse prognosis in patients with large deletions that include *GLI3*
11. Differential diagnosis:
    a. Preaxial polydactyly type IV
    b. GCPS contiguous gene syndrome
    c. Acrocallosal syndrome (ACLS):
       i. Inherited in an autosomal recessive manner.
       ii. Pre- or postaxial polydactyly.
       iii. Syndactyly.
       iv. Agenesis of the corpus callosum (rare in GCPS).
       v. Ocular hypertelorism.
       vi. Macrocephaly.
       vii. Moderate to severe mental retardation.
       viii. Intracerebral cysts.

ix. Seizures.
x. Umbilical and inguinal hernias.
xi. The milder end of the ACLS phenotype can overlap with the severe end of the GCPS phenotype caused by interstitial deletions of 7p13 that delete *GLI3* and additional neighboring genes.
xii. Frequency of consanguinity, sibling recurrences with unaffected parents, and preliminary mapping data suggest that ACLS can be a disorder distinct from severe GCPS.

d. Gorlin syndrome
e. Carpenter syndrome
f. Teebi syndrome

Diagnostic Investigations

1. Radiographic studies of digital anomalies
2. CNS imaging studies:
   a. For individuals showing signs of increased intracranial pressure, developmental delay, loss of milestones, or seizures
   b. To evaluate hydrocephalus or other CNS abnormalities
3. Chromosome analysis: performed either as a first test, or in all patients who have GCPS but no mutation was found by sequencing:
   a. Detection of visible pure chromosomal deletions involving 7p13 or a deletion combined with a translocation
   b. Detection of familial translocation: a risk for offspring with unbalanced translocations in addition to their risk of having a child with GCPS
4. Molecular genetic testing:
   a. Indications:
      i. Confirmatory diagnostic testing
      ii. Prenatal diagnosis
   b. FISH analysis: Using hybridization of the labeled BAC clone to metaphase spreads detects deletions in the estimated 5–10% of individuals with large deletions.
   c. Comparative genomic hybridization (CGH):
      i. An array of *GLI3* is available on a limited clinical basis.
      ii. CGH array would be expected to detect a deletion that encompasses more than one target on the array.
   d. Other methodologies:
      i. Loss-of-heterozygosity (LOH) analysis to detect large deletions
      ii. Sequencing of the *GLI3* coding exons or scanning with denaturing high-performance liquid chromatography (DHPLC), single-strand conformation polymorphism (SSCP), or other conformation detection methods: an appropriate first screen for patients with typical GCPS
      iii. Quantitative PCR

Genetic Counseling

1. Recurrence risk:
   a. Patient's sib:
      i. De novo cases: recurrence risk low
      ii. Fifty percent of siblings affected if one of the parents is affected
      iii. No instances of germline mosaicism reported, but it remains a possibility
      iv. Proband with an unbalanced structural chromosome constitution:
         a) Neither parents with a structural chromosome rearrangement: risk to sibs negligible
         b) A parent with a balanced structural chromosome rearrangement: risk to sibs increases and depends upon the specific chromosome rearrangement
   b. Patient's offspring
      i. Fifty percent risk of inheriting the mutation and having an affected offspring: Since intrafamilial variability is generally low, affected offspring are expected to have clinical findings similar to those of the parent.
      ii. Offspring of an individual with a balanced or unbalanced chromosomal rearrangement: at risk of having a similar or related rearrangement.
2. Prenatal diagnosis:
   a. Ultrasound studies in pregnancies at 50% risk may detect the following findings:
      i. Polydactyly
      ii. Ma
      iii. CNS malformations such as hydrocephalus
   b. Chromosome analysis of fetal cells in at-risk families with a parent having a cytogenetically visible 7p13 deletion or a balanced chromosomal rearrangement.

c. Molecular genetic testing: Antenatal molecular diagnosis is technically straightforward to perform.
d. Preimplantation genetic diagnosis (PGD): may be available for families in which the disease-causing mutation or chromosome abnormality has been identified in an affected family.

3. Management:
   a. Symptomatic treatment with plastic or orthopedic surgery indicated for significant limb malformations
   b. Surgical repair:
      i. Preaxial polydactyly of the thumbs: a higher priority for surgical correction than postaxial polydactyly of the hand or polydactyly of the foot because of the importance of the thumbs for prehensile grasp
      ii. Severe syndactyly of the fingers
      iii. Surgical correction of the feet for orthopedic complications, cosmetic benefits, and easier fitting of shoes

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Fig. 1 (**a**, **b**) A 34-year-old patient with typical facial features characterized by macrocephaly and hypertelorism. He also has mental retardation and seizure disorder. The hands show postaxial polydactyly and complete cutaneous syndactyly of digits 2–5 with fusion of nails. The feet show a partially duplicated hallux with cutaneous syndactyly of several digits

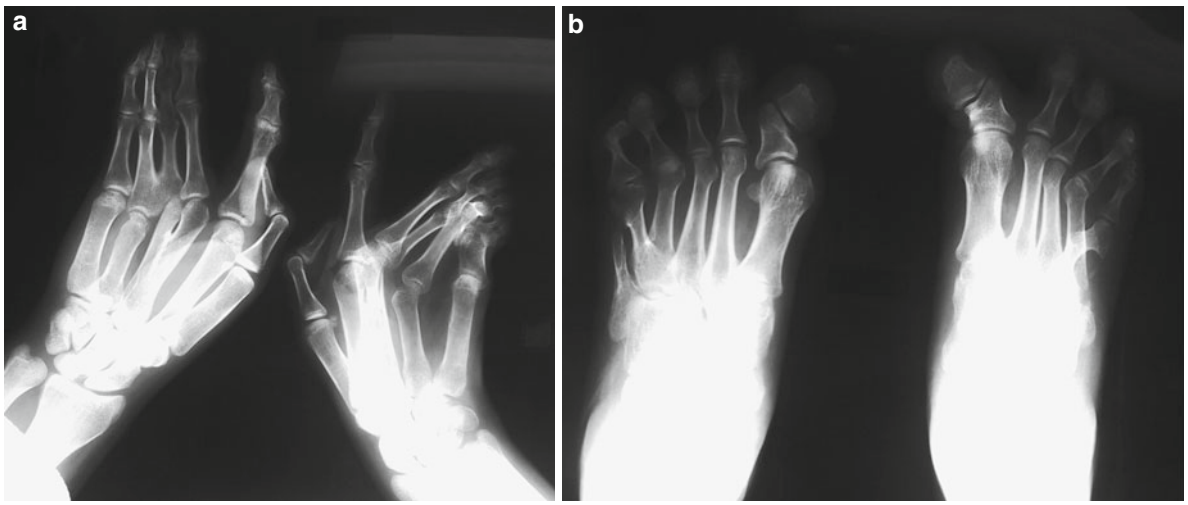

Fig. 2 (**a**, **b**) Radiographs of the same patient. The hands show six phalanges with partial fusion of the third and fourth metacarpals and partial fusion of the fourth and fifth proximal phalanges. The feet shows a partially duplicated hallux

Fig. 3 (**a**–**c**) Another patient with macrocephaly, ocular hypertelorism, and a partially duplicated great hallux

Hallermann-Streiff Syndrome

Hallermann-Streiff syndrome was independently described by Hallermann in 1948 and Streiff in 1950. The syndrome is characterized by proportionate short stature, craniofacial dysostoses consisting of skeletal, ophthalmologic, and cutaneous defects.

Synonyms and Related Disorders

Francois dyscephalic syndrome

Genetics/Basic Defects

1. Sporadic in virtually all cases
2. Inheritance pattern unknown

Clinical Features

1. Characteristic craniofacial features
   a. Dyscephaly (malformation of the cranium and bones of the face) (89–90%)
      i. Calvarium
         a) Brachycephaly
         b) Thin calvarium
         c) Delayed closure of fontanelles
         d) Wide cranial sutures
      ii. Cranial base
         a) Platybasia
         b) Depressed sella
         c) Elevated anterior cranial fossa
      iii. Parrotlike face
         a) A beaked nose
         b) Hypoplastic mandible
   b. Hypotrichosis (80–82%)
      i. Alopecia
         a) Characteristic sutural alopecia (hair loss following the lines of the cranial sutures)
         b) Frontal alopecia
         c) Alopecia at the scalp margins
      ii. Hypotrichosis involving the eye-brows and eyelashes
      iii. Brittle and sparse scalp hair
   c. Cutaneous atrophy (68–70%)
      i. Face
      ii. Scalp
   d. Ocular abnormalities
      i. Congenital cataracts (81–90%)
      ii. Microphthalmos (78–83%)
      iii. Nystagmus
      iv. Strabismus
      v. Glaucoma
      vi. Blue sclerae
      vii. Fundal anomalies
      viii. Conjunctival defects
      ix. Corneal abnormalities
      x. Down slanting palpebral fissures
      xi. Intraocular hypertension
      xii. Lower lid coloboma
      xiii. Iris atrophy
      xiv. Persistent pupillary membrane
      xv. Enophthalmos
      xvi. Bilateral retinal detachments (Haque et al. 2009)
      xvii. Epicanthal folds
   e. Mouth
      i. Microstomia
      ii. Narrow/high-arched palate

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iii. Dental abnormalities (80–85%)
a) Natal teeth
b) Partial anodontia/hypoplasia
c) Persistent deciduous teeth
d) Irregular implantation of the teeth
e) Anterior open bite

2. Musculoskeletal abnormalities
a. Proportionate short stature (45–69%)
b. Syndactyly
c. Lordosis
d. Scoliosis
e. Spina bifida
f. Winged scapulae
g. Hyperextensible joints including temporomandibular joints
h. Hip dislocation
i. Periodic osteoporosis

3. Other abnormalities
a. Mild to severe mental retardation (15%)
b. Calcified falx cerebri
c. Neurologic abnormalities
i. Neurofibromatosis
ii. Epilepsy
d. Genital anomalies (10–12%)
i. Hypogenitalism
ii. Cryptorchidism
iii. Hypospadias
iv. Subseptate uterus
v. Clitoral hypertrophy
e. Cardiac defects (2–9%)
i. Pulmonic stenosis
ii. Atrial septal defect
iii. Ventricular septal defect
iv. Patent ductus arteriosus
v. Tetralogy of Fallot
f. Endocrinological abnormalities
i. Immune deficiency
ii. Hypoparathyroidism
iii. Hypothyroidism
iv. Hypopituitarism
g. Ear anomalies (9%)
h. Hematopoietic abnormalities (7%)
i. Pulmonary anomalies (3%)
i. Obstructive sleep apnea
ii. Tracheomalacia
iii. Recurrent pulmonary infections
iv. Cor pulmonale
j. Gastrointestinal abnormalities (3%)
k. Muscular hypotrophy (3%)
l. Hepatic anomalies (2%)
m. Renal anomalies (1–2%): bilateral duplication of renal collecting system

4. Prognosis
a. Some patients succumb in infancy to respiratory infections and pulmonary insufficiency, possibly related to airway obstruction and abnormal compliance
b. Majority of patients with a normal life span

5. Diagnostic criteria
a. Major features
i. Dyscephaly with beak nose and mandibular hypoplasia
ii. Dental abnormalities
iii. Proportional short stature
iv. Hypotrichosis
v. Cutaneous atrophy
vi. Microphthalmia
vii. Congenital cataracts
b. Minor features
i. Narrow/high-arched palate
ii. Ocular features
a) Blue sclera
b) Antimongoloid palpebral fissures
c) Synechiae irides
d) Choroid atrophy
iii. Hypoplastic genitalia
iv. Musculoskeletal features
a) Elevated scapulae
b) Scoliosis
c) Lordosis
d) Hyperextensible joints
v. Mental retardation

Diagnostic Investigations

1. Radiography (Christian et al. 1991)
a. Skull
i. A large, poorly ossified skull
ii. Delayed closure of fontanelles with persistent wide sutures
iii. Presence of Wormian bones
iv. Brachycephaly
v. Platybasia
vi. Depressed sella turcica

vii. Frontal or parietal bossing
viii. Small orbits
ix. Disproportion between the large cranial vault and the small facial skeleton
x. Midfacial hypoplasia
a) Hypoplastic mandibular ramus
b) Possible absent condyles
c) Anteriorly displaced temporomandibular joint
d) Hypoplastic malar bones
xi. A birdlike nose
xii. Micrognathia
xiii. Dental anomalies
a) Presence of natal teeth
b) Retained decidual teeth
c) Partial anodontia
d) Supernumerary and hypoplastic teeth
e) Anterior open bite malocclusion

b. Long bones
i. Thin/gracile
ii. Retarded bone age

c. Other skeletal anomalies
i. Scaphocephaly
ii. Cervical vertebral anomalies
iii. Mild platyspondyly
iv. Scoliosis
v. Lordosis
vi. Elevated scapulae
vii. Hip dislocation
viii. Spina bifida
ix. Syndactyly

2. Overnight polysomnography to confirm obstructive sleep apnea
3. Endocrine evaluation for hypothyroidism, hypoparathyroidism, or hypopituitarism
4. Chromosome study: no diagnostic cytogenetic characteristics

Genetic Counseling

1. Recurrence risk
a. Patient's sib: not increased
b. Patient's offspring: not increased
2. Prenatal diagnosis: not been reported
3. Management
a. Surgery
i. Repair of cardiovascular defect
ii. Ophthalmological procedure (cataracts removal)
iii. Rhinoplasty
iv. Facial augmentation
v. Dental surgery (Patterson et al. 1982)
a) General restorative dentistry
b) Orthodontic palatal expansion
c) Realignment of the dental arches
vi. Mandibular advancement

b. General anesthesia and airway management
i. Difficult laryngoscopy and endotracheal intubation secondary to micrognathia, microstomia, and serious upper airway compromise
ii. Brittle and easily broken natal teeth during laryngoscopy
iii. Orotracheal intubation precluded by anterior placement or absence of the temporomandibular joints
iv. Difficult nasotracheal intubation secondary to hypoplastic nose and deviated nasal septum
v. Consider preoperative tracheotomy or prepare for emergency tracheotomy

c. Long-term nasal continuous positive airway pressure therapy for obstructive sleep apnea (Ryan et al. 1990)
d. Management for endocrine problem if present

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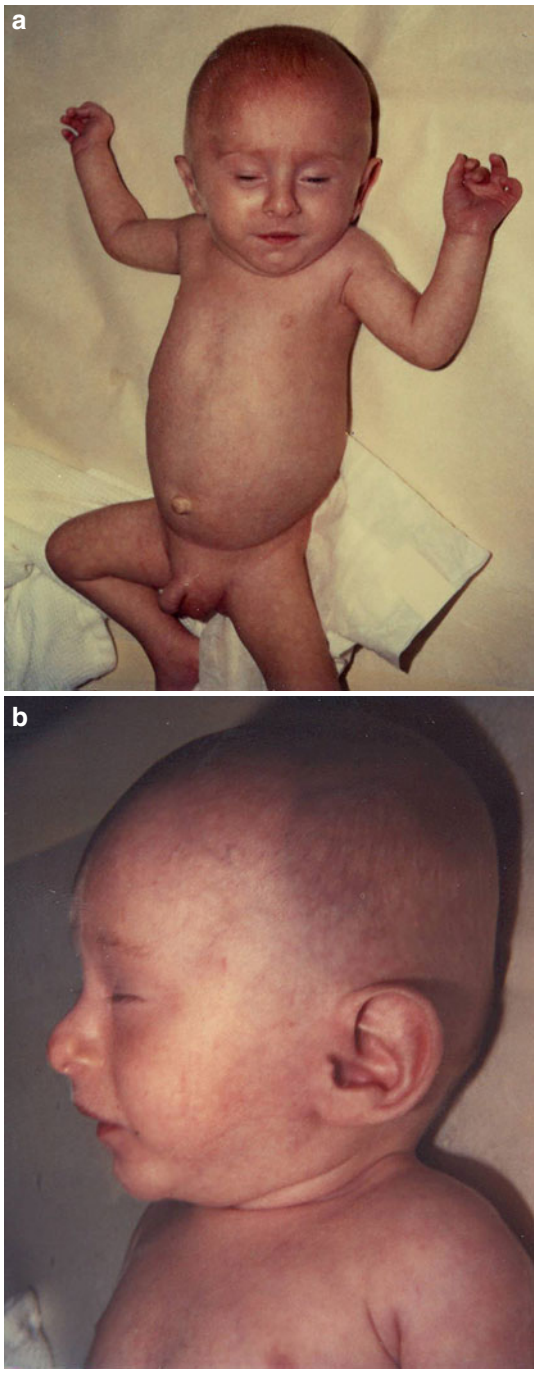

Fig. 1 (**a**, **b**) An infant with Hallermann-Streiff syndrome showing brachycephaly, frontal and parietal bossing, microphthalmia, thin, pointed nose, mandibular hypoplasia, and hypotrichosis

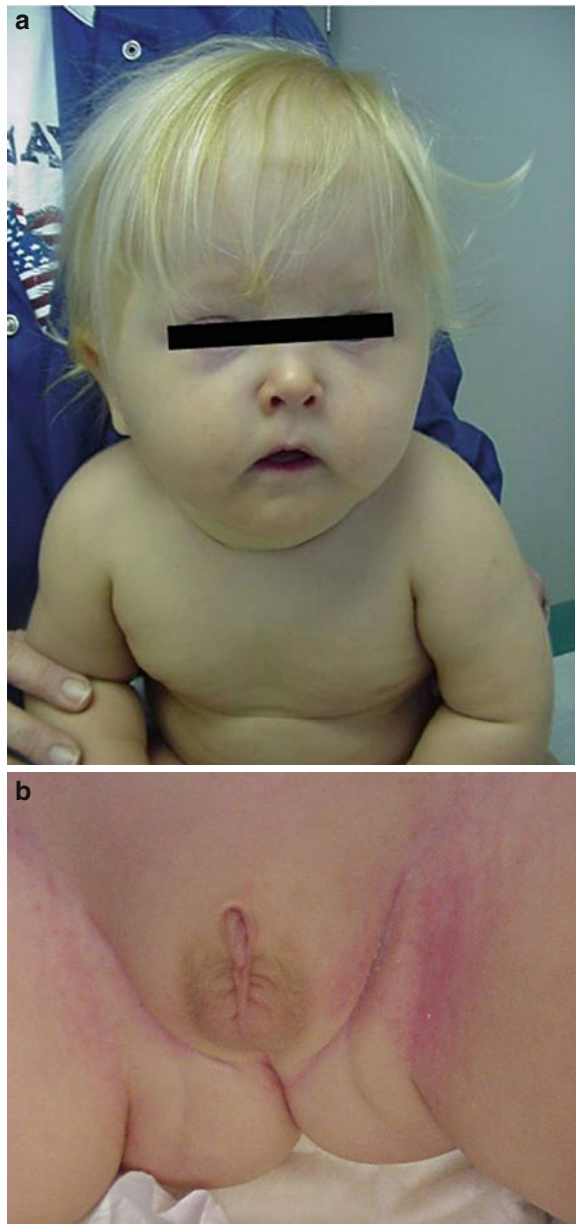

Fig. 2 (**a**, **b**) A male infant with Hallermann-Streiff syndrome showing frontal bossing, microphthalmia, thin nose, mandibular hypoplasia, hypotrichosis involving eyelashes and eyebrows, and genital hypoplasia

Fig. 3 (**a**, **b**) An adult with Hallermann-Streiff syndrome with mental retardation, short stature, alopecia, scanty eyelashes, a beaked nose, and scoliosis

Harlequin Ichthyosis

Harlequin ichthyosis is a rare severe scaling disorder and the most devastating congenital ichthyosis, which manifests in utero and is often fatal early in life.

Synonyms and Related Disorders

Congenital ichthyosis of harlequin type; Harlequin fetus

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. *ABCA12* gene
   a. Located on chromosome 2q34
   b. Consists of 53 exons and codes a 2595 amino acid protein member of the adenosine triphosphate (ATP)–binding cassette transporter family (Lefévre et al. 2003; Akiyama et al. 2005; Kelsell et al. 2005)
3. Caused by loss-of-function mutations in *ABCA12* (Akiyama and Shimizu 2008; Akiyama 2010)
   a. Truncation mutations: most mutations
      i. Nonsense mutations
      ii. Frameshift mutations (deletion/insertion mutations)
      iii. Splice site mutations
   b. Missense mutations
   c. Exon deletion
   d. Single amino acid deletions
4. Novel homozygous mutation p.R287X resulted from complete paternal isodisomy (Castiglia et al. 2009)
   a. Non-mosaic chromosome 2 trisomy from chorionic villus karyotyping while postnatal peripheral blood karyotype was normal female.
   b. These findings indicate that trisomic rescue is one step of the mutational cascade leading to reduction to homozygosity for the *ABCA12* mutation in the embryo.
5. Pathomechanisms of ichthyosis involving *ABCA12* mutations (Akiyama 2010): several morphologic abnormalities including abnormal lamellar granules in the keratinocyte granular layer and a lack of extracellular lipid lamellae within the stratum corneum observed in harlequin ichthyosis (Akiyama et al. 2005)
   a. Lack of *ABCA12* function subsequently leads to disruption of lamellar granule lipid transport in the upper keratinizing epidermal cells resulting in malformation of the intercellular lipid layers of the stratum corneum.
   b. Cultured epidermal keratinocytes from an harlequin ichthyosis patient carrying *ABCA12* mutations demonstrated defective glucosylceramide transport and this phenotype was recoverable by in vitro *ABCA12* corrective gene transfer.
   c. To date, intracytoplasmic glucosylceramide transport has been studied using cultured keratinocytes from a total of three patients harboring *ABCA12* mutations (Akiyama et al. 2005, 2006, 2007).
      i. One patient was a homozygote for a splice site mutation c.3295-2A > G.
      ii. Another patient was a compound heterozygote for p.Ser387Asn and p.Thr1387del.
      iii. Only one heterozygous mutation p.Ile1494Thr was identified in the other patient.

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iv. Cultured keratinocytes from all the three patients showed apparently disturbed glucosylceramide transport, although this assay is not quantitative.

6. Report of a male with harlequin ichthyosis with a de novo deletion of the long arm of chromosome 18 [46,XY,del(18)(q21.3)] suggesting the possible gene localization within the deleted region

Clinical Features

1. Major clinical features
   a. Large, thick, and yellowish armor-like plaques (platelike scales) with reddish, moist, oozing fissures and cracks, covering the whole body
   b. Severe ectropion (complete eversion of the non-keratinizing mucosa of the eyelids with occlusion of the eyes)
   c. Eclabium (eversion of the non-keratinizing mucosa of the lips)
   d. "Frog-like" grostesque appearance of the face
   e. Crumpled and flattened ears
   f. Flattened nasal tip with anteversion of the nares (nasal hypoplasia)
   g. Permanently opened mouth unable to suck properly
   h. Swollen extremities secondary to tight sausage-like encasement by the thickened stratum corneum
   i. Semiflexed rigid extremities (allowing little limb movement) with hypoplastic fingers
2. Minor clinical features
   a. Absent eyebrows and eyelashes
   b. Absent scalp hair
3. Associate anomalies
   a. Renal tubular defects
   b. Altered thymic structures
   c. Pulmonary hypoplasia
4. Natural history
   a. Restricted fetal movement caused by dense masses of hyperkeratotic scale
   b. Prematurity in most cases
   c. Perinatal death (usually in the first few weeks) secondary to:
      i. Respiratory compromise due to mechanical limitation of ribcage excursion
      ii. Sepsis
      iii. Hypothermia
      iv. Dehydration
      v. Malnutrition
      vi. Severe anemia
      vii. Renal failure
   d. Rare survivals
      i. Variable neurologic impairment
      ii. Short stature
      iii. Failure to thrive
      iv. At risk for severe keratitis due to ectropion of all eyelids

Diagnostic Investigations

1. Light microscopy findings
   a. Extraordinary compact orthohyperkeratosis (thickened orthokeratotic stratum corneum)
   b. Keratin plugs in hair follicles and sweat ducts
   c. Absent lamellar bodies and abundant vesicles in both the stratum granulosum and stratum corneum
   d. Abnormal lipid droplets and vacuoles in the cytoplasm of keratinized cells in the thick stratum corneum
2. Ultrastructural findings
   a. Abnormal lipid droplets and vacuoles in the cytoplasm of keratinized cells in the thick stratum corneum
   b. Absent normal lamellar granules in the cytoplasm of granular layer keratinocytes
   c. Lack of lamellar structure in the extracellular space between the first cornified cell and the granular cell
3. Biochemical analysis of skin samples: a defect of conversion from profilaggrin to filaggrin
4. Family history for evidence of consanguinity
5. Molecular genetic diagnosis by gene sequencing or deletion/duplication analysis of *ABCA12*

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: patient not surviving to reproductive age
2. Prenatal diagnosis possible in families at risk
   a. Ultrasonography (2D, 3D and 4D) at 18–24 weeks (Kudla and Timmerman, 2010).

i. Minimal fetal movement with stiff limbs in a semiflexed position
ii. Swollen limbs with hypoplastic fingers and toes and short phalanges
iii. Shriveled hands that do not open
iv. Characteristic facial features
  a) Flat face profile
  b) Open eyes
  c) Ectropion
  d) Cataracts
  e) Flat nose
  f) Thick lips
  g) Eclabium
  h) Absence of typical ear morphology (hypoplasia of the ears)
  i) Large open mouth
  j) Micrognathia
  k) Partitioned cystic formations in front of the eyes
v. Short neck
vi. Thick skin
vii. Choroid plexus cysts
viii. Short umbilical cord
ix. Hyperechogenic amniotic fluid
x. Absence of associated visceral anomalies

b. Amniocentesis: demonstration of clumping of keratinocyte cells in the amniotic fluid containing lipid droplets and amorphous electron dense material.
c. Electron microscopy of the fetal skin biopsy specimen from fetoscopy at 20–22 weeks.
  i. Abnormal vacuoles in keratinized cells
  ii. Abnormal lamellar granules in the hair canal
d. Molecular genetic testing: After identification of ABCA12 as the causative gene for harlequin ichthyosis, it is feasible to perform DNA-based prenatal diagnosis for harlequin ichthyosis by chorionic villus or amniotic fluid sampling (Akiyama et al. 2007; Yanagi et al. 2008) or preimplantation genetic diagnosis. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

3. Management
a. Temperature control.
b. Electrolyte and fluid balance.
c. Adequate caloric intake.
d. Prevention of infection with antibiotics.
e. Topical steroids to reduce secondary inflammation.
f. Tretinoin creams or ointments or oral retinoid treatment to reduce the amount of scale. Early use of systemic retinoids promotes accelerated shedding of the hyperkeratotic plates, whereas continued use reduces scale and improves ectropion and eclabium (Harvey et al. 2010).
g. Pain management with anti-inflammatory drugs and morphine sulfate if necessary.
h. Ocular management.
  i. Intensive topical eye ointment
  ii. Treat keratitis promptly
  iii. Surgical management of the ectropion by skin-release surgery with autologous skin grafting in patients with severe exposure keratitis or cosmetically unacceptable ectropion
i. Careful handling to avoid hard friction and physical contract for prevention of blistering.

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Fig. 1 (**a**–**d**) A newborn with harlequin ichthyosis, covered with yellowish plaques (severe hyperkeratosis) with moist fissures and cracks and grostesque appearance of face with ectropion, eclabium, a flat nose, crumpled/flat ears, and swollen/semiflexed rigid limbs

Hemophilia A

Hemophilia A is a congenital X chromosome–linked coagulation disorder characterized by deficiency in factor VIII clotting activity that results in prolonged oozing after injuries, tooth extractions, or surgery and delayed or recurrent bleeding prior to complete wound healing. It affects approximately 1 in 5,000–1 in 10,000 male births.

Synonyms and Related Disorders

Classic hemophilia

Genetics/Basic Defects

1. Inheritance (Hedner et al. 2000)
   a. An X-linked recessive disorder
   b. New mutations in approximately one third of patients
   c. Hemophilia A in females
      i. Rarely reported
      ii. Possible explanation
         a) Extreme skewing of X chromosome inactivation resulting in unusually low factor VIII levels in female hemophilia A carriers
         b) Rare individuals carrying a hemophilia A mutation associated with an X chromosome–autosome translocation or other cytogenetic abnormality, which may result in exclusive inactivation of the normal X chromosome
         c) Rare individuals carrying a hemophilia A mutation in the rearranged X-chromosome
2. Molecular genetics (Hedner et al. 2000)
   a. Caused by absent or decreased factor VIII (FVIII) procoagulant function, resulting from mutations in FVIII (*F8*) gene, mapped on chromosome Xq28.
   b. A unique rearrangement within the FVIII gene (intron 22 gene inversion), recently identified as a common, recurrent mechanism for hemophilia A.
      i. Accounting for approximately 45% of all severe hemophilia A patients.
      ii. The mutation almost always arises during a male meiosis.
      iii. The mother of an apparently new mutation patient with an identified gene inversion can generally be assumed to be a carrier, with the recombination event often identified in the maternal grandfather's allele.
   c. The remaining 55% of severe hemophilia patients are shown to have a more conventional molecular defect in the FVIII gene.
      i. Approximately 50% of patients with specific point mutations in exons or at splice junctions within the FVIII gene
      ii. Approximately 5% of patients with deletions which remove varying-sized segments of the FVIII gene
      iii. Rare small insertions and deletions
   d. Nearly all patients with mild or moderately severe hemophilia A have some residual level of FVIII activity, shown to have a point mutation within the FVIII coding sequence, resulting in a single amino acid substitution.
   e. Clinical severity of the hemophilia A phenotype correlates very closely with the amount of residual factor VIII activity.

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Clinical Features

1. Clinical features suspecting a coagulation disorder (Hedner et al. 2000)
   a. Hemarthrosis, especially with mild or no antecedent trauma
   b. Deep muscle hematomas
   c. Intracranial bleeding in the absence of major trauma
   d. Cephalohematoma or intracranial bleeding at birth
   e. Prolonged oozing or renewed bleeding after initial bleeding stops following tooth extractions, mouth injury, or circumcision
   f. Prolonged bleeding or renewed bleeding following surgery or trauma
   g. Unexplained gastrointestinal bleeding or hematuria
   h. Menorrhagia, especially at menarche
   i. Prolonged nosebleeds, especially recurrent and bilateral
   j. Excessive bruising, especially with firm, subcutaneous hematomas
2. Severe hemophilia A (43% of hemophiliacs)
   a. Spontaneous bleeding
      i. Joints: the most frequent symptom
      ii. Other sites
         a) Kidneys
         b) Gastrointestinal tract
         c) Brain
   b. Without treatment
      i. Bleeding from minor mouth injuries and large "goose eggs" from minor head bumps during the toddler period
      ii. Rare intracranial bleeding resulting from head injuries
      iii. Almost always with subcutaneous hematomas
      iv. Frequency of bleeding
         a) Relating to the FVIII clotting activity
         b) Varying from two to five spontaneous bleeding episodes each month
         c) Bleeding episodes more frequent in childhood and adolescence than in adulthood
   c. Age of diagnosis
      i. Usually diagnosed during the first year of life
      ii. Relating to the FVIII clotting activity
3. Moderately severe hemophilia A (26% of hemophiliacs)
   a. Seldom with spontaneous bleeding
   b. Without treatment
      i. Prolonged or delayed oozing after relatively minor trauma
      ii. Frequency of bleeding
         a) Varying from once a month to once a year
         b) Bleeding episodes more frequent in childhood and adolescence than in adulthood
   c. Usually diagnosed before the age of 5–6 years
4. Mild hemophilia A (31% of hemophiliacs)
   a. Absent spontaneous bleeding
   b. Without treatment
      i. Occurrence of abnormal bleeding with surgery, tooth extraction, and major injuries
      ii. Frequency of bleeding
         a) Varying from once a year to once every 10 years
         b) Bleeding episodes more frequent in childhood and adolescence than in adulthood
   c. Often not diagnosed until later in life
5. Carrier females
   a. Risk of bleeding in approximately 10% of carrier females
   b. Mild symptoms
6. Complications of untreated bleeding
   a. Intracranial hemorrhage: the leading cause of death
   b. Chronic joint disease: the major cause of disability
7. Life expectancy: 60–70 years
8. Differential diagnosis
   a. Inherited bleeding disorders associated with a low factor VIII clotting activity
      i. Type 1 vWD (mild von Willebrand disease)
         a) An autosomal dominant disorder
         b) Predominant feature: mucous membrane bleeding
         c) Quantitative deficiency of von Willebrand factor (low vWF antigen, factor VIII clotting activity, and ristocetin cofactor activity) in 80% of patients
      ii. Type 2 vWD
         a) Quantitative deficiency of vWF with a decrease of the high molecular weight multimers
         b) Low normal to mildly decreased vWF antigen and factor VIII clotting activity
         c) Low functional vWF level in a ristocetin cofactor assay

iii. Type 2 N (Normandy) vWD
  a) An uncommon variant due to several missense mutations in the amino terminus of the vWF protein, resulting in defective binding of factor VIII to vWF
  b) Low factor VIII clotting activity usually showing autosomal recessive inheritance
  c) Indistinguishable clinically from mild hemophilia A, which can be differentiated with molecular genetic testing of the FVIII gene, molecular genetic testing of the vWF gene, or measuring binding of factor VIII to vWF using ELISA or column chromatography
iv. Type 3 vWD (severe von Willebrand disease)
  a) An autosomal recessive disorder
  b) Frequent episodes of mucous membrane bleeding and joint and muscle bleeding similar to hemophilia A
  c) <1% vWF level
  d) Two to eight FVIII clotting activity
v. Mild combined factor V and factor VIII deficiencies
  a) A rare autosomal recessive disorder
  b) Deficiency of a chaperone protein (ERGIC-53)

b. Acquired hemophilia A (Collins et al. 2010)
  i. A bleeding disorder caused by an autoantibody to factor VIII
  ii. Estimated incidence: 1.5/million/year
  iii. Predominantly affects older patients
  iv. Acute onset of severe and life-threatening bleeding or widespread subcutaneous bleeds
  v. Bleeding sites atypical of congenital hemophilia
  vi. Presence of underlying diseases and conditions
  vii. No personal or family history of bleeding
  viii. High mortality with both early and late deaths: estimated at between 9% and 22%
  ix. Prolonged aPTT (activated partial thromboplastin time) with a normal prothrombin time (PT)
  x. Mixing test: failure of normal plasma to correct the aPTT by more than 50% is usually taken as evidence that an inhibitor is present (Kasper 1991)

c. Other bleeding disorders with normal factor VIII clotting activity
  i. Hemophilia B
    a) An X-linked recessive disorder caused by mutations in the factor IX (FIX) gene
    b) Clinically indistinguishable from hemophilia A
    c) Diagnosis based on factor IX clotting activity of <30%
  ii. Factor XI deficiency
    a) An autosomal recessive disorder
    b) Homozygotes with factor XI coagulant activity of <1–15%
    c) Heterozygotes with factor XI coagulant activity of 25–75%
  iii. Factor XII, prekallekrein, or high-molecular-weight-kininogen deficiencies
    a) Do not cause clinical bleeding
    b) A prolonged PTT
  iv. Prothrombin (factor II) or factors V, X, or VII deficiencies
    a) Autosomal recessive disorders
    b) Clinical features: easy bruising and hematoma formation, epistaxis, menorrhagia, bleeding after trauma and surgery
    c) Diagnosis established by specific coagulation factor assays
  v. Fibrinogen disorders
    a) Afibrinogenemia: an autosomal recessive disorder characterized by prolonged bleeding from minor cuts due to the lack of fibrinogen to support platelet aggregation
    b) Hypofibrinogenemia: inherited either in an autosomal dominant or recessive fashion with mild to moderate bleeding symptoms or may be asymptomatic
    c) Dysfibrinogenemia: an autosomal dominant disorder with symptoms similar to hypofibrinogenemia
  vi. Factor XIII deficiency
    a) An autosomal recessive disorder
    b) Occurrence of umbilical stump bleeding in >80% of cases
    c) Intracranial bleeding occurring spontaneously or following minor trauma in 30% of cases
    d) Subcutaneous hematomas
    e) Muscle hematomas

f) Defective wound healing
g) Recurrent spontaneous abortion
h) Rare joint bleeding

vii. Platelet function disorders
a) General features: bleeding problems similar to thrombocytopenia (skin and mucous membrane bleeding, recurring epistaxis, gastrointestinal bleeding, menorrhagia, excessive bleeding during or immediately after trauma and surgery)
b) Bernard-Soulier syndrome: an autosomal recessive disorder involving the vWF receptor and platelet GPIb characterized by thrombocytopenia and large platelets
c) Glanzmann thrombasthenia: an autosomal recessive disorder involving the GPIIb-IIIa receptor necessary for platelet aggregation

Diagnostic Investigations

1. Coagulation screening test
   a. Prolonged partial thromboplastin time (PTT) in severe and moderately severe hemophilia A
   b. PTT often normal in mild hemophilia A
2. Coagulation factor assay for factor VIII clotting activity
   a. Normal range: 50–150%
   b. Low to low normal: above 35%
      i. Usually do not have bleeding
      ii. Bleeding can occur in association with mild von Willebrand disease
   c. Factor VIII clotting activity unreliable in the detection of carriers
   d. Diagnosis of hemophilia A established in patients with low FVIII clotting activity (<35%) in the presence of a normal von Willebrand factor (vWF) level
      i. Activity <1%: severe hemophilia A
      ii. Activity 1–5%: moderately severe hemophilia A
      iii. Activity 5–35%: mild hemophilia A
3. Hemophilia imaging (Maclachlan et al. 2009)
   a. Hemophilia arthropathies: radiography, ultrasound, MRI
   b. Intramuscular hemorrhage: MRI
   c. Soft tissue hemorrhage (pseudotumors): CT/MRI
   d. Intracranial hemorrhage: CT/MRI
   e. Complications secondary to administration of blood products (liver cirrhosis, liver failure, hepatocellular carcinoma): CT/MRI
4. Molecular genetic diagnosis (Brower and Thompson 2008)
   a. Targeted mutation analysis
      i. An *F8* intron 22-A gene inversion: accounts for nearly half of families with severe hemophilia A (Kaufman et al. 2006)
      ii. An F8 intron 1 gene inversion: accounts for 2–3% of severe hemophilia A
   b. Mutation scanning or sequence
      i. Seventy-five to ninety-eight percent mutation detection rate in individuals with hemophilia A who do not have one of the two common inversions
      ii. Gross gene alterations (including large deletions or insertions, frame shift and splice junction changes, and nonsense and missense mutations) of F8: account for approximately 50% of mutations detected in severe hemophilia A (Kemball-Cook et al. 1998; El-Maarri et al. 2005; Kaufman et al. 2006)
      iii. Missense mutations within the exons coding for the three A domains or the two C domains: account for most of the mutations detected in mild to moderately severe hemophilia A (Kemball-Cook et al. 1998; Kaufman et al. 2006)
   c. Deletion analysis
      i. Available clinically to detect exonic, multiexonic, or larger deletions in affected males
      ii. Also available for direct diagnosis in potential carrier females
   d. Indirect genetic linkage analysis (Ljung and Tedgård 2003)
      i. Using linked polymorphic markers (restriction fragment length polymorphisms, RFLP) to trace the inheritance of the hemophilia gene within a pedigree if mutation is not found
      ii. Limitation of linkage analysis
         a) Uninformative patterns of polymorphic markers
         b) Ethnic variation
         c) Linkage disequilibrium
         d) Need for participation of family members
         e) Not useful in sporadic families which constitute more than half of the hemophilia families

Genetic Counseling

1. Recurrence risk
   a. Obligatory carrier (Ljung and Tedgård 2003)
      i. A woman whose father has hemophilia
      ii. A woman who has given birth to two boys with hemophilia, excluding identical twins
      iii. A woman who has given birth to one son with hemophilia and a daughter who has a son with hemophilia
   b. Establish the genetic probability for carriership for women in a pedigree who are not genetic obligatory carriers based on:
      i. Pedigree data
      ii. Clotting factor (FVIII:C) analysis
   c. Patient's sib (sib of a male proband): risk to the sibs depending on the carrier status of the mother
      i. Mother is a carrier: a 50% risk of having a male sib with hemophilia A and a 50% risk of having a carrier female sib
      ii. Possibility of maternal germline mosaicism: a low recurrence risk of having a male sib with hemophilia A if the mother has a normal factor VIII clotting activity and no evidence of her carrying her son's FVIII disease-causing mutation in her leukocytes, unless she has germline mosaicism
   d. Patient's offspring
      i. No sons will inherit the mutant allele and therefore will not be affected with hemophilia A
      ii. All daughters will be carriers for hemophilia A
2. Prenatal diagnosis available to pregnancies of carrier women with hemophilia A
   a. Fetal karyotyping to determine male fetus (46,XY)
   b. DNA extracted from fetal cells by amniocentesis or CVS analyzed for:
      i. The known FVIII disease-causing mutation
      ii. The informative linked polymorphic markers
   c. Fetal blood sample obtained by percutaneous umbilical blood sampling (PUBS) for assay of factor VIII clotting activity if the disease-causing FVIII mutation is not known and if linkage testing is not informative
   d. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified in an affected family member
3. Management
   a. Prophylactic treatment using plasma-derived concentrate of coagulation factor in the past (Mannucci 2003)
      i. Preventing majority of bleeding episodes
      ii. Minimizing the impact of arthropathy
      iii. Complications
         a) Concentrates manufactured from plasma, pooled from thousands of donors, invariably contaminated with blood-borne viruses that caused posttransfusion hepatitis B and non-A non-B (hepatitis C) in practically all treated hemophiliacs
         b) Optimistic perception of hemophilia: benefits of concentrates seemed to outweigh hepatitis risks
         c) Tragedy: 60–80% of persons with severe hemophilia became infected with the human immunodeficiency virus (HIV) with contaminated concentrates in the early 1980s
   b. Infusion of plasma-derived or recombinant FVIII (Helixate, Kogenate, Recombinate, ReFacto) (Bhattacharyya et al. 2003; Vandendriessche et al. 2003)
      i. Markedly improves both the life expectancy and the quality of life of patients suffering from hemophilia A
      ii. Still at risk for life-threatening bleeding episodes and chronic joint damage
      iii. Side effect of clotting factor substitution therapy: develop neutralizing antibodies against FVIII, rendering further substitution ineffective (10–40% of cases)
   c. Promising new recombinant factor VIII products are in advanced stages of clinical trials, and studies are underway to address how to optimally use current resources to improve quality of life for individuals with severe hemophilia A (Powell 2009)
   d. Orthopedic management (Rodriguez-Merchan 2008)
      i. Hemarthrosis: arthrocentesis
      ii. Synovitis: synoviorthesis and synovectomy
      iii. Flexion contractures
         a) Tendon-lengthening procedures
         b) Supracondylar osteotomy to correct a fixed-knee contracture
         c) Implantation of an external fixator

iv. Hemophilic arthropathy
  a) Subchondral bone cysts: cheilectomy and curettage
  b) Alignment osteotomy
  c) Joint debridement
  d) Arthrodesis
  e) Joint prosthesis
  f) Total knee arthroplasty
  g) Total hip arthroplasty
v. Intramuscular hematomas: usually reabsorb without complication when hematological treatment is adequate
  a) Iliopsoas hematoma
  b) Compartment syndrome (fasciotomy)
  c) Pseudotumors
vi. Orthopedic surgery in patients with inhibitors: contemporary orthopedic and hematological advances such as recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsværd, Denmark) and activated prothrombin complex concentrates (aPCC; FEIBA, Baxter Corp, Deerfield, IL) enable major orthopedic operations to be performed on hemophilia patients with inhibitors, despite these patients having a higher risk of bleeding complications than patients with hemophilia who do not have inhibitors (Rodriguez-Merchan et al. 2007)

e. Obstetrical issues
  i. Asymptomatic carrier
    a) Uncommon intracranial hemorrhage in affected male fetuses (1–2%)
    b) Cesarean section reserved for complicated deliveries
  ii. Symptomatic carrier (baseline factor VIII clotting activity <35%)
    a) Somewhat protected by the natural rise of factor VIII clotting activity during pregnancy
    b) Delayed postpartum bleeding when factor VIII clotting activity returns to baseline within 48 h

f. Neonatal issues
  i. Early determination of the genetic status of male infants at risk
    a) Assay factor VIII clotting activity from a cord blood sample obtained by venipuncture of the umbilical vein
    b) Molecular genetic testing for the FVIII mutation identified in the family
  ii. Avoid circumcision in infants with a family history of hemophilia A, unless:
    a) Hemophilia A is excluded or
    b) Factor VIII concentrate is administered just prior and subsequent to the procedure to prevent delayed oozing and poor wound healing

g. Analysis of patients's DNA
  i. Permits identification of the gene lesions that cause hemophilia
  ii. Allows the disease to be controlled through carrier detection and prenatal diagnosis

h. Future gene therapy (Vandendriessche et al. 2003)
  i. Providing a cure for the disease
  ii. Providing constant, sustained FVIII synthesis in the patient
    a) Obviate the risk of spontaneous bleeding
    b) Obviate the need for repeated FVIII infusions
    c) Obviate the risk of viral infections associated with plasma-derived FVIII
  iii. Requires the use of a gene delivery system that is efficient, safe, nonimmunogenic, and allows for long-term gene expression
  iv. Must compare favorably with existing protein replacement therapies
  v. Initiation of several gene therapy phase I clinical trials in patients suffering from severe hemophilia A
    a) Fewer bleeding episodes reported in some patients
    b) Occasional detection of low levels of clotting factor activity

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Fig. 1 A boy with hemophilia A who is asymptomatic with prophylactic infusions of recombinant FVIII

Fig. 2 An infant boy with hemophilia A who was found to have low factor VIII activity. The mother and maternal grandmother had histories of nosebleeds and prolonged bleeding after small cuts and bruise easily

Fig. 3 A 30-year-old man with hemophilia B

Hereditary Hearing Loss

Hearing loss can be divided into conductive, sensorineural, mixed, and central types (Gifford et al. 2009). Conductive hearing loss (CHL) results from interference with the mechanical transmission of sound through the external and middle ear. Sensorineural hearing loss (SNHL) results from a failure to transduce vibrations to neural impulses effectively within the cochlea or transmit these impulses down the vestibulocochlear nerve. Mixed hearing loss involves a combination of CHL and SNHL, usually due to damage throughout the middle ear and the inner ear. Central hearing loss refers to defects in the brainstem or higher processing centers of the brain. Both CHL and SNHL may be caused by a wide variety of congenital/hereditary and acquired factors.

Understanding genetic basis of hearing loss is important because almost 50% of profound hearing loss (affecting almost 1 in 1,000 newborns) is caused by genetic factors and more than 120 independent genes have been identified (Bayazit and Yilmaz 2006).

Genetics/Basic Defects

1. Causes of conductive hearing loss (Bayazit and Yilmaz 2006; Gifford et al. 2009; Hilgert et al. 2009)
   a. Congenital
      i. Microtia/atresia
      ii. Tympanic membrane abnormalities
      iii. Ossicular malformations
   b. Acquired
      i. Infections
         a) Acute otitis media
         b) Otitis externa
         c) Ossicular erosion
      ii. Otitis media with effusion
      iii. Foreign body including cerumen
      iv. Cholesteatoma
      v. Trauma
         a) Ossicular disruption
         b) Tympanic membrane perforation
2. Nonhereditary causes of sensorineural hearing loss (SNHL)
   a. In utero infections
      i. Cytomegalovirus: the most common environmental (nongenetic) cause of congenital hearing loss
      ii. Measles
      iii. Mumps
      iv. Rubella
      v. Varicella
      vi. Syphilis
   b. Anatomic abnormalities of the cochlea or temporal bone
   c. Exposure to ototoxic drugs during pregnancy
      i. Alcohol
      ii. Isotretinoin
      iii. Cisplatinum
   d. Hyperbilirubinemia
   e. Infections
   f. Trauma
      i. Physical
      ii. Acoustic
   g. Radiation therapy for head and neck tumors
3. Hereditary hearing loss: mutations and polymorphisms
   a. Recessive gene mutations
      i. Homozygosity
         a) Same mutation is present in both alleles

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b) Having two identical alleles as a specific autosomal (or X chromosome in a female) gene locus
c) Can cause hearing impairment

ii. Heterozygosity
a) Having two different alleles as a specific autosomal (or X chromosome in a female) gene locus
b) "Compound heterozygote": both alleles have different disease-causing mutations; can cause hearing impairment
c) "Carrier": only one of the alleles has the disease-causing mutation and the other allele is normal; does not have hearing impairment

b. Dominant gene mutations
i. Presence of a mutation in only one of the alleles: enough for the individual to have the disease
ii. Penetrance in the dominant gene
a) Likelihood that a person carrying a particular mutant gene will have an altered phenotype
b) May differ in different individuals
c) Presence of a dominant mutation in the parents does not always mean that the siblings will always have hearing impairment
iii. Expression of a disease-causing gene
a) May cause differences in the phenotype
b) Expression may be one of the reason why the same genotype or mutations are manifested by different phenotypes in genetic hearing loss

c. Genetic polymorphism
i. Most polymorphisms have no detectable clinical effects
ii. If one of the alleles is mutated and the other allele has a polymorphism, the individual will probably not have hearing impairment

4. Genetic nonsyndromic hearing loss (NSHL): to date, there are 46 nonsyndromic deafness genes reported in the literature (Hilgert et al. 2009)
a. Autosomal dominant NSHL
i. Constitutes 18% of NSHL
ii. Affects almost 50% of the siblings
iii. Usually postlingual hearing loss except for DFNA3, DFNA6, DFNA8, DFNA12, DFNA19 and DFNA14
iv. *WFS1* gene mutations cause:
a) Autosomal dominant low-frequency SNHL
b) Wolfram syndrome (hearing loss, diabetes mellitus, diabetes insipidus, and optic atrophy)
v. *KCNQ4* gene mutations
a) Frequent cause of autosomal dominant NSHL
b) Missense mutations cause hearing loss beginning at a young age and affecting all frequencies
c) Deletion mutations cause a milder phenotype with later onset and affecting only the high frequencies
d) W276S mutation in *KCNQ4*: may be a mutational "hot spot" (van Camp et al. 2002)
vi. *COCH* gene mutations
a) Frequent mutations: P51S in Belgium and the Netherlands
b) Cause progressive hearing loss and vestibular impairment with late onset
vii. Dominant mutations in *GJB2* cause:
a) Autosomal dominant NSHL
b) Syndromic hearing loss associated with diverse skin disorders (include diffused palmoplantar keratoderma-hyperkeratosis, Vohwinkel syndrome and keratitis-ichthyosis-deafness [KID] syndrome) (Richard et al. 2002; de Zwart-Storm et al. 2008)
viii. *TECTA* gene mutations cause autosomal dominant mid-frequency HL and high-frequency HL

b. Autosomal recessive NSHL
i. Constitutes 80% of all NSHL cases
ii. Usually prelingual and severe hearing loss except for DFNB8 in which hearing loss is postlingual and rapidly progressive
iii. Affects almost 25% of siblings
iv. DFNB1 (Kelsell et al. 1997; Denoyelle et al. 1999): caused by a mutation in the *GJB2* gene on chromosome 13q12-13 that codes for a gap junction protein called connexin 26
a) *GJB2* mutations: the most frequent cause of autosomal recessive nonsyndromic

hearing loss in most world populations, frequent in the Caucasian, Jewish, and Asian populations (Morell et al. 1998; Abe et al. 2000)
b) 35delG mutation: most frequent in the majority of Caucasian populations and may account for up to 70% of all *GJB2* mutations (Snoeckx et al. 2005)
v. *SLC26A4* gene mutations
a) The second most frequent cause of autosomal NSHL
b) Associated phenotypic spectrum: ranges from Pendred syndrome at one extreme to isolated NSHL with enlarged vestibular aqueduct at the other (DFNB4 locus)
vi. *MYO15A* gene mutations
a) Cause congenital severe-to-profound hearing loss at the DFNB3 locus
b) All 28 identified mutations have been found by linkage analysis in consanguineous families, most of which originate from Pakistan
vii. *OTOF* gene mutations
a) Cause prelingual, profound autosomal recessive NSHL
b) Suggest as the major cause of auditory neuropathy
viii. *CDH23* gene mutations: cause both Usher syndrome type 1D and moderate-to-profound progressive autosomal recessive NSHL at the DFNB12 locus
ix. *TMC1* gene mutations
a) One of the more frequent causes of autosomal recessive NSHL in consanguineous populations
b) Characterized by prelingual severe-to-profound hearing loss

c. X-linked recessive NSHL
i. Constitutes 1–3% of all NSHL cases
ii. Usually prelingual hearing loss except for DFN6
iii. Frequently affects boys
iv. DFN2 and DFN4: mostly cause severe prelingual sensorineural hearing loss
v. *POU3F4* gene (at locus DFN3) mutations
a) Cause X-linked mixed or purely sensorineural HL
b) May be associated with Mondini dysplasia, cochlear hypoplasia and/or stapes fixation

d. Mitochondrial hearing loss
i. Mutations in mitochondrial genes: the majority are the cause of a broad spectrum of maternally inherited multisystem disorders
ii. A subset of genes causes NSHL by a currently unknown mechanism
a) *MT-RNR1*
b) *MT-TS1*

5. Genetic syndromic hearing loss
a. Usher syndrome
i. The most common cause of autosomal recessive syndromic hearing loss (Smith et al. 1994)
ii. Affects almost 50% of the blind and deaf people in the USA
iii. Mutations
a) USH1A-G
b) USH2A-C
c) USH3

b. Pendred syndrome
i. Almost 50% of families with *SLC26A4* (PDS) gene mutation on chromosome 7q21-q34
ii. The same mutation can also cause DFNB4 (Li et al. 1998)

c. Jervell and Lange-Nielsen syndrome: mutations in the following potassium channel genes
i. JLNS1 locus in the *KVLQT1* gene located on chromosome 11p15.5
ii. JLNS2 locus in the *KCNE1* (*IsK*) gene located on chromosome 21q22.2

d. Biotinidase deficiency: resulting from deficiency of an enzyme required for the normal recycling of the vitamin biotin

e. Waardenburg syndrome (WS): has four subgroups (Van Camp and Smith 2010)
i. Type I: *PAX3* on 2q35
ii. Type II: *MITF* on 3p14.1-p12.3; *SLUG* on 8q11
iii. Type III: *PAX3* on 2q35
iv. Type IV: *EDNRB* on 13q22; *EDN3* on 20q13.2-q13.3; *SOX10* on 22q13

f. Branchio-oto-renal (BOR) syndrome
i. *EYA1* gene mutation on chromosome 8q13.3 (in 50% of patients)
ii. Mutations on chromosome 1q31 may also cause this syndrome (Abdelhak et al. 1997)

g. Stickler syndrome
   i. The STL1 locus in the *COL2A1* gene located on chromosome 12q13.11-q13.2 is responsible for type 1
   ii. The STL2 locus in the *COL11A1* gene located on chromosome 1p21 is responsible for type 2
   iii. The STL3 locus in the *COL11A2* gene located on chromosome 6p21.3 is responsible for type 3
h. Treacher-Collins syndrome (TCOF): caused by *TCOF1* gene mutation on chromosome 5q32-q33.1
i. Alport syndrome
   i. X-linked (85%): *COL4A5* gene (Xq22) mutation is responsible
   ii. *COL4A3* and *COL4A4* (on 2q36-q37) mutation: responsive for the autosomal recessive and autosomal dominant types
      a) Autosomal recessive (15%)
      b) Autosomal dominant (rare)
j. Norrie disease
   i. Caused by *Norrin* gene mutation on Xp11.3
   ii. *Norrin* gene is considered to control vascularization in the cochlea and retina

6. Mitochondrial hearing loss
   a. Constitutes <1% of all HHL cases
   b. Only maternal DNA is transmitted to the child while paternal DNA is not
   c. All children are at risk of having hearing impairment when the mitochondrion of the mother possesses a disease-causing mutation
7. Heterogeneity of genetic hearing loss
   a. Genetic hearing loss: a heterogeneous condition although it is mostly caused by a mutation in a single gene (Hardisty et al. 1999)
   b. Syndromic, nonsyndromic, recessive, or dominant hearing loss may be caused by the same mutation in a single gene
   c. Recessive or dominant NSHL can be caused by connexin 26, connexin 31, and *MYO7A* mutations
   d. *COL11A2*, PDS, *MYO7A*, and connexin 26 mutations can cause syndromic or nonsyndromic hearing loss (De Leenheer et al. 2001; Tamagawa et al. 2002)

Clinical Features

1. Usher syndrome (Bayazit and Yilmaz 2006)
   a. The most common cause of autosomal recessive syndromic hearing loss (Smith et al. 1994)
   b. Almost 50% of the blind and deaf people in the USA have this syndrome
   c. Type 1
      i. Severe hearing loss and vestibular dysfunction
      ii. Retinitis pigmentosa (a progressive degeneration of the retina leading to loss of night vision, restriction of the visual fields, and blindness) starting in childhood
   d. Type 2
      i. Mild to moderate hearing loss
      ii. Normal vestibular function
      iii. Retinitis pigmentosa occurring after childhood
   e. Type 3
      i. Progressive hearing loss and vestibular dysfunction
      ii. Retinitis pigmentosa occurring any time in life
2. Pendred syndrome (Reardon et al. 1997)
   a. Severe congenital sensorineural hearing loss
   b. Euthyroid goiter
      i. Due to a specific defect in the organification of iodine
      ii. Can be demonstrated by the perchlorate test
   c. Labyrinthine bone abnormality like Mondini dysplasia seen in 86% of cases
   d. Vestibular dysfunction can occur
   e. Onset may be delayed and clinically unapparent
   f. Rarely associated with hypothyroidism
3. Jervell and Lange-Nielsen syndrome (Splawski et al. 1997)
   a. Congenital hearing loss
   b. Elongation of the QT interval on electrocochleography (QT > 440 ms)
   c. Syncope and sudden death due to a cardiac problem
4. Biotinidase deficiency: clinical manifestations within the first few months of life if untreated
   a. Skin rashes
   b. Seizures

c. Hair loss
d. Hypotonia
e. Vomiting
f. Acidosis
g. Seventy five percent of the affected infants develop hearing loss if untreated
h. Biotinidase deficiency is a completely preventable form of genetic deafness with supplementation of biotin

5. Waardenburg syndrome
   a. Sensorineural hearing loss
      i. Accounts for 1–2% of individuals with profound hearing loss
      ii. Can be bilateral or unilateral of varying severity
   b. Pigmentation abnormality in the skin and hair
   c. White forelock
   d. Dystrophia canthorum (lateral displacement of the inner canthi of the eyes)
   e. Pinched nose
   f. Heterochromia iridis (different iris colors)
   g. Gastrointestinal features
      i. Constipation
      ii. Hirschsprung disease
   h. Neural tube and limb defects
6. Branchio-oto-renal (BOR) Syndrome
   a. Conductive, sensorineural, or mixed hearing loss
      i. Some degree of hearing loss in almost 80% of gene carriers
      ii. Can be delayed in onset
   b. Branchial cleft cyst
   c. Auricle or external auditory canal abnormality
   d. Preauricular pits
   e. Renal abnormalities
      i. Renal dysplasia
      ii. Polycystic kidney
      iii. Malformation of the calyces
   f. Inner ear abnormalities
      i. Mondini dysplasia
      ii. Stapes fixation
7. Stickler syndrome
   a. Progressive sensorineural hearing loss
   b. Cleft palate
   c. Abnormal development of the epiphysis
   d. Vertebral abnormalities
   e. Osteoarthritis
8. Treacher-Collins syndrome
   a. Hearing loss
      i. Conductive in 55% of cases
      ii. Sensorineural hearing loss usually occurs at high frequencies
   b. Symmetric and hypoplastic zygoma
   c. Lower palpebral fissure
   d. Malformed and small ear
   e. Auditory pit
9. Alport syndrome
   a. Progressive bilateral hearing loss
      i. In almost 50% of cases
      ii. Usually begins in the second decade
      iii. Initially involves high-frequency hearing loss
   b. Renal disorder
      i. Glomerulonephritis
      ii. Hematuria
      iii. Renal failure
   c. Ocular abnormalities
      i. Cataract
      ii. Spherophakia
      iii. Retinal flecks
      iv. Anterior lenticonus
10. Norrie disease
    a. Progressive sensorineural hearing loss
    b. Eye disorders
       i. Pseudotumor
       ii. Retinal lesions
          a) Hyperplasia
          b) Hypoplasia
          c) Necrosis
       iii. Cataract
    c. Mental retardation
11. Mitochondrial mutations causing syndromic hearing loss may be associated with:
    a. Diabetes mellitus
    b. Neurologic disorder
    c. Progressive myoclonic epilepsy
    d. Ataxia
    e. External ophthalmoplegia
    f. Retinopathy
    g. Arrhythmia
12. Mitochondrial mutations causing nonsyndromic hearing loss may be associated with:
    a. Palmoplantar keratoderma
    b. Neurologic disorder

Diagnostic Investigations

1. Obtain family history (ACMG Statement 2002; Smith et al. 2010; Gifford et al. 2009)
   a. Pedigree
      i. Consanguinity
      ii. Paternity
      iii. Hearing status of the parents and siblings
   b. Ethnicity and country of origin
   c. Inheritance pattern of hearing loss
      i. Autosomal dominant
      ii. Autosomal recessive
      iii. X-linked
      iv. Mitochondrial
   d. Audiometric characteristics in any deaf and hearing-impaired family members
      i. Age of onset
      ii. Progression
      iii. Conductive hearing loss
      iv. Nonsyndromic hearing loss
      v. Auditory neuropathy
   e. Evidence of vestibular dysfunction
   f. Syndromic versus nonsyndromic features
2. Evaluate and inquire the following conditions in the patient and/or relatives:
   a. Visual anomalies
      i. Heterochromia iridis
      ii. Retinitis pigmentosa
      iii. Myopia
      iv. Retinal detachment
      v. Early cataracts
   b. Facial/cervical dysmorphology
      i. Synophrys
      ii. Dystopia canthorum
      iii. Preauricular pits
      iv. Aural atresia
      v. Branchial cysts
      vi. Cleft palate
      vii. Dental anomalies
   c. Endocrine abnormalities
      i. Thyromegaly
      ii. Diabetes
   d. Cardiac signs and symptoms
      i. Syncope
      ii. Sudden death
      iii. Arrhythmia
      iv. Prolonged QT interval
      v. Fainting spells
      vi. Congenital heart defect
   e. Renal abnormalities
      i. Hematuria
      ii. Proteinuria
      iii. Structural defects
   f. Integumentary changes
      i. Premature graying
      ii. White forelock
      iii. Abnormal pigmentation
      iv. Dry skin/keratoderma
3. Obtain patient history with respect to specific risk factors
   a. Intrauterine infections such as:
      i. Toxoplasmosis
      ii. Rubella
      iii. CMV
      iv. Herpes simplex
   b. Meningitis
   c. Extracorporeal membrane oxygenation (ECMO)
   d. History of hypoxia
   e. Prenatal alcohol exposure
   f. Exposure to ototoxic drugs
4. Perform physical examination
   a. Otologic examination
   b. Airway examination
   c. Documentation of dysmorphisms
   d. Neurologic evaluation including assessment of vestibular function in older patients
5. Laboratory tests/imagings (Grundfast et al. 2000; Parving 2007; Martini et al. 2009)
   a. Viral antibodies
      i. Rubella
      ii. CMV
      iii. HIV
      iv. Others
   b. Bacterial antibodies
      i. Syphilis
      ii. Toxoplasmosis
      iii. Others
   c. Thyroid studies for suspected Pendred syndrome
      i. TSH
      ii. T3
      iii. T4
      iv. Perchlorate test
   d. Urine analysis
      i. A positive proteinuria or hematuria can reflect Alport syndrome

ii. Viral cultural isolation
iii. Measurement of electrolyte levels
e. Electrocardiogram for suspected Jervell and Lange-Nielsen syndrome
f. Ophthalmologic examination including electroretinography and slit-lamp examination
g. Renal and cardiac ultrasonography
h. Radiographic testing
i. Bilateral acoustic neuromas: frequently detected radiographically in NF2
ii. Temporal Bone CT scan
a) Can help visualize cochlear abnormalities such as the Mondini deformity in Pendred (enlarged vestibular aqueduct) and Waardenburg syndrome
b) Can detect internal auditory canal aberrations associated with X-linked mixed hearing loss with stapes gusher and might reveal cochlear dysplasia
iii. MR imaging
a) With gadolinium enhancement: the study of choice in patients with a family history of NF2
b) Used when the hearing loss is progressive but the CT scan is normal
i. Cytogenetic testing: FISH for velocardiofacial/DiGeorge syndrome
j. Array CGH
k. Mutation analysis
i. Connexins
a) *GBJ2*
b) *GBJ6*
ii. Other relevant genes such as:
a) *WFS1*
b) *SLC26A4*

6. Universal newborn hearing screening
a. Evoked otoacoustic emission (OAE) testing: detects the evoked sound from the cochlea in response to clicks or tones
b. Auditory brain stem response (ABR, also known as BAER or BSER)
i. Measures the electroencephalographic waveform response from the vestibulocochlear nerve
ii. Has potential of detecting the following hearing losses:
a) Hearing loss due to auditory neuropathy, a condition to which the newborn intensive care unit population is particularly prone
b) Hearing loss resulting from middle and inner ear disorders
c. Combination of OAE and ABR

7. Other hearing tests to diagnosis and characterization of hearing loss
a. Tympanometry
i. External ear canal of individuals (except newborn) is sealed with probe tip
ii. Measure sound reflection by tympanic membrane while ear canal pressure is varied
iii. An effective assessment of middle ear pressure and function
b. Audiometry
i. Behavioral observation audiometry
a) Infant in a soundproof room is presented with warbled pure-tones, speech, or white and narrow-band noise through loudspeakers
b) Observe responses such as the auropalpebral reflex, startle responses, and head turning
ii. Visual reinforcement audiometry: child is seated between two speakers and conditioned to look toward the active speaker
iii. Play audiometry
a) Tones of varying frequencies are delivered through headphones or a bone vibrator
b) Child is conditioned to perform play activities, such as dropping a block or placing a peg in a board
iv. Conventional audiometry
a) Tones of varying frequencies are delivered through headphones or a bone vibrator
b) Child is instructed to raise a hand or push a button when a tone is heard
v. Pure-tone audiometry (air and bone conduction): involves determination of the lowest intensity at which an individual "hears" a pure tone
vi. Air conduction audiometry
a) Presents sounds through earphones
b) Threshold depends on the condition of the external ear canal, middle ear, and inner ear

vii. Bone conduction audiometry
  a) Presents sounds through a vibrator placed on the mastoid bone or forehead, thus bypassing the external and middle ears
  b) Thresholds depend on the condition of the inner ear
viii. Conditioned play audiometry
  a) Used to test children from age 2.5–5 years
  b) A complete frequency-specific audiogram for each ear can be obtained from a cooperative child
ix. Audioprofile
  a) Recording of several audiograms on a single graph
  b) These audiograms may be from one individual at different times, but more frequently they are from different members of the same family segregating deafness usually in an autosomal dominant fashion
  c) By plotting numerous audiograms with age on the same graph, the age-related progression of hearing loss can be appreciated within these families
  d) Often the composite picture is characteristic of specific genetic causes of autosomal dominant nonsyndromic hearing loss
  e) One of the most characteristic audioprofiles is associated with DFNA6/14/38 hearing loss caused by mutations in *WFS1*

8. Degree and effects of hearing loss (Bachmann and Arvedson 1998; Gifford et al. 2009)
  a. Normal hearing (no hearing loss) (0–15 dB loss): can detect all aspects of speech
  b. Minimal hearing loss (16–25 dB loss)
    i. May miss up to 10% of speech
    ii. May respond inappropriately
  c. Mild hearing loss (26–40 dB loss)
    i. May miss up to 50% of speech
    ii. May be labeled as "behavior problem" and "poor listener"
  d. Moderate hearing loss (41–55 dB loss)
    i. May miss 50–100% of speech
    ii. Speech quality likely to be poor
    iii. Limited vocabulary
    iv. Low self-esteem possible
  e. Moderate to severe hearing loss (56–70 dB loss)
    i. 100% of normal volume speech lost
    ii. Delayed speech and poor intelligibility
    iii. Social isolation likely
  f. Severe hearing loss (71–90 dB loss)
    i. Loud voices only heard within 12 in. of ear
    ii. Delayed speech and language if loss is prelingual
    iii. Declining speech abilities and atonal voice if loss is postlingual
  g. Profound hearing loss (>90 dB loss)
    i. Sound vibrations felt rather than heard
    ii. Visual cues primary for communication
    iii. Peer group of hearing-impaired children preferred
9. Triage/testing and triage paradigm (ACMG Statement 2002)
  a. If a form of syndromic deafness is suspected: perform gene-specific mutation screening
  b. If nonsyndromic deafness is suspected and the patient is a simplex case:
    i. CMV testing should be performed
      a) A negative test for CMV antibodies in early infancy may exclude CMV-related hearing loss
      b) A positive result must be interpreted with caution
    ii. *GJB2* (connexin 26) mutation screening by sequence analysis
      a) A negative test result does not exclude a genetic etiology
      b) A positive test result may make it possible to avoid other expensive and potentially invasive tests
  c. If nonsyndromic deafness is suspected and the patient is a multiplex case with other hearing impaired first-degree relatives: proceed directly to connexin 26 testing
  d. If nonsyndromic deafness is suspected and the pedigree suggests dominant inheritance: connexin-related deafness is not excluded and gene-specific mutation screening for other loci may be available
  e. If nonsyndromic deafness is suspected and the pedigree suggests mitochondrial DNA inheritance: testing for the A1555G mutation (associated with aminoglycoside-induced hearing loss) and the A7445G mutation, both of which are associated with some rare familial

cases of hearing loss, may be appropriate after common *GJB2* mutations are excluded

f. If nonsyndromic deafness is suspected and both parents are deaf:
   i. Connexin-related deafness will be strongly suspected (since mutations in *GJB2* are the most common cause of deafness in the United States and the vast majority of marriages between deaf individuals who produce deaf offspring are between individuals with *GJB2* mutations)
   ii. Possible to ascribe a genetic etiology to the hearing loss in many persons after triage/testing:
      a) For example, a child may be diagnosed with *GJB2*-related deafness
      b) If two clearly pathologic alleles are found, the cause of that child's deafness will be known with virtual certainty and can accurately predict the chance of recurrence in a subsequent child
   iii. Alternatively, mutation screening may be negative:
      a) A negative mutation screen must not be taken to mean that the deafness is not genetic: important to be conveyed to parents of deaf children who undergo genetic testing (Brunger et al. 2000)
      b) The probability that the deafness is genetic in patients with an unremarkable family history of deafness and a negative test result for connexin 26 will vary based on the number of hearing siblings. The proportional distribution of the different mutations in the connexin 26 locus also varies in different ethnic groups (Kenneson et al. 2002)

Genetic Counseling

1. Recurrence risk (Smith et al. 2010)
   a. Patient's sib
      i. Autosomal dominant hereditary hearing loss
         a) A 50% risk of inheriting the mutant allele if one of the proband's parents has a mutant allele
         b) Clinical severity and disease phenotype may differ between individuals with the same mutation, depending on the specific syndrome; thus, age of onset and/or disease progression may not be predictable
      ii. Autosomal recessive hereditary hearing loss
         a) A 25% risk of being deaf
         b) A 50% risk of having normal hearing and being a carrier
         c) A 25% risk of having normal hearing and not being a carrier
         d) Clinical severity and disease phenotype may differ between individuals with the same mutation, depending on the specific syndrome; thus, age of onset and/or disease progression may not be predictable
         e) For siblings with the identical *GJB2* genotype as the probands with severe-to-profound deafness: a 91% risk of having severe-to-profound deafness and a 9% risk of having mild-to-moderate deafness
         f) For siblings with the identical *GJB2* genotype as the proband with mild-to-moderate deafness: a 66% risk of having mild-to-moderate deafness and a 34% risk of having severe-to-profound deafness
      iii. X-linked hereditary hearing loss
         a) A carrier mother has a 50% risk of transmitting the deafness-causing mutation with each pregnancy: sons who inherit the mutation will be deaf; daughters who inherit the mutation are carriers and likely to have normal hearing
         b) A non-carrier mother: the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism
         c) Clinical severity and disease phenotype may differ between individuals with the same mutation, depending on the specific syndrome; thus, age of onset and/or disease progression may not be predictable
      iv. Mitochondrial disorders with hearing loss as a possible feature
         a) The risk to the sibs depends on the genetic status of the mother: the mother of a proband usually has the

mitochondrial mutation and may or may not have symptoms (note that the father is not at risk of having the disease-causing mtDNA mutation)
b) If the mother has the mitochondrial mutation, all sibs are at risk of inheriting it

b. Patient's offspring
i. Autosomal dominant hereditary hearing loss
a) A 50% risk of transmitting the mutant allele to each child
b) In case of an apparent de novo mutation in the proband (neither parent of a proband with an autosomal dominant condition has the deafness-causing mutation or clinical evidence of the disorder), explore possible nonmedical explanations (alternate paternity or maternity such as with assisted reproduction or undisclosed adoption)
c) Clinical severity and disease phenotype may differ between individuals with the same mutation, depending on the specific syndrome; thus, age of onset and/or disease progression may not be predictable
ii. Autosomal recessive hereditary hearing loss: all of the offspring are obligate carriers
iii. X-linked hereditary hearing loss: males with X-linked hereditary hearing loss will pass the deafness-causing mutation to all of their daughters and none of their sons
iv. Mitochondrial disorders with hearing loss as a possible feature
a) All offspring of females with an mtDNA mutation are at risk of inheriting the mutation
b) Offspring of males with a mtDNA mutation are not at risk

2. Prenatal diagnosis
a. Prenatal diagnosis for some forms of hereditary hearing loss is technically possible by analysis of DNA extracted from fetal cells obtained by:
i. Amniocentesis usually performed at approximately 15–18 weeks' gestation
ii. Chorionic villus sampling (CVS) at approximately 10–12 weeks' gestation
b. The deafness-causing allele(s) of a deaf family member must be identified before prenatal testing can be performed
c. Preimplantation genetic diagnosis (PGD): may be available for families in which the deafness-causing mutation(s) have been identified

3. Management
a. Multidisciplinary team consisting of:
i. An otolaryngologist
ii. An audiologist
iii. A clinical geneticist
iv. A pediatrician
v. An educator of the deaf
vi. A neurologist
vii. A pediatric ophthalmologist
b. Treatment
i. Determine the appropriate habilitation option such as:
a) Hearing aids
b) Vibrotactile devices
ii. Cochlear implantation: considered in children over age 12 months with severe-to-profound hearing loss
iii. Early auditory intervention through amplification, otologic surgery, or cochlear implantation is essential for optimal cognitive development in children with prelingual deafness

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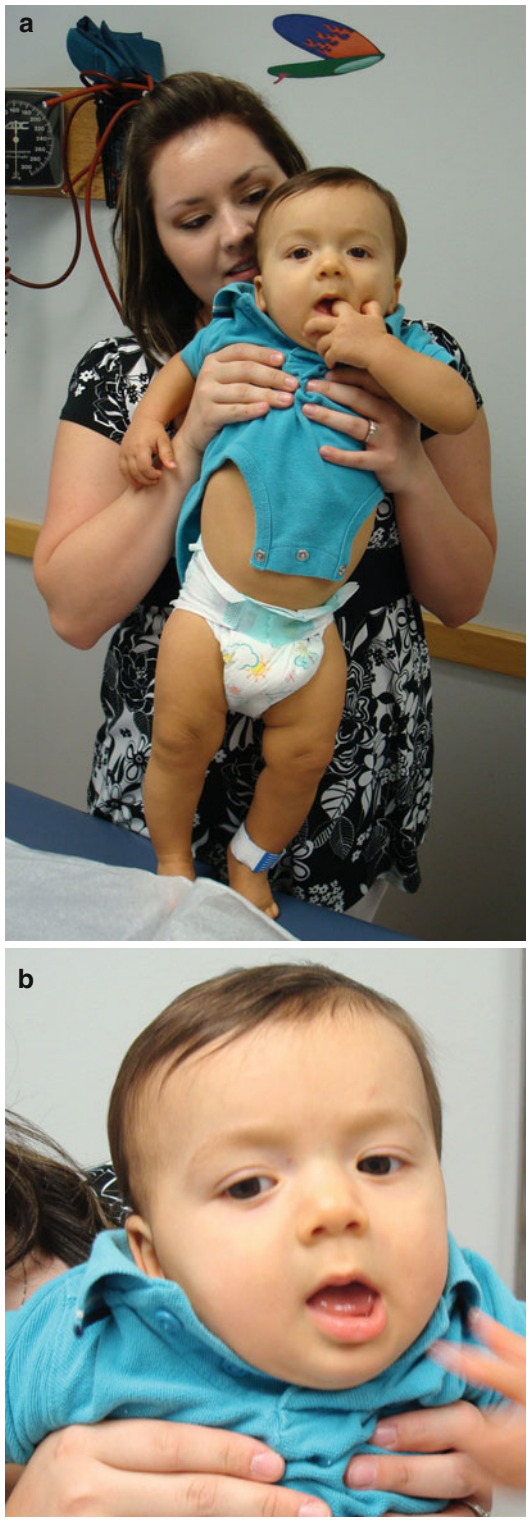

Fig.1 (**a**, **b**) A 9-month-old boy with nonsyndromic hearing loss

Fig. 2 A 29-year-old man with nonsyndromic hearing loss

Hereditary Hemochromatosis

Hereditary hemochromatosis (HHC; *HFE* 1) is a common hereditary disorder of iron metabolism and the most common inherited autosomal recessive disorder in Caucasians with a prevalence of 1 in 300 to 1 in 500 individuals. It is characterized by inappropriately high iron absorption resulting in progressive iron overload.

Synonyms and Related Disorders

Hemochromatosis

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Cause: result of a single faulty *HFE* gene on chromosome 6p21.3 near the *HLA* complex that codes for a glycoprotein called HFE, which binds to the transferrin receptor and reduces its affinity for iron-bound transferrin, allowing cellular uptake of iron-based transferrin
3. Two common mutations (missense)
   a. C282Y.
      i. Accounts for most cases of HHC
      ii. Homozygotes for C282Y mutation (>80% cases world-wide) are at high risk for HHC.
      iii. Heterozygote for C282Y mutation.
         a) Have increased levels of transferrin saturation
         b) Rarely have organ damage
   b. H63D: Homozygotes for H63D (often has a potentiator, such as hepatitis C infection, β-thalassemia trait) are unlikely to develop HHC.
   c. C282Y/H63D (11% present phenotypically): Compound heterozygotes for C282Y/H63D have a milder form of HHC than C282Y homozygotes.
4. Other *HFE* mutations
   a. Missense mutations
      i. S65C: the third most common mutation
      ii. G93R
      iii. I105T
      iv. Q127H
      v. R330M
   b. Frameshift mutations
      i. P160ΔC
      ii. V68ΔT
   c. Nonsense mutations
   d. Spice site mutation
5. Clinical expression of the disease
   a. Homozygotes: affected clinically
   b. Heterozygotes
      i. Can have minor abnormalities of the parameters that reflect body iron status
      ii. Can develop significant iron overload only when other diseases that affect iron metabolism coexist, such as:
         a) Heterozygous β-thalassemia
         b) Hereditary spherocytosis
         c) Sporadic porphyria cutanea tarda
6. Hereditary hemochromatosis not attributable to mutations in *HFE*
   a. A subgroup of hereditary hemochromatosis indistinguishable from *HFE*-associated HHC
   b. Does not have mutations in *HFE*.
   c. The disease does not appear to be linked to the HLA complex.
   d. The genetic basis has not been defined.

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7. Pathophysiology (Whittington and Kowdley, 2002)
   a. Inappropriately high intestinal iron absorption: the most important pathophysiological step in body iron loading
   b. Effects of mutations on iron absorption: central to the understanding of the pathological basis of hereditary hemochromatosis

Clinical Features

1. Variable clinical presentation
2. Median age at presentation of symptoms
   a. Fifty one years in males
   b. Female homozygotes
      i. Less likely to develop symptomatic disease
      ii. Median age: age 50
3. Asymptomatic: abnormal serum iron studies on routine screening
4. Early manifestations
   a. Often subtle
   b. Vague arthralgias
   c. Fatigue
   d. Lethargy
   e. Apathy
   f. Weight loss
5. Later manifestations as tissue iron progressively accumulates
   a. Discoloration of the skin
   b. Arthropathy
      i. Due to iron accumulation in joint tissues.
      ii. Arthritis with joint swelling most commonly involves:
         a) Metacarpophalangeal (MCP) joints
         b) Proximal interphalangeal joints
         c) Knees
         d) Feet
         e) Wrists
         f) Back
         g) Neck
      iii. Chondrocalcinosis.
         a) Involves the knees and wrists
         b) May be asymptomatic
      iv. Symptoms usually do not respond to iron removal.
   c. Liver involvement
      i. Abdominal pain associated with hepatomegaly
      ii. Hepatomegaly, the most common physical abnormality
      iii. Splenomegaly
      iv. Cirrhosis
      v. Portal hypertension
         a) Ascites
         b) Encephalopathy
      vi. Hepatocellular carcinoma in about 30% of cases
   d. Cardiac involvement
      i. Dilated cardiomyopathy
      ii. Arrhythmias
      iii. Cardiac failure
   e. Endocrine abnormalities
      i. Diabetes mellitus
      ii. Pituitary hypogonadism
         a) Decreased libido and impotence (testicular atrophy) in men
         b) Amenorrhea in women
      iii. Hypothyroidism
6. Suspect diagnosis from characteristic clinical manifestations
   a. Classical clinical triad of "bronzed cirrhosis with diabetes" in a middle-aged man:
      i. Diffuse hyperpigmentation (melanodermia), often with a metallic gray or "bronze" rather than a brown discoloration
      ii. Hepatomegaly, with the liver markedly enlarged, firm and sharp to palpation but without signs of hepatocellular insufficiency (no palmar erythema, no spider nevi, no bruises, normal prothrombin time) or of portal hypertension
      iii. Diabetes mellitus, often requiring insulin
   b. Presence of cardiomyopathy
   c. Diagnosis at this late stage: considered a diagnostic failure
7. Suspect diagnosis from earlier signs and symptoms
   a. Sex and age: Both young adults and older women are at risk.
   b. "Rule of three A's"
      i. Asthenia: unexplained chronic fatigue
      ii. Arthralgia
         a) A "painful" handshake: resulting from chronic arthritis of the second and third MCP joints.
         b) Other joints affected especially the knees and wrists.

c) Can also suffer from pseudogout (pyrophosphate arthropathy).
d) Arthritis greatly diminishes the quality of life.

iii. Aminotransferase (transaminases) elevation

8. Cause of death
   a. Liver failure
   b. Cancer
   c. Congestive heart failure
   d. Arrhythmia
9. Other conditions associated with significant iron overload
   a. Non-*HFE* hereditary hemochromatosis (Pietrangelo, 2010)
      i. Transferrin receptor 2 gene (*TFR2*, on 7q22) hemochromatosis
         a) Caucasian or non-Caucasian
         b) Male or female
         c) Thirty to forty years
         d) Cardiomyopathy
         e) Endocrinopathy
         f) Liver disease
         g) Elevated transferrin saturation (TS) and serum ferritin (SF)
      ii. Hemojuvelin (*HJV* on 1q21) or hepcidin gene (*HAMP*, on 19q13) juvenile hemochromatosis
         a) Caucasian or non-Caucasian
         b) Male or female
         c) Fifteen to twenty years
         d) Impotence/amenorrhea and/or cardiomegaly
         e) High TS and SF
      iii. Ferroportin disease (SLC40A1, on 2q32)
         a) Caucasian or non-Caucasian
         b) Male or female
         c) Ten to eighty years
         d) One patient with unexplained hyperferritinemia
         e) Unexplained elevation of SF and normal TS
   b. Secondary iron overload
      i. Iron-loading anemias (ineffective erythropoiesis, increased iron absorption, blood transfusions)
         a) β-thalassemia
         b) Congenital dyserythropoietic anemias
         c) Sideroblastic anemia
         d) Pyridoxine-responsive anemia
      ii. Hypoplastic anemias (blood transfusions)
         a) Aplastic anemia
         b) Myelodysplastic syndromes
         c) Pure red cell aplasia
      iii. Chronic hemolytic anemias (increased iron absorption)
         a) Spherocytosis
         b) Sickle cell anemia
         c) Pyruvate kinase deficiency
      iv. Parental iron overload
         a) Red blood cell transfusion
         b) Iron dextran injections
         c) Long-term hemolysis
      v. Neonatal hemochromatosis
      vi. Ceruloplasmin deficiency (aceruloplasminemia) (decreased ferroxidase activity)
      vii. Sub-Saharan iron overload (increased dietary iron, increased iron absorption)
      viii. Porphyria cutanea tarda (increased iron absorption)
      ix. Hepatic disorders
         a) Chronic viral hepatitis
         b) Alcoholic cirrhosis
         c) Portacaval shunts (increased iron absorption)

Diagnostic Investigations

1. Biochemical testing
   a. High serum ferritin levels
   b. High transferrin-iron saturation value: an early and reliable indicator for risk of iron overload/HFE-HHC
      i. A fasting transferrin-iron saturation of $\geq$60% for men and $\geq$50% for women on at least two occasions, in the absence of other known causes of elevated transferrin-iron saturation, is observed in about 80% of individuals with HFE-HHC and is considered suggestive of HFE-HHC.
      ii. A threshold transferrin-iron saturation of 45% is more sensitive for detecting HFE-HHC suggested by recent studies.
      iii. Some overlap occurs in serum transferrin-iron saturation among homozygotes and heterozygotes.

2. Radiography
   a. Arthropathy
      i. Squared-off bone ends and hook-like osteophytes in the MCP joints, particularly in the second and third MCP joints
      ii. Subchondral arthropathy
      iii. Chondrocalcinosis
3. MRI of the liver
   a. The most promising noninvasive technique for identification of HHC. High hepatic iron content causes:
      i. A decrease in signal intensity of the liver
      ii. A marked decrease in transverse (T_2) relaxation time
4. Liver biopsy to assess histologic hepatic iron stores
   a. Usually not indicated for diagnostic purposes in HFE-HHC.
   b. Recommended to C282Y homozygotes with a serum ferritin concentration of >1,000 ng/mL to determine if cirrhosis is present; those with a serum ferritin concentration <1,000 ng/mL need not undergo biopsy.
   c. Useful to determine hepatic iron overload, particularly in patients with presumed hemochromatosis who lack the common *HFE* mutations associated with HFE-HHC.
5. Molecular genetic testing (Kowdley et al. 2006)
   a. Mutation analysis for the disease-causing alleles in the *HFE* gene (C282Y and H63D)
      i. C282Y/C282Y homozygotes (60–90%)
      ii. C282Y/H63D compound heterozygotes (3–8%)
      iii. H63D/H63D homozygote (1%)
      iv. H63D/? (4%)
      v. C282Y/? (1%)
      vi. ?/? (6%)
   b. Testing strategy for a proband
      i. Mutation analysis warranted in adults with serum transferrin-ion saturation of >45%
      ii. Individuals with homozygous C282Y/C282Y or compound heterozygous C282Y/H63D: have genetic makeup to develop HFC-HHC
      iii. Individuals who are not C282Y homozygotes
         a) Generally represent a heterogeneous group.
         b) Many have liver disease unrelated to HFE-HHC or other metabolic syndromes.
         c) Some may have primary iron overload in a pattern identical to HFE-HHC.
         d) The next diagnostic step: perform liver biopsy with assessment of histology and measurement of hepatic iron concentration
   c. Carrier detection: identification of carriers and noncarriers in at-risk family members possible provided both *HFE* alleles have been identified in the proband
6. Screening for HHC
   a. HHC: a prime target for screening because of its high prevalence, morbidity, and mortality, as well as the benefits of early diagnosis and treatment
   b. Initial screening probe for HHC diagnosis
      i. Transferrin saturation
      ii. Unsaturated iron-binding capacity

Genetic Counseling

1. Recurrence risk (Kowdley et al. 2006)
   a. Patient's sib
      i. Twenty-five percent if both parents are HFE-HHC heterozygotes
      ii. Fifty percent if one parent is HFE-HHC heterozygotes and other parent HFE-HHC homozygote
   b. Patient's offspring: 5% risk to be affected due to the high carrier rate for *HFE* mutant alleles in the general population
      i. The risk that the partner of an individual with HFE-HHC is heterozygous for the C282Y allele is 1/9
      ii. Therefore, the risk to the offspring to be a homozygote for C282Y allele is $1/2 \times 1/9 = 1/18$ (about 5%)
2. Prenatal diagnosis
   a. Technically feasible when both parents carry identified *HFE* mutations
   b. Highly unusual to request prenatal diagnosis because HHC is an adult-onset, treatable disease
3. Management (Kowdley et al. 2006)
   a. Early diagnosis and treatment
      i. Can completely prevent the development of clinical complications
      ii. Offer patients a normal life expectancy

b. Treatment of iron overload
   i. Periodic phlebotomy
      a) Goal of therapy: to achieve and maintain a serum ferritin concentration of ≤50 ng/mL
      b) Usual therapy: removal of the excess iron by weekly phlebotomy until the serum ferritin concentration is ≤50 ng/mL
   ii. Dietary management
      a) Avoid medicinal iron
      b) Avoid mineral supplements
      c) Avoid excess vitamin C which increases intestinal absorption of inorganic iron
      d) Avoid uncooked shellfish or other seafood which can be contaminated with *V vulnificus* causing sepsis in patients with HHC
      e) Avoid alcohol consumption for patients with liver involvement
   iii. Iron chelation therapy: not recommended unless the patient has an elevated serum ferritin concentration and concomitant anemia that makes therapeutic phlebotomy impossible
c. Conventional therapies for diabetes, hepatic failure, and cardiac failure
d. Cirrhosis: screen for hepatocellular cancer
   i. Biannual abdominal ultrasound
   ii. Annual serum alpha-fetoprotein testing
e. Orthotopic liver transplantation for end-stage liver disease from decompensated cirrhosis
f. Surveillance of at-risk asymptomatic adults with C282Y homozygotes
   i. Monitor serum ferritin concentrations yearly starting in early adulthood
   ii. Initiate therapeutic phlebotomy when serum ferritin concentrations are elevated

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Fig. 1 Father (40-year-old) and son (12-year-old) both carry heterozygous C282Y mutation. H63D and S65C were not detected. The father currently receives periodic phlebotomy with fasting transferrin-iron saturation level of 56% (15–50) and ferritin level of 1,238 ng/mL (20–345). The son is currently asymptomatic. Approximately 3–5% of patients with hereditary hemochromatosis have this genotype. The molecular results do not rule out the possibility of disease causing mutations in other regions of the *HFE* gene or in other as yet undefined genes

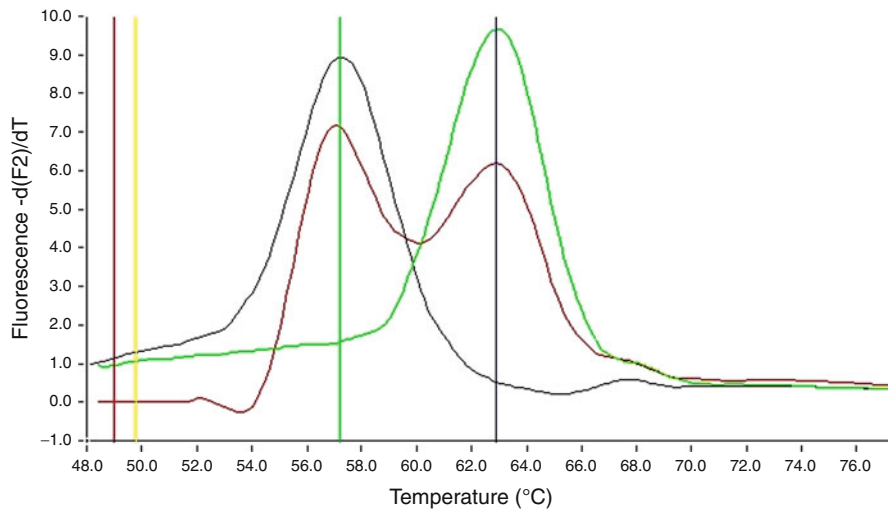

Fig. 2 Real-time PCR of HFE gene in another patient. The patient is homozygous for *C282Y* mutation, demonstrated by the green line (melting point (Tm) = 62.89)

Hereditary Multiple Exostoses

Hereditary multiple exostoses (HME) is a type of skeletal dysplasia characterized by osteochondral growths (osteochondromas) on the periphery of bones, comprised of bone surrounded by a cap of cartilage. The estimated prevalence is about 1 in 50,000 Caucasians (Schmale et al. 1994).

Synonyms and Related Disorders

Diaphysis aclasis; Hereditary multiple osteochondromas; Hereditary multiple osteochondromatosis; Multiple cartilaginous exostoses

Genetics/Basic Defects

1. Exostoses (Schmale et al. 1994)
   a. Result of dysplasia of the peripheral aspect of the growth plate
   b. The most common type of benign bone tumors
   c. Small exostoses may not be discovered because many do not cause symptoms
   d. Multiple lesions develop in individuals who have a hereditary type
2. Inheritance
   a. Autosomal dominant with nearly complete penetrance
   b. About 90% of patients have an affected parent.
   c. About 10% of patients result from a de novo gene mutation.
3. Genetic heterogeneity: Linkage analysis identified the following three genes associated with hereditary multiple exostoses:
   a. *EXT1* gene
      i. A ubiquitously expressed gene located on chromosome 8q24.1.
      ii. Normal gene product: exostosin 1.
      iii. Mutations in *EXT1* are responsible for about half of cases.
   b. *EXT2* gene
      i. A ubiquitously expressed gene located on chromosome 11p11-p12
      ii. Normal gene product: exostosin 2
      iii. Mutations in *EXT2* are responsible for about one third of cases.
   c. *EXT3* gene
      i. A gene located on chromosome 19p
      ii. Mutations in *EXT3* are implicated in a minority of cases
4. Loss of heterozygosity in the *EXT1* or *EXT2* implicated in causing osteochondromas, which are the most common bone tumors in children, characterized by cartilage-capped, bony excrescences (exostoses) arising from the metaphyseal ends of rapidly growing long bones
5. Deletion of *EXT1* gene and adjacent *TRPS1* gene (a gene located on chromosome 8 proximal to the *EXT1* gene) resulting in Langer–Giedion syndrome (trichorhinophalangeal syndrome, type II) in which multiple exostoses are distinguishing features

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6. EXT genes
   a. Encode glycosyltransferases
   b. Catalyze heparin sulfate polymerization
7. Genotype-Phenotype correlations (Pannier and Legeai-Mallet 2008)
   a. More severe disease in individuals with *EXT1* mutations than *EXT2* mutations on the basis of short stature, skeletal deformity (shortened forearm or bowing, knee deformity) and function (elbow, forearm and knee range of motion) (Francannet et al. 2001; Porter et al. 2004).
   b. The risk of chondrosarcoma may also be higher in individuals with an *EXT1* mutation than in those with an *EXT2* mutation, but *EXT1* mutations are responsible for most cases of HME.

Clinical Features

1. Exostoses (cartilage-capped bony growths)
   a. Bony swellings (bumps) near the growing ends of the long bones: initially painless but later the majority of patients experiences pain
   b. Onset during childhood (often asymptomatic)
   c. Sites
      i. Humerus
      ii. Distal end of the femur
      iii. Proximal end of the tibia and fibula
      iv. Distal ends of the radius
      v. Ribs
      vi. Scapula
      vii. Ilium
   d. Types
      i. Pedunculated with a narrow pedicle
      ii. Sessile with a broad pedicle
   e. Size and number
      i. Grow in size and gradually ossify during skeletal development
      ii. Ceases with skeletal maturity (when the growth plates close at puberty) after which no new exostoses develop
2. Bowing
   a. Often occurs without exostoses
   b. Bowing of forearms: ulnar deviation of the wrist secondary to a bowing of the radius and shortening of the ulna
   c. Bowing of lower legs
3. Genu valgum
4. Deformities observed in children
   a. Most common deformities
      i. Disproportionate short stature (40%)
      ii. Limb length discrepancies
      iii. Valgus deformities of the knee and ankle
      iv. Asymmetry of the pectoral and pelvic girdles
      v. Bowing of the radius with ulnar subluxation of the carpus
      vi. Subluxation of the radial head
      vii. Relative shortening of the metatarsals, metacarpals, and phalanges
   b. Less common deformities
      i. Scoliosis
      ii. Coxa valga
      iii. Acetabular dysplasia
5. Prognosis and complications
   a. Normal life span
   b. Normal intelligence
   c. Cosmetic concern (one of the most common clinical complaints)
   d. Mechanical restriction of adjacent joint movements
   e. Adventitious bursa with bursitis
   f. Compression or displacement of the adjacent nerves (22%)
      i. Pain (one of the most common clinical complaints)
      ii. Sensory or motor deficits
   g. Compression or displacement of the adjacent vessels (11%)
   h. Spontaneous hemothorax as a result of rib exostoses (rare)
   i. Urinary or intestinal obstruction resulting from large pelvic exostoses (rare)
   j. Compression of spinal cord
      i. Very rare occurrence
      ii. Extremely serious complication
   k. Slipping of the adjacent tendons
   l. Fractures at the pedicle
   m. Malignant transformation of osteochondroma to osteochondrosarcoma (0.5–5%): the most important complication
      i. Rapid growth
      ii. Increasing pain
      iii. A bulky cartilage cap

6. Differential diagnosis (Pannier and Legeai-Mallet 2008)
   a. Metachondromatosis
      i. An autosomal-dominant disorder
      ii. In contrast to HME, the exostoses of metachondromatosis point toward the joints and frequently regress spontaneously
      iii. Exostoses do not result in shortening of affected long bones or produce bowing, joint deformity or subluxation as seen in HME
   b. Langer–Giedion syndrome
      i. A contiguous gene deletion syndrome involving *EXT1* and *TRPS1* genes (trichorhinophalangeal syndrome I)
      ii. Affected individuals have exostoses, mental retardation, craniofacial abnormalities (laterally protruding ears, broad nasal bridge and bulbous nose, sparse hair) and digital anomalies (cone-shaped epiphyses)
   c. 11p11.2 deletion syndrome (formerly known as Potocki–Shaffer syndrome) (Wu et al. 2000)
      i. A contiguous gene deletion syndrome involving *EXT2* and *ALX4* (homeobox) genes
      ii. Affected patients have multiple exostoses, an ossification defect of the skull (enlarged parietal foramina), craniofacial dysostosis, and mental retardation
   d. Enchondromatosis (Ollier disease)
      i. Enchondromas
         a) Common benign cartilage tumors of bone
         b) Can occur as solitary lesions or as multiple lesions in enchondromatosis, often with unilateral predominance
      ii. Usually a nonhereditary disorder
      iii. Association of hemangiomas is referred to as "Maffucci syndrome"
      iv. Risk of malignant transformation into chondrosarcomas (20–50%)

Diagnostic Investigations

1. Radiographic features.
   a. Pedunculated or sessile exostoses pointing away from the joint.
   b. Cortex of exostoses continuous with that of the underlying bone.
   c. Exostoses originated in the metaphysis in the long bones and migrate to the diaphysis as growth continues in the epiphysis.
   d. Cartilagenous cap.
      i. Usually radiolucent
      ii. Appearance of irregular zones of calcification after puberty
      iii. Extensive calcification with irregularities of the cap suggesting possibility of malignant change
   e. Exostoses prevent normal bone tabulation resulting in metaphyseal widening and growth retardation.
   f. Broad and barrel-shaped metaphyses without normal remodeling.
   g. Wrist.
      i. Shortening of the ulna
      ii. Bowing of the radius with subluxations of the inferior radioulnar joint
2. CT and MRI imagings: evaluate spinal cord compression from an osteochondroma (Roach et al. 2009).
   a. Presence of a risk of having a lesion within the spinal canal
   b. Potential occurrence of serious neurologic injury
3. Serial technetium bone scans: Increased radionucleotide uptake suggests malignancy.
4. Histology of exostosis.
   a. Core: cancellous bone
   b. Surrounding: cortical bone
   c. Apex: covered with a cap of hyaline cartilage
5. DNA analysis of mutations in the *EXT1*, *EXT2*, and *EXT3* genes available clinically for *EXT1* and *EXT2*.
   a. FISH on metaphase cells.
   b. Genomic microarray analysis.
   c. Screening of the entire coding region.
   d. A combination of sequence analysis and deletion analysis of the entire coding regions of both *EXT1* and *EXT2* detects mutations in 70–95% of affected individuals (Schmale et al. 2008).

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Usually with 50% risk of inheriting the gene alteration, since most probands (about 90%)

have a parent with the altered gene and 95% risk of manifesting symptoms (penetrance)
   ii. Low risk if both parents are normal
   b. Patient's offspring: 50% risk of inheriting the mutant allele
2. Prenatal diagnosis: available clinically for pregnancies at risk
   a. Molecular genetic analysis on fetal DNA obtained from amniocentesis or CVS for *EXT1* or *EXT2* mutation, provided the disease-causing allele of an affected family member has been identified prior to prenatal diagnosis
   b. Preimplantation diagnosis using embryonic cells available to couples at 50% risk of having a child with hereditary multiple exostosis, provided the disease-causing mutation of the *EXT1* or *EXT2* gene has been identified in the affected parent
3. Management
   a. Exostoses without clinical problems required no therapy
   b. Surgical intervention of exostoses
      i. Simple excision of exostoses
         a) Painful lesion without bony deformity
         b) Slowing growth disturbance
         c) Improving cosmesis
      ii. Angular deformities
      iii. Pain due to irritation of skin, tendons, or nerves
      iv. Either epiphysiodesis of the longer leg or lengthening of the involved leg for leg length discrepancy greater than one inch
      v. Excision of the exostoses and corrective osteotomies for forearm deformity (pain and stiffness of the elbow and wrist are a common cause of disability)
   c. Sarcomatous degeneration
      i. Surgical resection
      ii. Adjuvant radiotherapy and chemotherapy for secondary osteosarcoma

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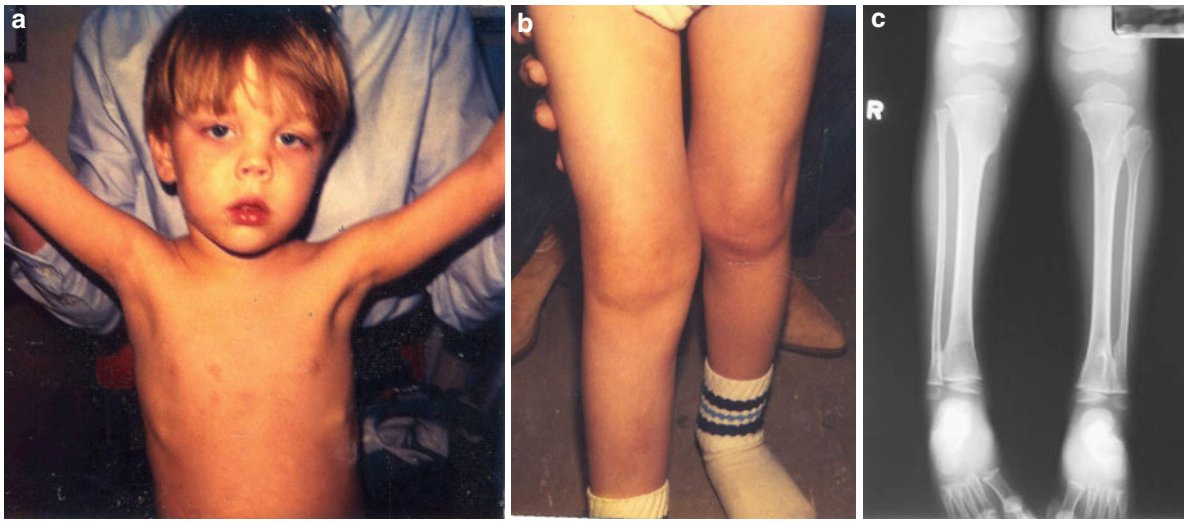

Fig. 1 (**a**–**c**) A boy with hereditary multiple exostoses showing bony growths on both sides of the ribs and the lower legs, illustrated by the radiograph

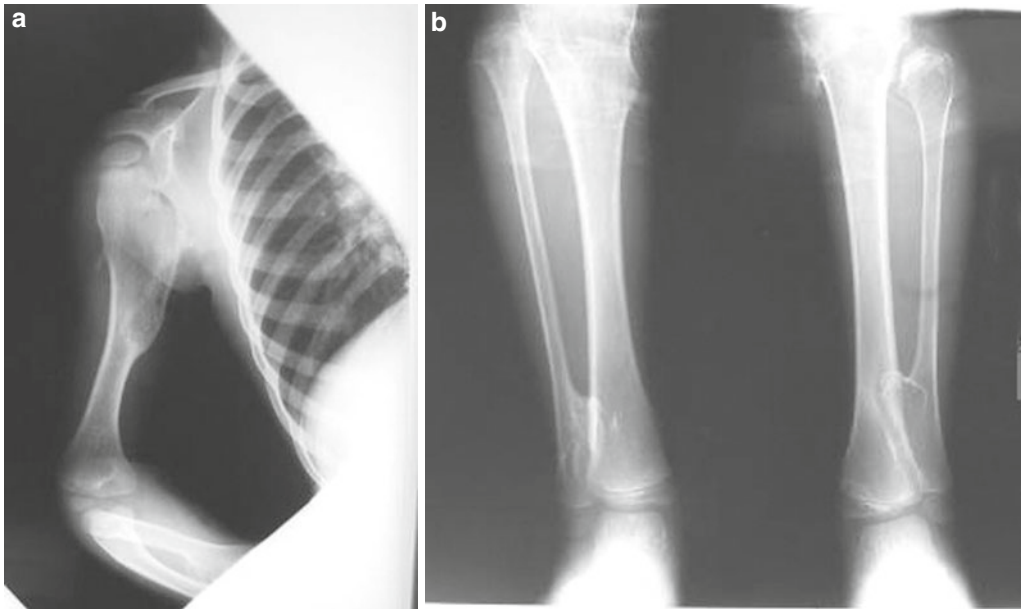

Fig. 2 (**a**, **b**) Radiographs of a 5-year-old boy with hereditary multiple exostoses showing multiple exostoses of the humerus, radius, tibia, and fibula

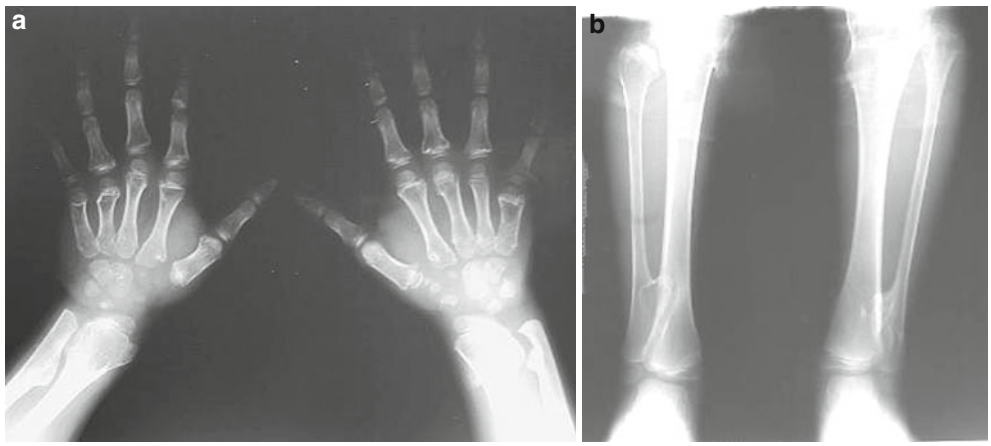

Fig. 3 (**a**, **b**) A 7-year-old boy with hereditary multiple exostoses showing more severe degree of multiple exostoses of the humerus, radius, tibia, and fibula

Fig. 4 (**a**–**c**) A 20-year-old female with hereditary multiple exostoses showing pedunculated exostosis on the left proximal tibia and fibula, exostosis on the shaft of the left fibula, and exostoses on the distal radius and ulna. She was discovered to have multiple exostoses since 1 year of age and has had multiple surgeries to remove multiple tumors from right femur, left tibia, and left fibula. Currently, she has bumps on the right distal femur, right proximal fibula, right distal tibia, left distal fibula, left distal forearm, right distal phalange of the right fifth finger, and left second toe. Her father is also affected

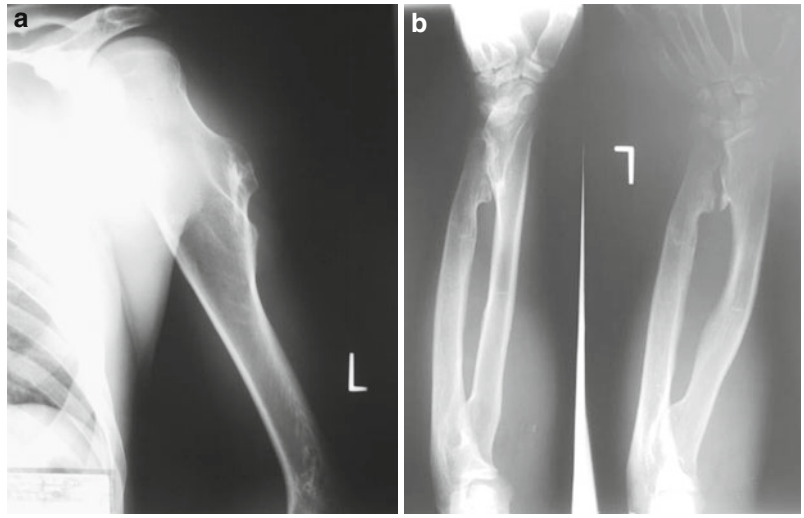

Fig. 5 (**a**, **b**) A 27-year-old male with hereditary multiple exostoses showing exostoses, ulnar shortening, and ulnar carpal drift

Fig. 6 (**a**–**c**) A 9-year-old girl with hereditary multiple exostoses showing typical radiographic features of both distal femurs

Herlyn-Werner-Wunderlich Syndrome

Herlyn-Werner-Wunderlich syndrome is a rare Müllerian anomaly consisting of a didelphic uterus, a hemivaginal septum, and ipsilateral renal agenesis. The diagnosis should be suspected in adolescent females with a pelvic mass and ipsilateral renal agenesis.

Synonyms and Related Disorders

Blind hemivagina with ispsilateral renal agenesis

Genetics/Basic Defects

1. Anatomical defect is caused by a failure of lateral fusion of Müllerian ducts (didelphic/septate uterus and double vagina) combined with a failure of vertical fusion between the Müllerian duct and the urogenital sinus (hemivaginal septum) ipsilateral to the side of the renal agenesis.
2. Various types of uterine anomalies secondary to nondevelopment or failure of fusion of the distal segments of the Müllerian ducts
   a. Hypoplasia/agenesis of the uterus
   b. Unicornuate uterus
   c. Didelphic uterus
   d. Bicornuate uterus
   e. Septate uterus
   f. Arcuate uterus
3. Various types of vaginal anomalies secondary to the different embryological origin of the upper two thirds of the vagina (originates from the Müllerian ducts of mesodermal origin) and the lower third of the vagina (originates from the urogenital sinus of endodermal origin): the anomaly may exist alone or in association with Müllerian anomalies.
   a. Hypoplasia/aplasia
   b. Duplication
   c. Septa
4. Close interrelationship between the urinary and reproductive systems during embryogenesis may explain the coexistence of urinary and reproductive tract abnormalities.
5. Specific association of a didelphic uterus, an obstructed hemivagina, and an ipsilateral renal agenesis is a rare malformation concomitantly involving both Müllerian and Wolffian ducts.
6. Mode of inheritance: unclear but Wiersma et al. (1976) had reported mother and daughter with uterus bicornis bicollis with partial vaginal septum and unilateral hematocolpos with ispsilateral renal agenesis, suggesting possible sex-limited autosomal dominant inheritance.

Clinical Features

1. Major complaints: the median age of presentation is 13 years. The condition is usually discovered at puberty shortly after menarche. The diagnosis is generally made only if the suspicion of the existence of this syndrome is raised.
   a. Abdominal pelvic mass due to hemihematocolpos resulting from retained longstanding, partially clotted menstrual blood in the obstructed hemivagina

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   b. Recurrent and progressive pelvic pain
   c. Menstrual bleeding
   d. Menstrual irregularity
   e. Intraabdominal abscess
   f. Fever and vomiting can be the presenting symptoms
2. A didelphic uterus
   a. Characterized by two uterine bodies and two cervices
   b. Presence of a longitudinal vaginal septum in the majority of cases
3. Consequences of blood stasis and retrograde menstruation in the obstructed system
   a. Hematocolpos (a dilated hemivagina)
   b. Hematometros (a dilated uterine cavity)
   c. Hematosalpinx (bleeding/dilated fallopian tube)
4. Other vaginal anomalies
   a. Imperforate hymen variants
   b. Vaginal atresia
   c. Duplicated vagina
   d. Fused labia
5. Ipsilateral renal agenesis
6. Occasional gastrointestinal tract malformations
   a. Esophageal atresia
   b. Imperforate anus
7. Natural history if untreated
   a. Endometriosis
   b. Pelvic adhesions
   c. Pyosalpinx
   d. Pyocolpos
8. Unusual dichotomy in reproductive function
   a. Fertility not compromised with high spontaneous abortion rate (40%)
   b. No obstetric difficulties when a pregnancy is carried to term

Diagnostic Investigations

1. Abdominal examination finding of a suprapubic mass with tenderness to palpation
2. Pelvic and/or rectal examination findings of a paravaginal cystic mass
3. Abdominal and pelvic imagings
   a. Ultrasonography allows the correct diagnosis by showing uterovaginal duplication, hematocolpos or hematometrocolpos, and the absence of the ipsilateral kidney.
   b. Computed tomography scan
   c. Magnetic resonance imaging provides more detailed information regarding uterine morphology, the continuity with each vaginal channel (obstructed and nonobstructed), and the bloody nature of the contents.
4. Unilateral renal agenesis can be diagnosed prenatally. Female fetuses or neonates with renal malformations or multidysplastic kidneys need to be screened for genital malformations and to look for an obstructed Müllerian system. The uterine anomaly can be better detected in the neonatal period because the uterus is still under maternal hormonal stimulation and is characterized by a prominent myometrium and an echogenic endometrium. It is advisable that follow-up ultrasonographic examination of these asymptomatic patients be performed until the end of puberty.

Genetic Counseling

1. Recurrence risk: possible sex-limited autosomal dominant inheritance
   a. Patient's sib: recurrence risk not increased in female sibs unless the mother is affected
   b. Patient's offspring: a 50% risk for female offspring
2. Prenatal diagnosis: not yet reported
3. Management
   a. Operative management
      i. Vaginal septectomy with marsupialization and drainage of hematocolpos/hematometrocolpos to provide relief of pain and prevent further complications: a preferred surgical approach with a good long-term outcome
      ii. Salpingectomy for pyosalpinx if needed
   b. Errors in the surgical management can occur when the diagnosis is not suspected, and laparotomy to explore and resect the intra-abdominal mass is performed.
   c. Hemihysterectomy with or without salpingo-oophorectomy is rarely indicated and should be

avoided to provide the best chance for a successful reproductive outcome.

d. Post-operative considerations
   i. To achieve the goal of normal sexual relations and successful reproductive outcomes
   ii. Vaginal adenosis in the previously obstructed vagina

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Fig. 1 A 13-year-old female was evaluated for vaginal bleeding and lower abdominal pain. Abdominal ultrasonography showed a very unusual appearance of the uterus with two horns which converge to form one lower uterine segment which then go into a prominent cervix where there was a large amount of fluid (blood) within the cervix and vagina

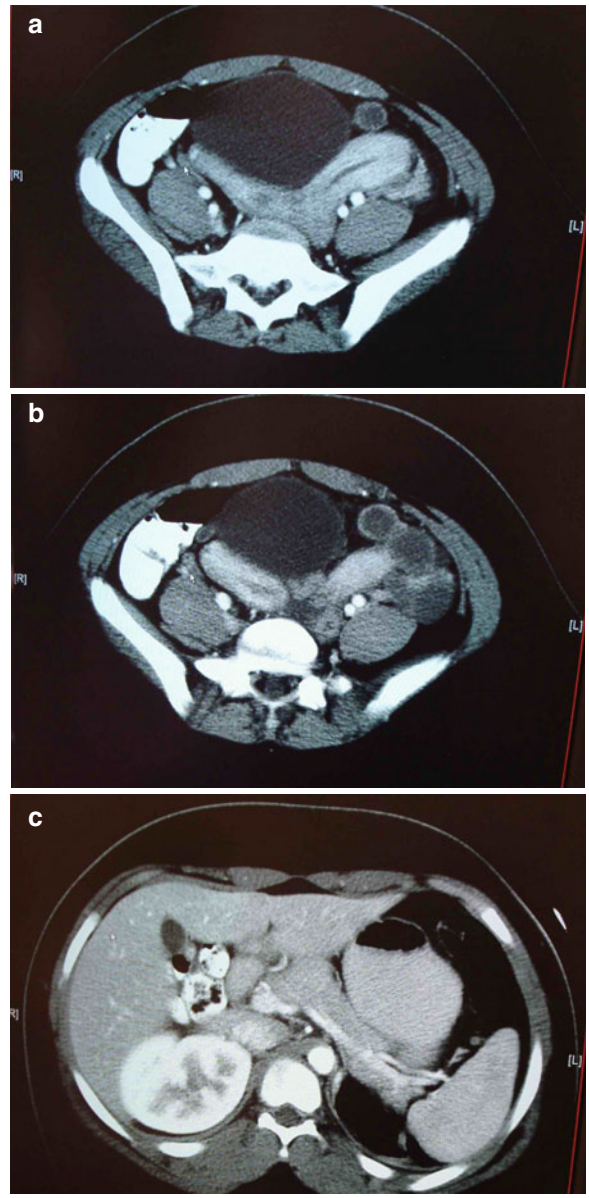

Fig. 2 (**a**–**c**) CT scan of the abdomen and pelvis showed congenital uterine anomaly likely didelphic uterus, absence of left kidney, and presence of hypertrophic right kidney

Holoprosencephaly

Holoprosencephaly (HPE) is a heterogeneous entity of CNS anomalies caused by the impaired midline cleavage of the embryonic forebrain. The incidence is estimated to be 1 in 16,000 live births and observed in 1 of 250 spontaneous abortions (Roessler and Muenke 2001).

Synonyms and Related Disorders

Arrhinencephaly; Cebocephaly; Ethmocephaly; Holoprosencephaly (alobar, lobar, semilobar); Holoprosencephaly facies syndrome; Premaxillary agenesis

Genetics/Basic Defects

1. Isolated and sporadic in most cases
2. Genetically heterogeneous, involving at least 12 loci on 11 chromosomes. There are at least five putative loci for HPE:
   a. *HPE1*
      i. Map locus: 21q22.3
      ii. Familial alobar holoprosencephaly
   b. *HPE2* (*SIX3*)
      i. Map locus: 2p21
      ii. Chromosome 2 form of holoprosencephaly, including midline cleft syndrome and DeMyer sequence
      iii. Caused by mutations in the homeobox-containing *SIX3* gene
   c. *HPE3* on 7q36-qter, characterized as the locus containing the human *sonic hedgehog* gene (*SHH*)
      i. Either loss-of-function mutation or disruption of one of the *sonic hedgehog* alleles at 7q36 (haploinsufficiency) shown to cause variable phenotype of holoprosencephaly
      ii. A broad spectrum of holoprosencephaly present in patients with de novo 7q, or with autosomal dominant holoprosencephaly having a linkage on 7q36
      iii. 7q deletion syndrome without typical holoprosencephaly in some patients
      iv. Interaction of partial trisomy 3p and partial monosomy 7q: invariably associated with severe forms of holoprosencephaly and facial dysmorphism. This delineates an autosomal imbalance syndrome or a dosage effect involving distal 3p duplication/terminal 7q deletion and dysmorphogenesis of the forebrain and midface.
   d. *HPE4* (TG-interacting factor, *TGIF*) on 18p11.3. Mutations of *TGIF* have been associated with holoprosencephaly and premaxillary agenesis.
   e. *HPE5* (*ZIC2*) on 13q32
3. SHH signaling pathway or the Nodal/TGF pathway (Cohen 2006; Bertolacini et al. 2010)
   a. *SHH* is the major gene implicated in holoprosencephaly (12.7% of HPE cases: 50% of overall point mutations and 38% of overall large deletions) (Dubourg et al. 2004)
   b. *ZIC2* is the second HPE gene by order of involvement (9.2% of HPE cases: 31% of overall point mutations and 38% of overall large deletions)

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c. Point mutations and large deletions in *SIX3* represent 3% and 1% of HPE cases, respectively. They are generally found in severe phenotypes (Pasquier et al. 2005).
d. Mutations in *TGIF* account for 1% of studied cases and large deletions for nearly 1% (Gripp et al. 2000).

4. *GLI2* mutations (Rahimov et al. 2006): nucleotide change and diverse phenotype
   a. 451A → G (Arg151Gly): holoprosencephaly-like phenotype
   b. 3,677C → T (Pro1226Leu): lobar HPE
   c. 1,809C → T (Pro604Ser)
      i. Anophthalmos
      ii. Branchial arch anomalies
      iii. CNS anomalies
   d. 3,348G → A (Met1116Ile)
      i. Heminasal aplasia
      ii. Orbital anomalies
5. *FAST1* (forkhead activin signal transducer 1) mutations: *FAST1* is the first human gene with mutations causing both midline defects (holoprosencephaly) and lateral defects (anomalies of cardiac looping) (Ouspenskaia et al. 2002)
6. Other known HPE-associated genes
   a. *PTCH*
      i. Patched mutations in humans result in haploinsufficiency.
      ii. A few of such mutations cause holoprosencephaly
      iii. Common in nevoid basal cell carcinoma syndrome and in isolated basal cell carcinomas
   b. *DHCR7*
      i. Mutations resulting in reduced serum cholesterol and accumulation of 7-dehydrocholesterol in autosomal recessive Smith–Lemli–Opitz syndrome
      ii. Four percent of cases with Smith–Lemli–Opitz syndrome have holoprosencephaly
   c. *DISP1*: Loss-of-function mutations may be associated with normal brain structure and development but facial features usually seen in conjunction with frank HPE (Roessler et al. 2009).
   d. *NODAL*: Mutations may result in HPE but are more commonly associated with cardiac and laterality defects (Roessler et al. 2009).
   e. *FOXH1* (part of the NODAL signaling pathway): Mutations may result in HPE or cardiac defects (Roessler et al. 2008)
   f. *FGF8*: A loss-of-function mutation has been described in three members of one family with a range of classic HPE-spectrum features (Araúz et al. 2010).
7. Subtypes of holoprosencephaly and the range of possible craniofacial features
   a. Alobar holoprosencephaly
      i. Cyclopia (a single eye or a partially divided eye in a single orbit with or without proboscis above the eye)
      ii. Ethmocephaly (extreme ocular hypotelorism with proboscis located between the eyes)
      iii. Cebocephaly (ocular hypotelorism with a single-nostril nose)
      iv. Premaxillary agenesis (ocular hypotelorism with median cleft lip and palate)
      v. Bilateral cleft lip
      vi. Ocular hypotelorism only
      vii. Anophthalmia or microphthalmia
      viii. Relatively normal facial appearance
   b. Semilobar holoprosencephaly
      i. Bilateral cleft lip with median process representing the philtrum-premaxilla anlage
      ii. Flat nasal bridge
      iii. Absent nasal septum
      iv. Flat nasal tip
      v. Midline cleft lip and/or palate
      vi. Ocular hypotelorism
      vii. Flat nose
      viii. Anophthalmia/microophthalmia
      ix. Relatively normal facial appearance
   c. Lobar holoprosencephaly
      i. Bilateral cleft lip with median process
      ii. Ocular hypotelorism
      iii. Flat nose
      iv. Relatively normal facial appearance
8. Causes
   a. Detectable chromosome abnormalities (24–45%)
      i. Numerical chromosomal abnormalities
         a) Trisomy 13 (most common)
         b) Trisomy 18
         c) Triploidy
         d) Mosaic trisomy 9
      ii. Structural chromosomal abnormalities: reported in virtually all chromosomes. The most frequent ones are as follows:
         a) Involving 13q [del(13q), r(13), dup(13q)]
         b) Del(18p)
         c) Del(7)(q36) (20%)

d) Dup(3)(p24-pter) (10%)
e) Del(2)(p21)
f) Del(21)(q22.3)
g) Del(22q11)
h) Partial monosomy 14q

b. Monogenic holoprosencephaly (18–25%)
i. Autosomal dominant
a) Pallister–Hall syndrome
b) Rubinstein–Taybi syndrome
c) Kallmann syndrome
d) Martin syndrome (with club foot and spinal anomalies)
e) Steinfeld syndrome (with congenital heart disease, absent gallbladder, renal dysplasia, and radial defects)
f) Ectrodactyly and hypertelorism
ii. Autosomal recessive
a) Meckel-Gruber syndrome
b) Smith–Lemli–Opitz syndrome
c) Pseudotrisomy 13 syndrome
d) XK aprosencephaly syndrome
e) Heterotaxy and holoprosencephaly
f) Genoa syndrome (with craniosynostosis)
g) Lambotte syndrome (with microcephaly, prenatal growth retardation, and hypertelorism)
h) Hydrolethalus syndrome (with hydrocephalus, polydactyly, and other anomalies)
i) Facial clefts and brachial amelia
iii. X-linked recessive (holoprosencephaly with fetal hypokinesia/akinesia)
c. Agnathia–otocephaly (10%)
d. Fronto-nasal dysplasia (6.7%)
e. Sirenomelia association
f. Holoprosencephaly, ectopia cordis, and embryonal neoplasms

9. Nongenetic risk factors (Johnson and Rasmussen 2010):
a. Maternal diabetes
i. One to two percent of newborn infants of diabetic mothers develop holoprosencephaly.
ii. The most commonly studied with the strongest association of the risk factor
b. Salicylates use, respiratory and sexually transmitted infections, and use of assisted reproductive technologies: identified in epidemiologic studies as possibly associated with increased risk of HPE
c. Quality of diet and use of multivitamin supplements: associated with a decreased risk
d. Retinoic acid
i. CNS anomalies, particularly hydrocephalus
ii. Holoprosencephaly
e. Ethyl alcohol
i. Holoprosencephaly/arhinencephaly
ii. Agnathic cyclopia
iii. Midline cerebral dysgenesis with hypothalamic–pituitary dysfunction
iv. Hydrocephalus
v. Agenesis of the corpus callosum and anterior commissure
f. Estrogen/progestin
g. Anticonvulsants
h. Low-calorie weight reduction diets
i. Prenatal infections
i. Cytomegalovirus
ii. Rubella
iii. Toxoplasma
j. Poverty
k. Previous pregnancy loss

Clinical Features

1. Variable expression, ranging from a small brain with a single cerebral ventricle and cyclopia to clinically unaffected carriers in familial holoprosencephaly
2. Face: Holoprosencephaly is often associated with distinct facial appearance (holoprosencephaly facies syndrome). The face predicts the brain approximately 80% of the time. In decreasing order of severity:
a. Absence of eye(s) (the most severe form)
b. Cyclopia
i. The most severe dysmorphism
ii. A median monophthalmia (a single midline eye)
iii. Synophthalmia (fusion of two eyes in a single midline orbit)
iv. Anophthalmia
v. Presence of a single median orbit (sine qua non for the diagnosis)
vi. Without or with proboscis (single or double protruding from the glabella, just above the median eye)

vii. Complete arhinia with no nose, no nasal bones
viii. Degree of facial dysmorphism strongly correlated with the severity of brain malformation (facial and the oculo-orbital phenotype reflect the underlying central nervous system pathology)

c. Ethmocephaly
i. Rarest type
ii. Close-set eyes (ocular hypotelorism) located in two separate orbits
iii. A median proboscis between the two eyes as a rudimentary tube-like nose
iv. Hypoplastic or absent median facial bones

d. Cebocephaly
i. Close-set eyes (ocular hypotelorism) into separate orbits
ii. A nose with a single nostril
iii. No cleft lip

e. Premaxillary agenesis
i. Close-set eyes (ocular hypotelorism)
ii. Median cleft lip and palate

3. Eyes
a. Anophthalmia
b. Microphthalmia
c. Cyclopia
d. Fused eyes
e. Coloboma
f. Hypotelorism
g. Bulging eyes
h. Other eye malformations
i. Fused lids
ii. Optic disk hypoplasia
iii. Cataract

4. Nose
a. Proboscis
b. Arhinia with or without proboscis
c. Flat nose
i. With proboscis
ii. Absent or nonpatent nares
iii. Other malformations

5. Mouth
a. Median cleft lip
b. Bilateral cleft lip
c. Unilateral cleft lip
d. Cleft palate alone
e. Cleft lip with cleft palate
f. Cleft lip alone
g. Cleft uvula
h. Microstomia
i. Macrostomia
j. Agnathia
k. Micrognathia

6. Ear
a. Fused ears
b. Other ear malformations

7. Neurodevelopmental deficits
a. Hoarse or "barking" voice, high-pitched crying
b. Major feeding problems with choking spells
c. Common growth delay
d. Seizures
e. Spasticity or floppy muscle tone
f. Brain-stem dysfunction with irregular breathing and heart rate and erratic body temperature control
g. Profound developmental delay with very limited expressive language and minimal attainment of motor skills
h. Behavioral problems

8. Endocrine disorders
a. Occasional diabetes insipidus with episodes of dehydration
b. Rare panhypopituitarism

9. Presence of microforms of holoprosencephaly in relatives of patients with holoprosencephaly
a. Microcephaly
b. Single central maxillary incisor
c. Ocular hypotelorism
d. Anosmia/hyposmia secondary to absent olfactory tracts and bulbs
e. Iris coloboma
f. Absent superior labial frenulum
g. Midface hypoplasia
h. Congenital nasal pyriform aperture stenosis
i. Developmental delay

10. Holoprosencephaly-agnathia spectrum (Kauvar et al. 2010)
a. Holoprosencephaly, the most common developmental disorder of the human forebrain, is occasionally associated with the spectrum of agnathia, or virtual absence of the mandible
b. This condition results in a constellation of structural cerebral and craniofacial abnormalities
c. The majority of these patients are female and have the most severe forms of HPE, with cyclopia present more frequently than is usually observed in cohorts of patients with HPE. Also,

many patients have additional clinical findings not typical in patients with classic HPE, particularly situs abnormalities

11. Prognosis
    a. Infants born with cyclopia, ethmocephaly, and cebocephaly: virtually all die within a week of birth
    b. Infants born with premaxillary agenesis, unilateral or bilateral cleft lip, or more normal facies
        i. Half of the patients die before 4–5 months.
        ii. Twenty to thirty percent of the patients live to 1 year of age. Longer survival is possible to at least 11 years.
    c. Cases diagnosed in utero will have an extremely poor neurologic development after birth.
    d. Causes of death most often due to brain-stem malfunction (unable to control the respiration and heart rate) aggravated by infections and other stresses

Diagnostic Investigations

1. Neuroimagings (MRI/CT of the brain)
    a. A single ventricle
    b. Absence of olfactory bulb and tracts
    c. Absence of corpus callosum
    d. Absence of inferior frontal and temporal regions
    e. Fused thalami
    f. Absence of optic nerve
    g. Incomplete anterior and posterior pituitary
    h. Normal brainstem and cerebellum
    i. Lack of ethmoid bone
2. Cytogenetic analysis (Bendavid et al. 2009)
    a. An essential diagnostic tool
    b. Initially, karyotype approach led to the identification of several recurrent chromosomal anomalies predicting different HPE loci
3. Molecular genetic diagnoses
    a. Subsequently, several genes were isolated from these critical HPE regions, but point mutations and deletions in these genes were found only in 25% of the genetic cases
    b. In order to identify other HPE genes, a more accurate investigation of the genome in HPE patients was necessary: If HPE is isolated and nonsyndromic, including sporadic cases, the study of the four major genes involved in the disease should be undertaken.
    c. To date, high-resolution cytogenetic techniques such as subtelomeric multiplex ligation-dependent probe amplification (MLPA) and microarray-based comparative genomic hybridization (array CGH) have enhanced chromosomal aberration analysis.
        i. A systematic search for gains or losses in the subtelomeres by MLPA
            a) Leads to identification of 4% more anomalies
            b) Rearrangements, deletions, or duplications must be verified by FISH on the karyotype of the proband and parents, so the identification of a cryptic-balanced translocation in a parent can change the approach to genetic counseling.
        ii. Array-CGH analysis
            a) A part of the molecular diagnosis algorithm to help clinicians get more disease markers for difficult HPE genetic counseling (Pineda-Alvarez et al. 2010)
            b) Indicates a high prevalence of genomic rearrangements in HPE (Bendavid et al. 2009)
            c) Detects a high frequency of submicroscopic anomalies with a yield of 25%, especially in severe forms and in fetuses
            d) Helpful in identification of unbalanced anomalies, as MLPA for subtelomeres, and leading secondarily to identification of parental cryptic-balanced translocations by FISH (Bendavid et al. 2009)
            e) Would allow identification of new HPE loci
4. Necropsy and anatomical classification (Demyer and Zeman 1963; Delezoide et al. 1990; Dubourg et al. 2007): Holoprosencephaly is generally classified into three major types and one milder subtype. The distinction among the following three types is not always clear.
    a. Alobar holoprosencephaly
        i. The most severe form
        ii. Complete failure of brain tissue to develop into the normal right and left cerebral hemispheres
        iii. The brain consisting of a single fused cerebral hemispheres located in the frontal region
        iv. Total absence of interhemispheric fissure and falx cerebri

v. The brain surface is smooth with sparse convolutional markings
vi. A single dilated ventricle communicating with a large dorsal cyst
vii. Absence of the third ventricle, neurohypophysis, and olfactory bulbs and tracts
viii. Absence of corpus callosum
ix. Fused thalami and basal ganglia
x. Migrational anomalies often present

b. Semilobar holoprosencephaly
i. The less severe form
ii. Rudimentary cerebral lobes. Only partial separation into two cerebral hemispheres; the hemispheres are not separated across the midline in the front part of the brain
iii. A single ventricle
iv. Olfactory bulbs and corpus callosum are usually absent.
v. Partial presence of the septum pellucidum and corpus callosum pending on the severity

c. Lobar holoprosencephaly
i. The least severe form
ii. Well-formed cerebral lobes that may be of normal size
iii. Virtual complete separation of the cerebral hemispheres
iv. Various degree of rostral and basilar non-separation
v. Absent, hypoplastic, or normal olfactory bulbs, tracts and corpus callosum
vi. Gray matter heterotopias and other associated migrational anomalies

d. Middle interhemispheric variant or syntelencephaly
i. Failure of separation of the posterior frontal and parietal lobes
ii. Callosal genu and splenium normally formed
iii. Absence of corpus callosum
iv. Hypothalamus and lentiform nuclei normally separated
v. Heterotopic gray matter

Genetic Counseling

1. Based on a rigorous clinical evaluation exploring family history, environmental factors, and associated features (Mercier et al. 2010)

2. Recurrence risk: depending on the basis for the actual condition
a. Patient's sib
i. Empirical estimate of 20% for holoprosencephaly, 15% for a microform, and 15% for normal phenotype
ii. Increased recurrence risk depending on the type of Mendelian inheritance (autosomal recessive and dominant conditions with holoprosencephaly). Existence of incomplete penetrance or an incomplete form or microform of holoprosencephaly makes the interpretation of familial occurrence difficult.
iii. Fifty percent recurrence risk of having affected siblings with variable clinical symptoms and severity if a parent is affected with holoprosencephaly
iv. Germline mosaicism in which apparently unaffected parents with negative family history having more than one affected child
v. Sibs of a child with a numeric chromosome abnormality: have a slightly increased risk of having a similar chromosome abnormality (depending on the specific abnormality and the age of the mother) with a similar or different phenotype.
vi. Increased in a case where a parent carries a chromosome translocation or other chromosome rearrangement

b. Patient's offspring
i. Severe cases of prosencephaly: not surviving to reproductive age
ii. Individuals with mild form or microform holoprosencephaly (with a gene mutation for the autosomal dominant nonsyndromic holoprosencephaly): 50% recurrence risk of having an affected child

3. Prenatal diagnosis
a. Prenatal ultrasonography: can detect CNS and facial abnormalities of severe HPE as early as the first trimester, but is less sensitive for detection of milder forms of HPE, such as lobar HPE
i. General characteristics
a) Polyhydramnios
b) Ocular hypotelorism
c) Cleft lip/palate
d) Arhinia

e) Cyclopia and proboscis: identifiable at the beginning of the ninth week of gestation by 2-D and 3-D ultrasonography
f) Absence of central falx
g) Demonstration of a single rudimentary cerebral ventricle

ii. Alobar holoprosencephaly
a) Single ventricle
b) Presence or absence of dorsal sac
c) Fused thalami
d) Absence of cavum septum pellucidum

iii. Semilobar holoprosencephaly
a) Single ventricles with rudimentary occipital horns
b) Presence or absence of dorsal sac
c) Fused thalami
d) Absence of cavum septum pellucidum

iv. Lobar holoprosencephaly
a) Almost divided ventricles except at frontal horns of lateral ventricles
b) Some enlargement of lateral ventricle
c) Flat roof of frontal horns in microtonal view
d) Wide communication between the frontal horns and the inferior third ventricles
e) Absence of dorsal sac
f) Divided thalami
g) Absence of cavum septum pellucidum

b. Fetal MRI: provides better characterization of brain malformations, but only later in the third trimester of pregnancy (Hahn and Barnes 2010; Mercier et al. 2010)

c. Cytogenetic analysis from CVS or amniocytes
i. Parent with a balanced chromosomal rearrangement
ii. Fetus with multiple anomalies including holoprosencephaly from prenatal ultrasonography

d. Prenatal diagnosis by molecular analysis on fetal DNA obtained from amniocentesis or CVS for the disease-causing mutation previously identified in the proband
i. Sequence analysis or deletion/duplication analysis
a) *SIX3*-related holoprosencephaly
b) *SHH*-related holoprosencephaly
c) *TGIF*-related holoprosencephaly
d) *ZIC2*-related holoprosencephaly
e) *GLI2*-related holoprosencephaly
f) *PTCH1*-related holoprosencephaly
g) *TRAPPC10*-related holoprosencephaly
h) *ZIC2*-related holoprosencephaly
ii. Pallister–Hall syndrome: mutation analysis for mutation panel GLI3 (2023delG and 2012delG)
iii. Rubinstein–Taybi syndrome: FISH analysis of the deletion of the *CREBBP* gene on chromosome 16 (16p13.3)
iv. Smith–Lemli–Opitz syndrome
a) Detection of two disease-causing mutations in the *DHCR7* gene previously identified in the proband
b) Abnormal concentration of 7-dehydrocholesterol levels

e. Preimplantation genetic diagnosis
i. May be available for families in which the disease-causing mutation has been identified
ii. Reported for sonic hedgehog mutation causing familial holoprosencephaly (Verlinsky et al. 2003)

4. Management
a. Care for common medical problems (Levy et al. 2010)
i. Hydrocephalus
ii. Seizures
iii. Motor impairment
iv. Oromotor dysfunction with risk of poor nutrition and aspiration
v. Chronic lung disease
vi. Gastroesophageal reflux
vii. Constipation
viii. Hypothalamic dysfunction with disturbed sleep–wake cycles and temperature dysregulation
ix. Endocrine dysfunction: Diabetes insipidus in particular is found in about 70% of children with classic HPE

b. Treatment strategies based on the types of brain malformations and associated anomalies
i. Lethal entity: no specific treatment available
ii. Nonlethal entity
a) Ventriculoperitoneal shunt for hydrocephalus
b) Cleft lip and palate repair if indicated
c) Monitoring of fluid and electrolyte intake in patients with diabetes insipidus
d) Hormone replacement therapy for pituitary dysfunction

c. Supportive
   i. Multidisciplinary team approach
   ii. Support and counseling of the parents
   iii. Seizure management
   iv. Gastrostomy tube placement and fundoplication for gastroesophageal reflux and vomiting

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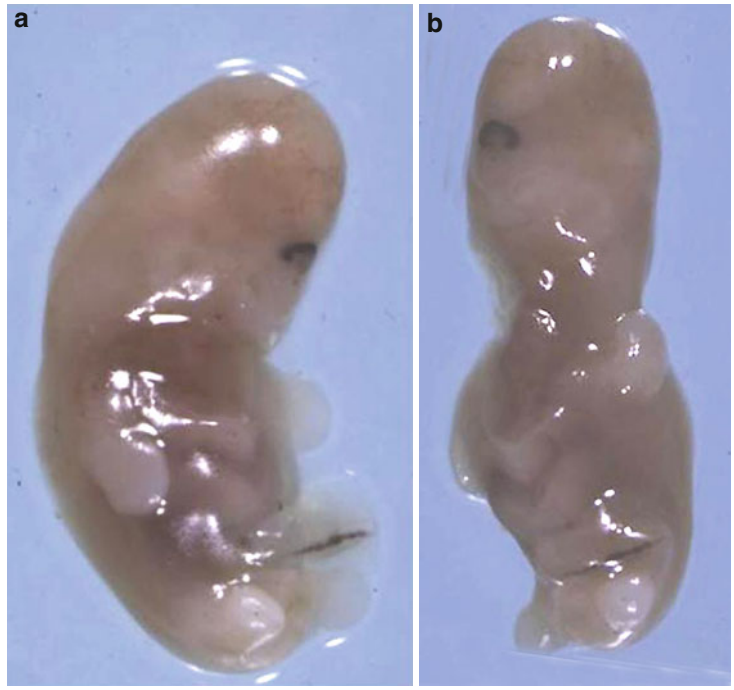

Fig. 1 (**a**, **b**) An aborted embryo with cyclopia

Fig. 2 A neonate with cyclopia. The infant had holoprosencephaly (arrhinencephaly), agenesis of olfactory and optic nerves, agenesis of pituitary, cor binoculare, left diaphragmatic hernia, bilobar spleen, agenesis of adrenal glands, and absence of right umbilical artery

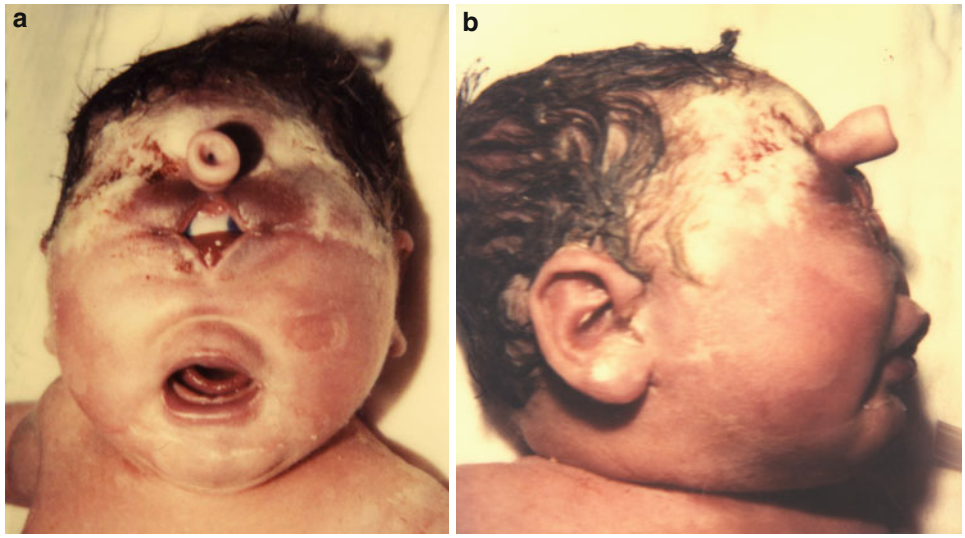

Fig. 3 (**a**, **b**) Another neonate with cyclopia

Fig. 4 An infant with ethmocephaly

Fig. 5 Postmortem brain with holoprosencephaly (dorsal view) showing a dilated single ventricle. The large dorsal cyst was ruptured during dissection, and the remnants of the membranous cyst wall are vaguely visible at the margins of the ventricle, especially on right side

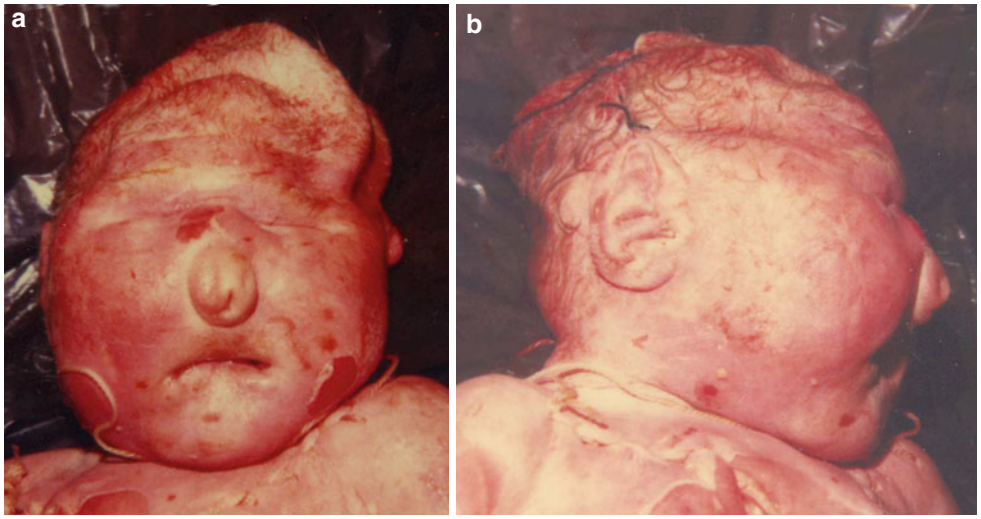

Fig. 6 (**a**, **b**) A neonate with cebocephaly

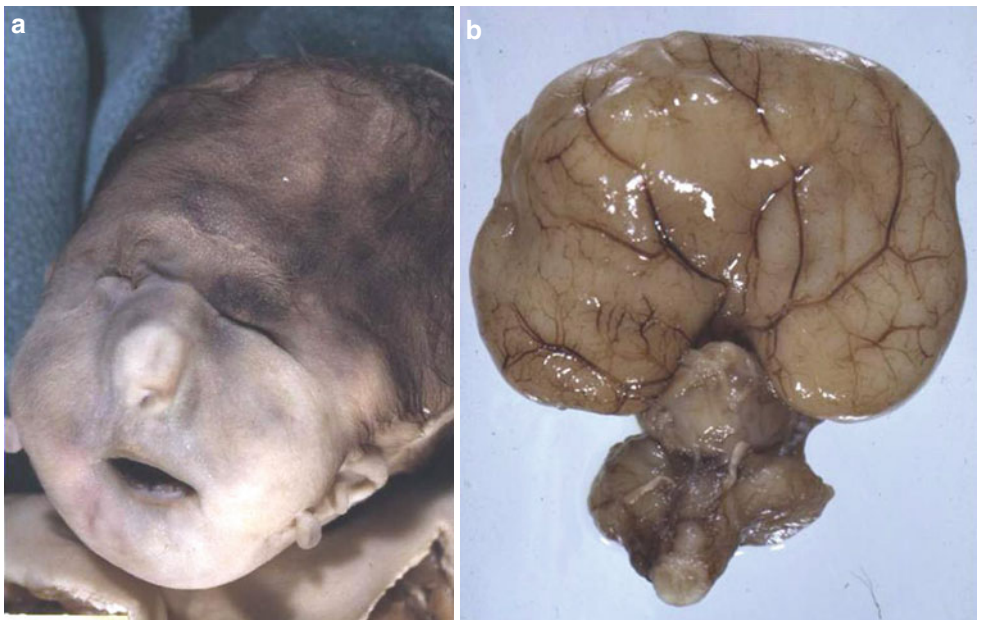

Fig. 7 (**a**, **b**) A premature neonate with cebocephaly. The infant had anophthalmia; bilateral nasal atresia; alobar holoprosencephaly (*ventral view*) with a 4.5 × 5.5 × 6.0 cm dorsal cyst (not shown), atresia of left external auditory canal with hypoplastic malformed auricle; agenesis of left lung; left kidney and left ureter; hypoplasia of left posterior cranial fossa and left cerebellum; multiple skin tags; hemivertebrae; and absence of right umbilical artery

Fig. 8 A neonate with cebocephaly and 48,XXY,+13

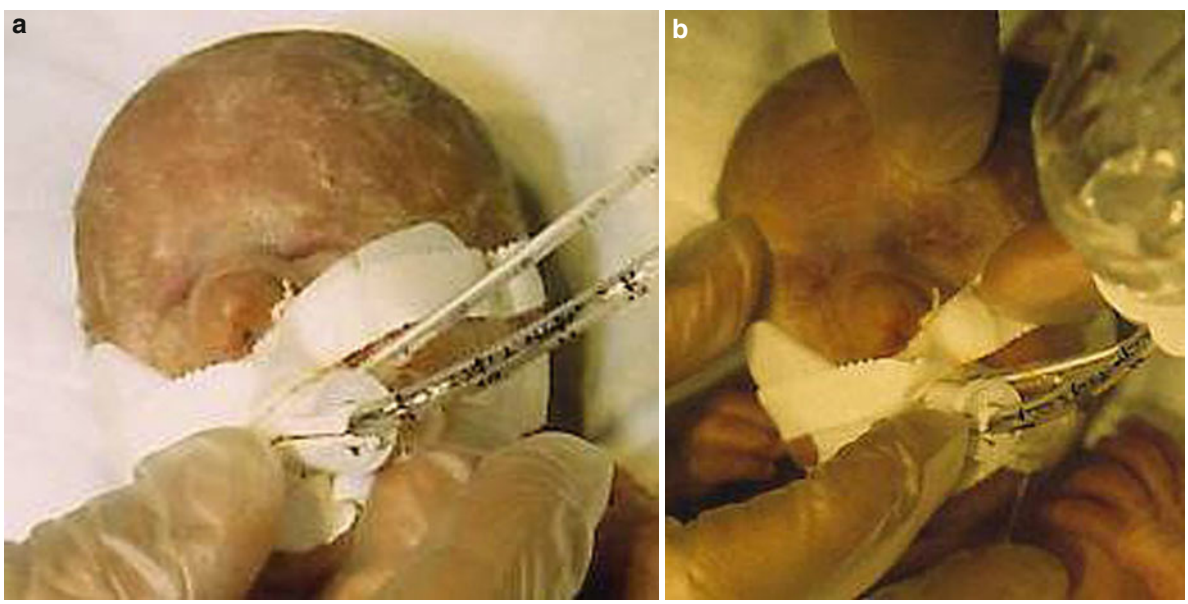

Fig. 9 (**a**, **b**) A newborn with trisomy 13 showing ocular hypotelorism and extreme microphthalmia

Fig. 10 (**a**, **b**) A neonate with trisomy 13 showing ethmocephaly, transverse reduction of the left forearm, and polydactyly of the right hand and both feet

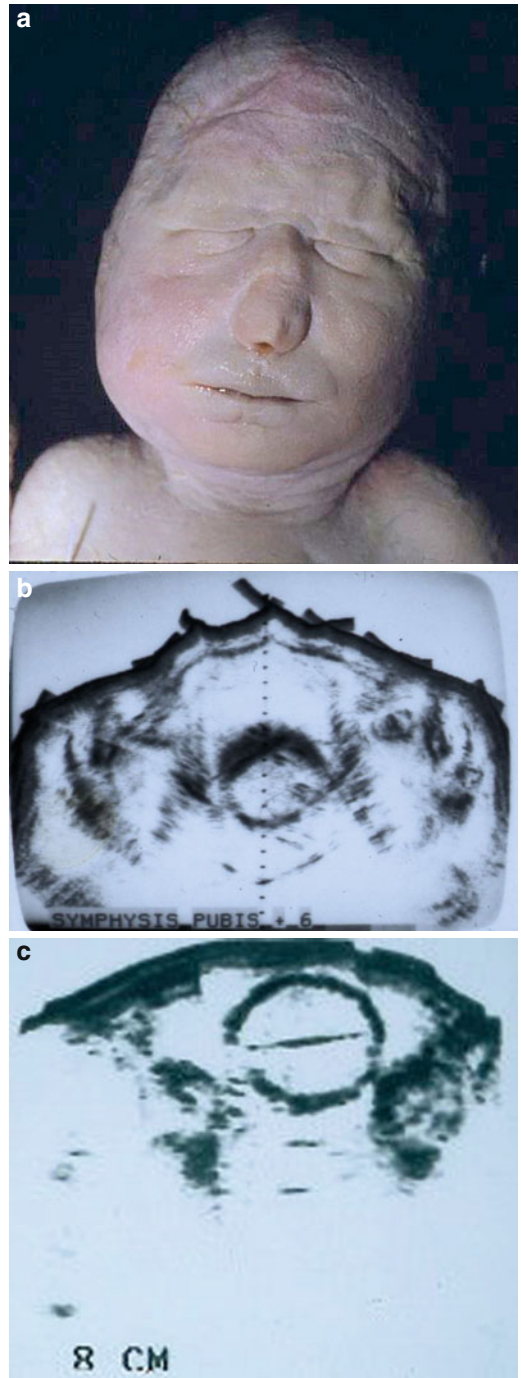

Fig. 11 (**a**–**c**) A neonate with trisomy 18 showing cebocephaly. The prenatal ultrasound showed fetal scalp edema, microcephaly, and holoprosencephaly (a normal brain ultrasound at the same gestation is illustrated here)

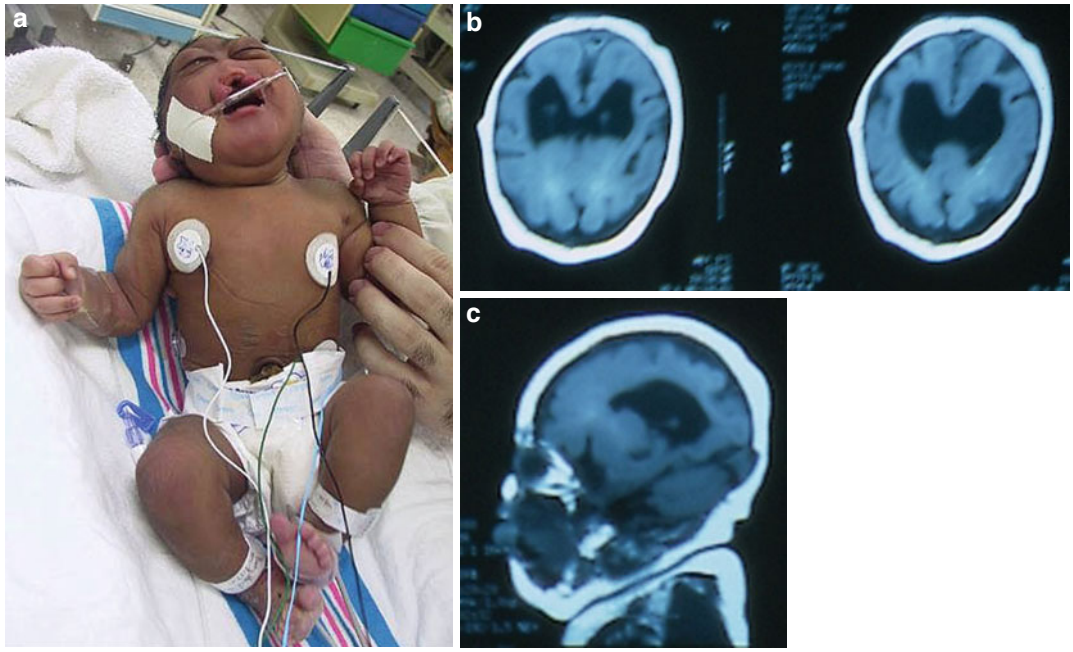

Fig. 12 (**a**–**c**) A neonate with semilobar holoprosencephaly illustrated by MRI of the brain

Fig. 13 (**a**–**d**) Front and lateral views of an infant with arrhinencephaly. The postmortem brain showed absence of olfactory tract and sulci and septum pellucidum and fused thalami

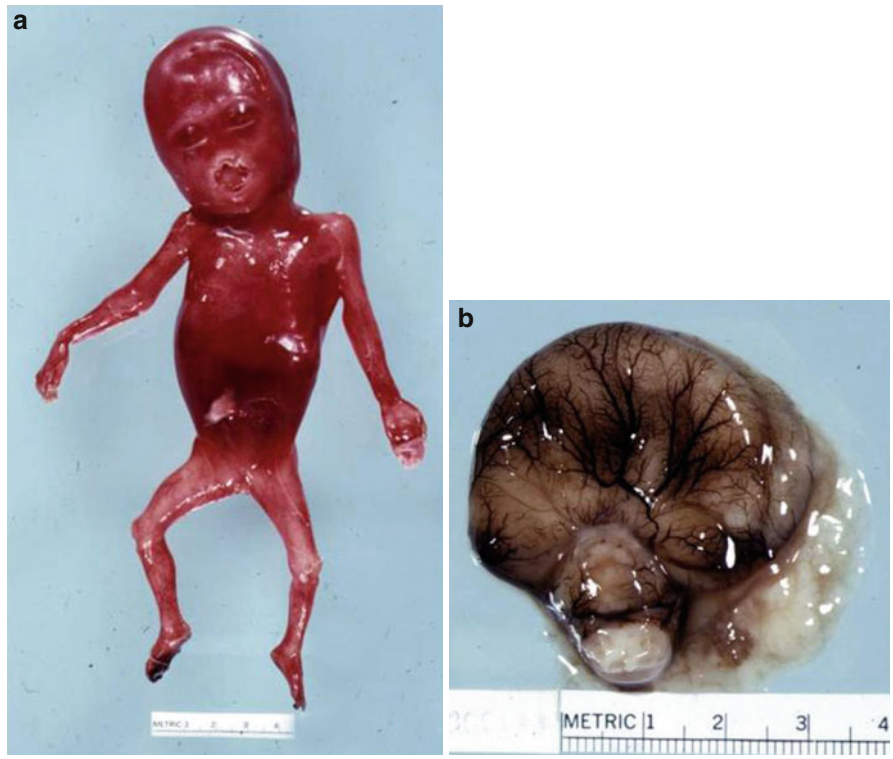

Fig. 14 (**a**, **b**) A fetus with premaxillary agenesis showing facial dysmorphism, including hypotelorism, absence of nose, median cleft lip and palate, and low-set ears. In addition, the fetus had 13 pairs of ribs and absence of uterus and left kidney. The pregnancy was terminated at 17 weeks gestation because of alobar holoprosencephaly detected by ultrasonography. The postmortem brain showed alobar prosencephaly with a cerebral vesicle. Gyri were not developed

Fig. 15 A newborn with sirenomelia associated with holoprosencephaly

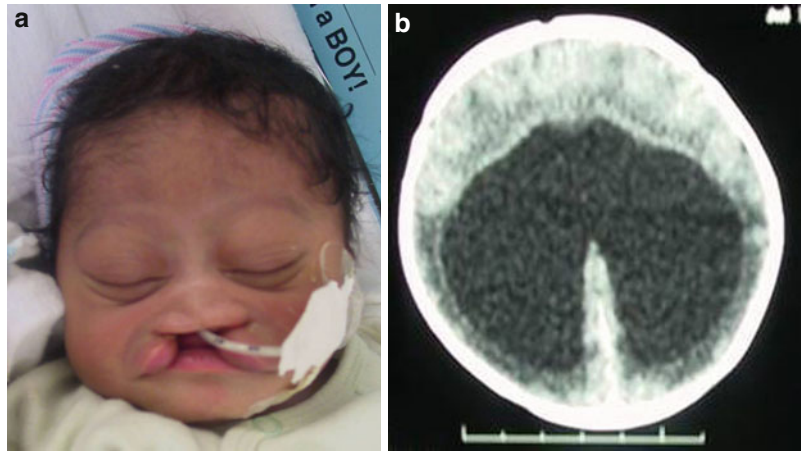

Fig. 16 (**a**, **b**) A neonate with premaxillary agenesis and holoprosencephaly illustrated by MRI of the brain

Fig. 17 (**a**–**c**) A child with premaxillary agenesis and upper limb defects

Fig. 18 (**a**–**d**) Four infants with premaxillary agenesis

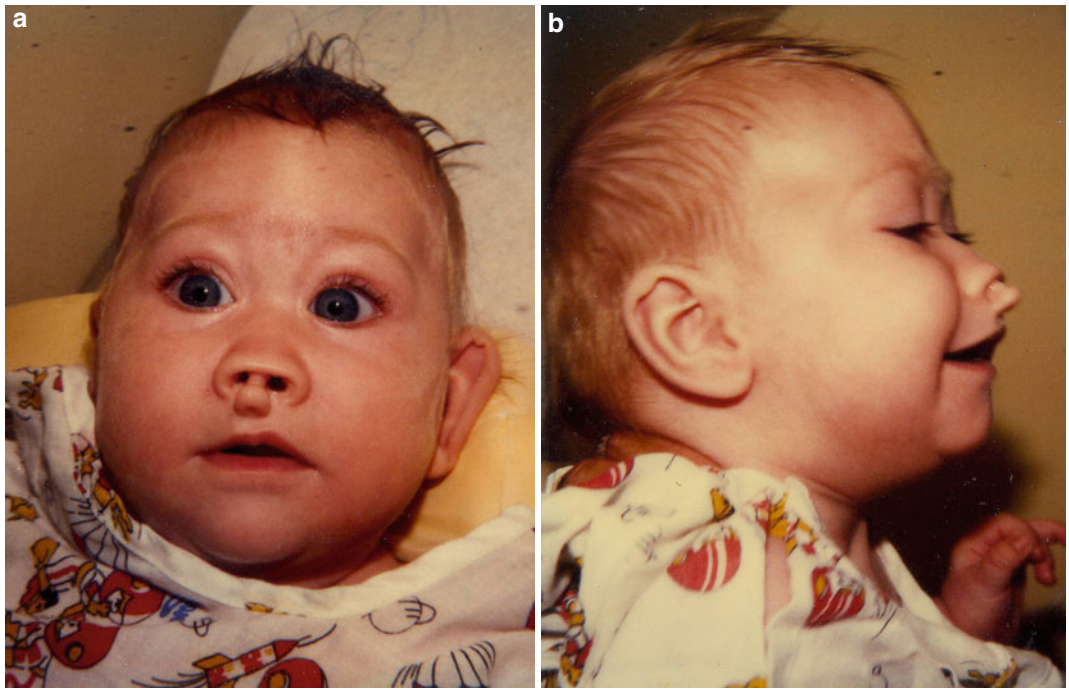

Fig. 19 (**a**, **b**) An infant with hypotelorism and duplicated nose

Fig. 20 (**a**, **b**) A girl with mild hypotelorism, antimongoloid slant, and a central incisor

Holt-Oram Syndrome

In 1960, Holt and Oram described a family in which nine members in four generations were affected by skeletal abnormalities of the upper limbs, cardiac malformations, and arrhythmias. The prevalence is about 1 in 100,000 live births. About 40–85% of cases are due to fresh mutation.

Synonyms and Related Disorders

Atrialdigital dysplasia; Heart-hand syndrome

Genetics/Basic Defects

1. An autosomal dominant disorder
   a. Complete penetrance
   b. Widely variable expression
2. Holt-Oram syndrome frequently linked to the gene *TBX5*, which is mapped to 12q24.1
3. Caused by mutations in the *TBX5* gene, a member of the T-box family that encodes a transcription factor (Huang 2002)
   a. Mutations predicted to create null alleles cause substantial abnormalities in both the limb and heart.
   b. Nonsense mutations of *TBX5* produce distinct phenotypes.
      i. One class of missense mutations: causes significant cardiac malformations but only minor skeletal abnormalities
      ii. Other class of nonsense mutations: causes extensive upper limb malformations but few significant cardiac abnormalities.
      iii. Several novel missense mutations in *TBX5* lead to functional haploinsufficiency and result in a reduced transcriptional activation of target genes, which is likely central to the pathogenesis of Holt-Oram syndrome (Boogerd et al. 2010)
4. Intrafamilial variations of the malformations: suggest that genetic background or modifier genes play an important role in the phenotypic expression of Holt-Oram syndrome (Huang 2002).
5. Hand-heart syndromes (syndromes with frequent association of congenital cardiac and upper limb malformations): genetically heterogeneous (Basson et al. 1995)
   a. Holt-Oram syndrome: the most common form
   b. Heart-hand syndrome type II (Tabatznik syndrome)
      i. Hypoplastic deltoids
      ii. Skeletal anomalies in the humeri, radii, ulnae, and thenar bones
      iii. Brachydactyly type D
      iv. Congenital cardiac arrhythmias (junctional rhythms and atrial fibrillation)
   c. Heart-hand syndrome type III
      i. Cardiac conduction defects (intraventricular delays and sick sinus syndrome)
      ii. Skeletal malformations limited to the hands and feet (brachydactyly type C)
   d. Autosomal dominant "partial phenocopy" conditions
      i. Familial atrial septal defects with conduction disease occurring without limb deformities
      ii. Familial limb malformations occurring without cardiac defects

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Clinical Features

1. Preaxial radial ray abnormalities of the upper limb(s) (Newbury-Ecob et al. 1996)
   a. Almost always present
   b. Unilateral or bilateral
   c. Symmetric or asymmetric (left side more affected than the right side)
   d. Severe (phocomelia) to mild phenotype due to aplasia, hypoplasia, fusion, or anomalous development of involved bones
   e. Thumbs
      i. Aplasia
      ii. Hypoplasia
      iii. Triphalangeal
      iv. Syndactyly
      v. Long
      vi. Normal
   f. Fingers
      i. Clinodactyly
      ii. Brachydactyly
      iii. Hypoplasia
      iv. Absent
      v. Syndactyly
      vi. Normal
   g. Radial bones
      i. Hypoplasia
      ii. Aplasia
   h. Ulnar
      i. Hypoplasia
      ii. Aplasia
   i. Carpal bones
      i. Deformed
      ii. Extra
   j. Thenar bones: hypoplastic thenar eminence
   k. Humerus
      i. Hypoplasia
      ii. Abnormal head
      iii. Aplasia
      iv. Normal
   l. Clavicles
      i. Hypoplasia
      ii. Prominent acromioclavicular joint
      iii. Normal
   m. Thorax
      i. Pectus excavatum
      ii. Hypoplasia pectoralis major
   n. Limited supination
   o. Limited extension of the elbow
2. Cardiac anomaly (75% of cases)
   a. Structural defects
      i. Atrial septal defect (most common type, usually of secundum variety)
      ii. Ventricular septal defect
      iii. Pulmonary stenosis (including peripheral arterial)
      iv. Mitral valve prolapse
      v. Complex cardiac malformations (tetralogy of Fallot, hypoplastic left heart, endocardial cushion defects, truncus arteriosus)
   b. Cardiac conduction defects
      i. Paroxysmal tachycardia
      ii. Prolonged PR interval (ECG)
      iii. Wandering atrial pacemaker
      iv. Atrial ectopics
      v. Sinus bradycardia
      vi. Syncope
      vii. Sinus arrest
      viii. Atrioventricular block
      ix. Atrial fibrillation
3. Mild to no symptoms in children and young adult
   a. Recurrent respiratory infections
   b. Failure to thrive
4. Older adults
   a. Congestive heart failure
   b. Supraventricular arrhythmia, especially atrial fibrillation
5. Differential diagnosis (Huang 2002)
   a. Fanconi anemia syndrome
      i. Multiple congenital anomalies consisting of malformations of the thumbs, forearms, and heart
      ii. Progressive bone marrow failure with pancytopenia, typically in the first decade
      iii. An increased risk for myelodysplasia or acute myelogenous leukemia
      iv. Diagnosis based on detection of chromosomal breakage or rearrangement in the presence of diepoxybutane or mitomycin C
   b. Thrombocytopenia-absent radius
      i. Both radii always absent
      ii. Thumbs always present
      iii. Occasional phocomelia

iv. Possible involvement of lower limbs.
  a) Club foot
  b) Knee instability
v. Thrombocytopenia
  a) Present in infancy
  b) Generally improves with time
vi. Heart defect can be present

c. Heart-hand syndrome II (Tabatznik)
  i. Type D brachydactyly (shortening of the distal phalanx of the thumb with or without shortening of the fourth and fifth metacarpals)
  ii. Sloping shoulders
  iii. Short upper limbs
  iv. Bowing of the distal radii
  v. Absence of the styloid process of the ulna
  vi. Supraventricular tachycardia
  vii. Possible mild mental retardation and mild facial dysmorphism
d. Heart-hand syndrome III
  i. Type C brachydactyly (shortening of the middle phalanges)
  ii. An accessory wedged-shaped ossicles on the proximal phalanx of the index fingers
  iii. Sick sinus syndrome
e. Okihiro syndrome
  i. Duane syndrome
    a) A congenital eye-movement disorder resulting from abnormal development of cranial nerve VI
    b) Absence of abduction of the globe
    c) Narrowing of the palpebral fissure on adduction of the globe
  ii. Upper extremity reduction defects
  iii. Cardiac malformations
f. Long-thumb brachydactyly syndrome
  i. Elongation of the thumb distal to the proximal interphalangeal joint
  ii. Often associated with index finger brachydactyly and clinodactyly
  iii. Narrow shoulders
  iv. Secondary short clavicles
  v. Pectus excavatum
  vi. Occasional rhizomelic limb shortening
  vii. Frequent with cardiac conductive defect
g. VACTERL association
  i. Radial defect usually unilateral
  ii. Accompanied by other malformations such as imperforate anus and tracheoesophageal fistula, and congenital heart defect

Diagnostic Investigations

1. Radiography
  a. Phocomelia of the upper limbs
  b. Shortened humeri
  c. Shortened forearms
    i. Aplasia/hypoplasia of the radius
    ii. Hypoplastic ulna
    iii. Radioulnar synostosis
    iv. Humeral-ulnar synostosis
  d. Thumbs
    i. Absent thumbs
    ii. Triphalangeal thumbs
    iii. Clinodactyly
    iv. Syndactyly
    v. Absent first metacarpals
    vi. Hypoplastic thenar eminences
  e. First metacarpals
    i. Absent
    ii. Hypoplastic
  f. Fifth fingers
    i. Short middle phalanx
    ii. Clinodactyly
  g. Carpal bones
    i. Deformed
    ii. Extra carpals
    iii. Fused
    iv. Irregular
    v. Delayed formation
  h. Shoulders
    i. Deformed scapula and/or clavicle
    ii. Deformed head of the humerus
    iii. Accessory bones
  i. Deformed sternum
2. Echocardiography for structural cardiac defects
3. Electrocardiography for cardiac conduction defects (Bossert et al. 2002)
  a. Sinus arrest
  b. Various degrees of atrioventricular block
  c. Right bundle branch block
  d. Sinus node dysfunction
  e. Wandering pacemaker

   f. Bradycardia
   g. Atrial fibrillation/flutter
   h. Supraventricular tachycardia and WPW syndrome
   i. Premature ventricular complexes
4. Molecular genetic testing of *TBX5* by sequencing of entire coding region or mutation scanning

Genetic Counseling

1. Recurrence risk
   a. Probands
      i. Sixty to seventy percent have an affected parent
      ii. Thirty to forty percent have a de novo mutation
   b. Patient's sib: not increased unless a parent is affected in which case, there is 50% recurrence risk
   c. Patient's offspring: 50%
2. Prenatal diagnosis
   a. Ultrasonography of Holt-Oram syndrome for fetuses at risk involving severe anomalies by demonstrating cardiac defect associated with upper limb defects, especially the radial ray defects
   b. Molecular genetic testing of *TBX5* of fetal DNA obtained from amniocentesis or CVS, provided the disease-causing mutation has been identified in the family
   c. Preimplantation genetic diagnosis
      i. May be available for families in which the disease-causing mutation has been identified
      ii. Reported for Glu69ter *TBX5* mutation causing Holt-Oram syndrome (McDermott et al. 2005)
3. Management
   a. A permanent pacemaker for advanced heart block
   b. Surgery for severe cardiac defect
   c. Prostheses for children with severe limb shortening
   d. Orthopedic management of severe limb defects

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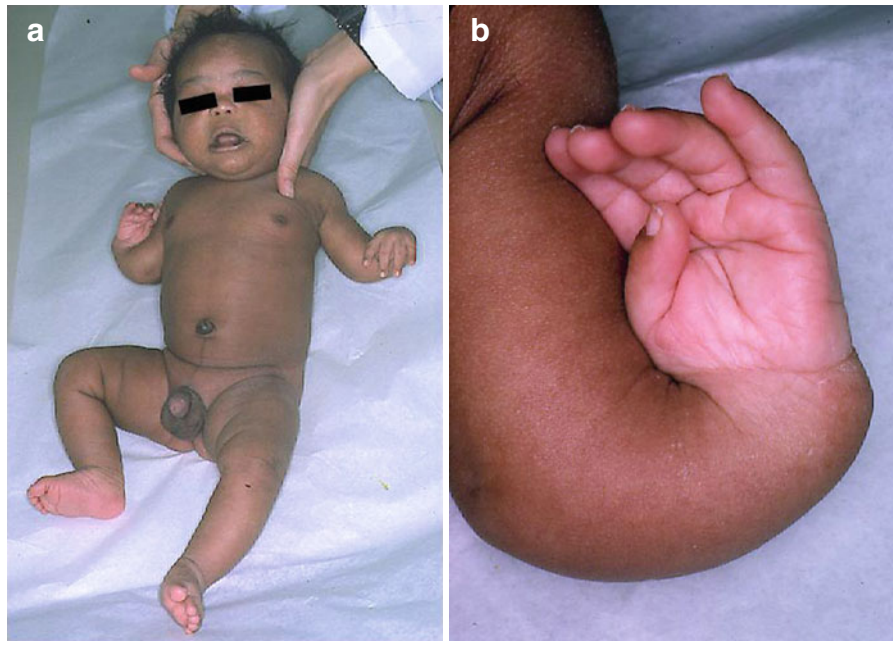

Fig. 1 (**a**, **b**) An infant with Holt-Oram syndrome showing club hands and fingerlike thumbs

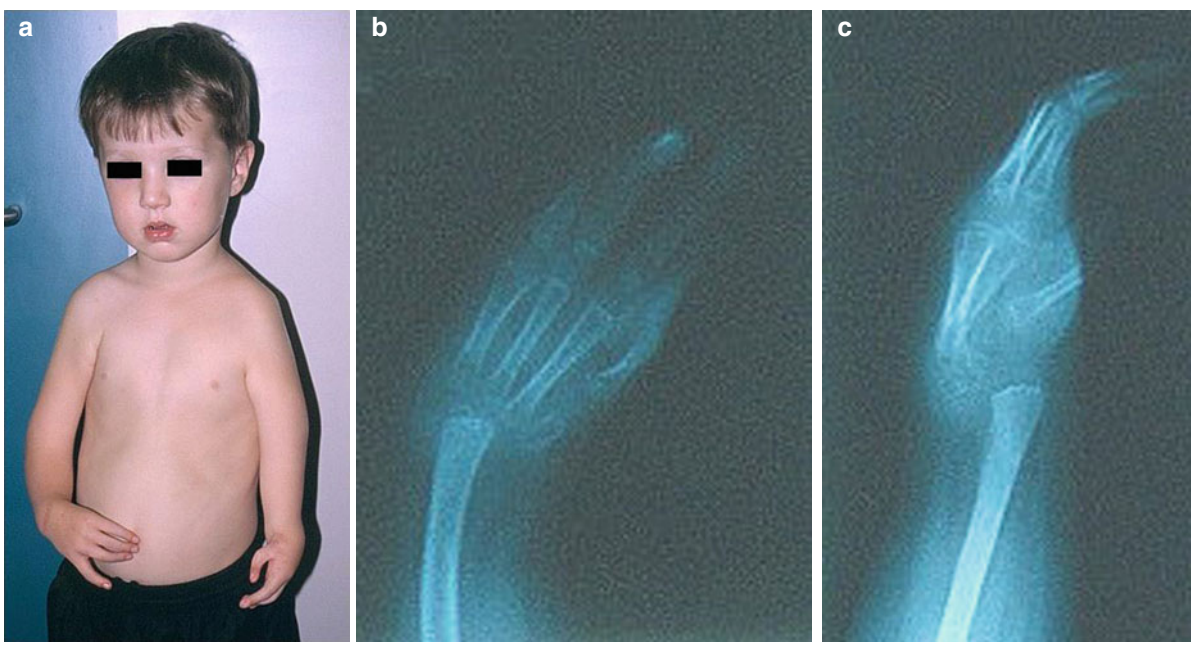

Fig. 2 (**a**–**c**) A child with Holt-Oram syndrome showing bilateral club hands, absent radius, and absent thumbs, demonstrated by radiographs

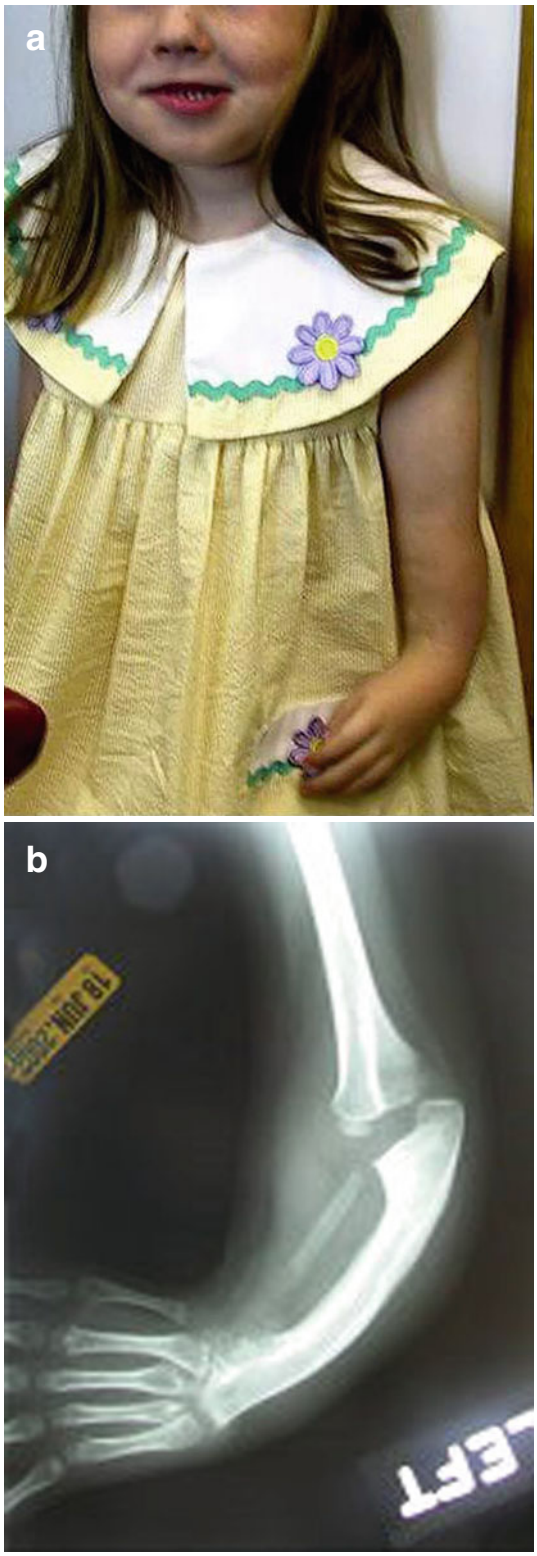

Fig. 3 (**a**, **b**) A child with Holt-Oram syndrome showing left club hand and hypoplastic radius, illustrated by radiography

Huntington Disease

Huntington disease (HD) is an autosomal dominant, progressive neurodegenerative disorder, typically characterized by a movement disorder, affecting middle-aged adults. It is the most frequent cause of genetic chorea with reported prevalence rates in North America and Europe ranging from 3 to 7 per 100,000 (Cardoso et al. 2006).

Synonyms and Related Disorders

Huntington chorea

Genetics/Basic Defects

1. Caused by a mutation in the *IT15* gene, which is a 210-kb gene located near the tip of the short arm of chromosome 4 (4p16.3), resulting in the N-terminal region of huntingtin protein (Htt) (The Huntington's Disease Collaborative Research Group 1993; Cardoso 2009; Harris et al. 2009)
2. Patients with Huntington disease have an expanded and unstable trinucleotide CAG (cytosine-adenine-guanine) repeat in the *IT15* gene within exon 1 (Rubinsztein et al. 1996). Huntington disease is, therefore, considered one of the trinucleotide repeat disorders.
   a. Normal CAG repeat length in the *HD* gene: 35 or lower
   b. Expansions of 40 or more cause HD with complete penetrance.
   c. Individuals with 36–39 repeats may also develop HD but penetrance is incomplete (Rubinsztein et al. 1996).
   d. A CAG repeat range between 27 and 35: considered normal allele with particular risk for expansion into the HD range in the paternal germline (Ranen et al. 1995; Laccone et al. 1999)
   e. The number of CAG repeats
      i. Has significant implications for age at onset, disease severity, and stability of the gene between generations
      ii. Presence of a robust inverse correlation between the number of polyglutamine repeats and the age at disease onset so that longer repeat lengths are associated with earlier onset of Huntington disease (Shelbourne et al. 2007)
      iii. The number of CAG repeats, however, is not an absolute prediction of disease onset.
3. The nature of the genetic defect in the *HD* gene (Myers et al. 1998) explains many of the genetic features of the disorder, including:
   a. The variability in age at onset
   b. The tendency for juvenile disease to be inherited from fathers
      i. Merritt et al. (1969) first observed that a disproportionate number of cases with onset before the age of 21 had inherited the *HD* gene from affected fathers.
      ii. The observation of earlier ages at onset in successive generations, termed "anticipation," is seen in several of the trinucleotide repeat disorders including HD.
      iii. Meiotic instability of the *HD* repeat in paternal transmission explains the observation of anticipation in HD.
   c. The sporadic appearance of new mutations to HD

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4. Pathophysiology (Roze et al. 2008)
   a. The expanded polyglutamine repeat alters the normal functions of Htt.
   b. The mutated protein, Exp-Htt, is itself toxic.
   c. Htt interacts with an array of proteins in neuronal cells
   d. One important characteristic of Huntington disease is the particular vulnerability of a particular brain region, the caudate–putamen, despite similar expression of the mutated protein in other brain areas.

Clinical Features

1. A triad of HD (Cardoso 2009; Harris et al. 2009)
   a. Movement disorder (Leigh et al. 1983; Carella et al. 1993; Jankovic and Ashizawa 1995; Reuter et al. 2000; Tan et al. 2000)
      i. Full spectrum of motor impairment
         a) Eye movement abnormalities
         b) Parkinsonian features
         c) Dystonia (particularly in juvenile HD)
         d) Myoclonus
         e) Tics
         f) Ataxia
         g) Dysarthria
         h) Dysphagia
         i) Spasticity with hyperreflexia and extensor plantar responses
      ii. Chorea: often superseded by dystonia or akineto-rigid parkinsonian features with progressing illness
      iii. Dystonia: found in more than 90% of patients with HD in one study (Louis et al. 1999) although rarely it becomes as prominent as in idiopathic dystonias
   b. Cognitive decline
      i. Universally go through cognitive decline, mental slowing, impaired problem-solving abilities, and other signs of a frontal dysexecutive syndrome, and they eventually become demented. These patients present with the prototype of so-called subcortical dementia (Lawrence et al. 1996; Kirkwood et al. 2001; Ho et al. 2003).
      ii. Cognitive decline also heralds the juvenile onset of HD (Ribai et al. 2007).
      iii. Asymptomatic carriers of the HD gene have decreased phonemic fluency (Larsson et al. 2008).
   c. Behavioral changes
      i. Universal and may occasionally antedate motor manifestations
      ii. Major depression is common, diagnosed in more than 40% of subjects, and responsible for increased suicide rates in HD
      iii. Broad spectrum of behavioral abnormalities (Caine and Shoulson 1983; Mendez 1994; Schoenfeld et al. 1984; Shiwach 1994; Rosenblatt and Leroi 2000; Rosenblatt et al. 2003; Guttman et al. 2003)
         a) Anxiety or panic attacks
         b) Obsessive compulsive symptoms
         c) Manic features
         d) Psychosis
         e) Irritability and aggressive behavior
         f) Sexual disinhibition
         g) Apathy
         h) In presymptomatic HD, significantly more psychiatric symptoms (specially depression, anxiety, and obsessive-compulsiveness) were reported than for the controls (Duffin et al. 2007)
         i) Similarly, psychiatric difficulties are indicators of juvenile HD onset (Ribai et al. 2007).
2. End-stage HD
   a. Relentlessly progressive course with death occurring 15–20 years after symptom onset with particularly rapid progression in the juvenile Westphal variant
   b. Typically rigid and akinetic, demented, and mute
   c. Immobility and dysphagia often lead to aspiration pneumonia, the most common cause of death in these patients (Marshall 2004; Sorensen and Fenger 1992; Lanska et al. 1988).
3. Differential diagnosis
   a. Choreoacanthocytosis: the most likely disorder to be confused
      i. Dementia
      ii. Involuntary movements
      iii. Caudate atrophy
      iv. Abnormal red blood cell morphology

v. Neuropathy
vi. Seizures
vii. Myopathy
viii. Elevated creatine phosphokinase
ix. Self-mutilation
x. An unusual eating dystonia

b. Different causes of chorea
i. Genetic causes
a) Huntington disease
b) Huntington disease–like illnesses
c) Neuroacanthocytosis
d) McLeod syndrome
e) Wilson disease
f) Benign hereditary chorea
g) Spinocerebellar atrophy types 2, 3, 17
h) Dentatorubropallidoluysian degeneration
i) Ataxia-telangiectasia
j) Ataxia associated with oculomotor apraxia
k) Neuroferritinopathy
l) Pantothenate kinase associated degeneration
m) Leigh disease and other mitochondriopathies
n) Lesch–Nyhan disease
o) Creutzfeldt–Jakob disease
p) Neuronal ceroid lipofuscinosis
q) Glutaric aciduria
r) Polycythemia vera
s) Celiac disease
t) Benign familial chorea
ii. Immunologic causes
a) Sydenham chorea
b) Systemic lupus erythematosus
c) Antiphospholipid antibody syndrome
iii. Drug-induced chorea
a) Amantadine
b) CNS stimulants (amphetamines, methylphenidate, cyproheptadine)
c) Anticholinergics
d) Anticonvulsants (carbamazepine, phenytoin)
e) Carbon monoxide
f) Cocaine
g) Dopamine agonists
h) Dopamine-receptor blockers
i) Estrogens
j) Ethanol
k) Levodopa
l) Levofloxacin
m) Lithium
n) Sympathomimetics
o) Theophylline
p) Tricyclic antidepressants
q) Carbamazepine
r) Drugs that cause tardive dyskinesia
s) Withdrawal emergent syndrome
iv. Infections
a) AIDS-related (toxoplasmosis, progressive multifocal leukoencephalopathy, HIV encephalitis)
b) Bacteria (diphtheria, scarlet fever, whooping cough)
c) Encephalities (B19 parvovirus, Japanese encephalitis, measles, mumps, West Nile river encephalitis, others)
d) Parasites (neurocysticercosis)
e) Protozoan (malaria, syphilis)
v. Endocrine-metabolic dysfunction
a) Adrenal insufficiency
b) Hyper/hypocalcemia
c) Hyper/hypoglycemia
d) Hypomagnesemia
e) Hypernatremia
f) Liver failure
vi. Vascular
a) Postpump chorea (cardiac surgery)
b) Stroke
c) Subdural hematoma
vii. Miscellaneous
a) Anoxic encephalopathy
b) Cerebral palsy
c) Kernicterus
d) Multiple sclerosis
e) Normal maturation (less than 12 months old)
f) Nutritional (e.g., B12 deficiency)
g) Posttraumatic (brain injury)
h) Chorea gravidarum hyperthyroidism
i) External pallidal atrophy
j) Pick disease
k) Paraneoplastic syndromes
l) Acute disseminated encephalo myelopathy
m) Multiple system atrophy

Diagnostic Investigations

1. A confirmed family history of Huntington disease combined with clinical manifestations: sufficient for diagnosis (Harris et al. 2009)
2. Neuroimaging (MRI and CT)
   a. Severe atrophy of the caudate nucleus in moderately disabled patients
   b. May be relatively normal in patients in the early stages
3. Pet scan: Atrophy of the caudate nucleus can be detected in a presymptomatic state by the finding of head of caudate hypometabolism
4. Neuropathological features
   a. Neuronal loss and gliosis in the cortex and striatum, particularly the caudate nucleus: the most prominent neuropathologic features (Roth et al. 2005)
   b. Neuronal injury occurs initially in the caudate tail, in the medial paraventricular caudate, and in the dorsal part of the putamen.
   c. Further neuronal loss and an increase in astrocytes can be observed in widespread cortical and subcortical regions as the neurodegenerative process progresses.
   d. Pathologic observation of affected striatum shows loss of GABAergic spiny projection neurons with preservation of the aspiny interneurons and large aspiny acetylcholinesterase-positive neurons.
   e. A decrease of important neurotransmitters and neuropeptides, such as γ-aminobutyric acid (GABA), calbindin, enkephalin, and substance P, as a result of selective loss of the medium spiny neurons
5. Three main types of genetic testing of HD
   a. To confirm or rule out disease
   b. Presymptomatic testing to determine the carrier status of an individual at genetic risk for inheriting the disease
      i. To assist in making decisions about marriage, procreation, or career
      ii. The emotional impact of the result can be difficult to anticipate and can evoke substantial adverse emotional reactions (Taylor and Myers 1997; Almqvist et al. 1999).
      iii. Appropriate pretest counseling is important to assist the at-risk individual in considering the risks and benefits of genetic testing for diseases such as HD for which available treatment does not justify testing
   c. Prenatal testing to determine the carrier status of a fetus

Genetic Counseling

1. Recurrence risk (Warby et al. 2010)
   a. Patient's sib
      i. A 50% risk if a parent is affected or has a CAG size of 40 or greater.
      ii. An estimated risk as high as 5% (50% × 10%) of inheriting a mutant allele (≥36 CAG repeats) if the father has an intermediated allele (Chong et al. 1997)
      iii. A sib who inherits an *HD* allele with reduced penetrance may or may not develop symptoms of HD.
   b. Patient's offspring
      i. A 50% risk of inheriting the disease-causing mutation from a parent with heterozygosity for the *HD* allele
      ii. A 100% risk of inheriting the disease-causing allele from a parent with homozygosity for CAG repeat expansion in the *HD* gene
2. Prenatal diagnosis (Warby et al. 2010)
   a. Prenatal diagnosis is possible for pregnancies at 50% risk by analyzing DNA extracted from fetal cells obtained by amniocentesis or CVS, provided the disease-causing allele in the affected parent or in an affected relative has been confirmed.
   b. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified in an affected family member.
3. Management (Harris et al. 2009)
   a. No definitive cure
   b. Limited therapeutic options currently
   c. Multidisciplinary team approach
      i. Medical
      ii. Social work
      iii. Physical therapy
   d. Selective serotonin reuptake inhibitors: effective in treating depression symptoms:
      i. Depression
      ii. Mania

iii. Delusions
iv. Paranoia
v. Chorea
vi. Other symptoms related to depression
  a) Rumination
  b) Perseveration
  c) Obsessive-compulsive disorder
  d) Suicide
vii. Mood stabilizers (valproate, carbamazepine, lamotrigine, or lithium) for bipolar disorders

e. Neuroleptic for delusions and paranoia symptoms as well as chorea
f. Atypical antipsychotics (risperidone, clozapine, olanzapine, and quetiapine): provide sufficient control of psychotic symptoms with a lower risk for extrapyramidal adverse effects and tardive dyskinesia.
g. Nutritional management
h. Palliative care in managing the latter stage of the disease
  i. Bedridden
  ii. Mute
  iii. Rigid
  iv. Dysphagia
  v. Aspiration

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Fig. 1 The patient, a 42-year-old lady, was evaluated for increasing weakness of her legs over the past 1 year, dropping things out of her hands and increased balance difficulties. She was ambulatory but had difficulty going upstairs and on uneven surfaces. She later developed typical movement disorders, chorea, dystonia, cognitive decline, and behavioral changes. The family history was significant for affected family members (mother and two brothers). The diagnosis of Huntington disease was confirmed by the presence of over 40 CAG repeats

Hydrolethalus Syndrome

Hydrolethalus syndrome was coined by Salonen et al. in 1981 in patients with severe CNS malformations, hydrocephalus, micrognathia, cleft lip/palate, lung hypoplasia club foot, and polydactyly, distinguishable from the Meckel syndrome by the absence of polycystic kidneys (Salonen et al. 1981). The majority of cases were reported from Finland.

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Hydrolethalus syndrome locus: assigned to 11q23-q25 in Finnish families
3. *HYLS1* gene mutation
   a. Responsible for hydrolethalus syndrome in the Finnish population, HYLS1
   b. c.632A > G (D211G) mutation: the common mutation carried in the Finnish population

Clinical Features

1. A lethal condition: stillborn or died within a few hours of birth in majority of cases
2. Hydramnios
3. Severe midline CNS malformations
   a. A midline cerebral cleft: more common
   b. Absence of the corpus callosum
   c. Absence of septum pellucidum
   d. Hydrocephalus secondary to aqueductal stenosis
   e. Dorsal midline defect of the foramen magnum, forming a keyhole-shaped opening (occipitoschisis)
   f. Cerebellar heterotopias
   g. Brain stem malformations
   h. Cerebral gyral abnormalities
   i. Absent olfactory lobes
   j. Hypothalamic hamartomas
   k. Dandy-Walker malformation
4. Craniofacial features
   a. Microphthalmia
   b. Nasal anomalies
   c. Small mandible
   d. Cleft lip/palate
   e. Small tongue
   f. Low-set, malformed ears
5. Pulmonary anomalies
   a. Abnormal larynx, trachea, and bronchi
   b. Pulmonary hypoplasia/agenesis
   c. Defective lung lobulation
6. Congenital heart defects
   a. Ventricular septal defect
   b. Open foramen ovale
   c. Common atrioventricular canal
7. Renal anomalies
8. Duplex/bicornis uterus
9. A typical "keyhole" occipital bone defect
10. Polydactyly
    a. Hands: always postaxial
    b. Feet: almost always preaxial
11. Differential diagnosis
    a. Acrocallosal syndrome
       i. Macrocephaly
       ii. Craniofacial anomalies
       iii. Hallux duplication
       iv. Postaxial polydactyly
       v. Absence of corpus callosum
       vi. Mental retardation

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b. Smith-Lemli-Opitz syndrome (severe form)
   i. Hydrocephalus
   ii. Cerebellar hypoplasia
   iii. Cardiac anomalies
   iv. Genital anomalies
   v. Polydactyly
c. Orofacialdigital syndrome, type VI
   i. Cerebellar anomalies
   ii. Hypertelorism
   iii. Micrognathia
   iv. Midline cleft lip
   v. Cleft palate
   vi. A small tongue with lingual nodules and multiple frenula
   vii. Laryngeal anomalies
   viii. Cardiac anomalies
   ix. Preaxial polysyndactyly of hands and feet
   x. Postaxial polysyndactyly of the feet
d. Pallister-Hall syndrome
   i. Hypertelorism
   ii. Micrognathia
   iii. Midline cleft lip
   iv. Cleft palate
   v. A small tongue with lingual nodules and multiple frenula
   vi. Laryngeal anomalies
   vii. Lung segmental anomalies
   viii. Cardiac anomalies
   ix. Postaxial polysyndactyly of the feet
e. Walker-Warburg syndrome
   i. Overlapping features
      a) Encephalocele
      b) Agenesis of midline brain structures
      c) Hydrocephalus
   ii. Features usually not seen
      a) Eye abnormalities
      b) Polydactyly

Diagnostic Investigations

1. Radiologic studies
   a. Skull
      i. Microcephaly
      ii. Occipital bone defect continuous with foramen magnum
      iii. A keyhole shaped defect at the base of skull
   b. Digital anomalies
      i. Postaxial polydactyly of the hands
      ii. Preaxial polydactyly or hallux duplication of the feet
2. Ultrasound or MRI of the brain for delineation of brain anomalies
3. Echocardiogram for delineation of congenital heart defects
4. Molecular genetic study: target mutation analysis of *HYLS1* gene (c.632A > G)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Recurrence risk: 25%
      ii. Unaffected sibs of a proband: two thirds chance of being heterozygotes
   b. Patient's offspring: a lethal entity not surviving to reproduction
2. Prenatal diagnosis
   a. Possible by prenatal ultrasonography in at-risk families
   b. Possible for pregnancies at risk when the disease-causing mutation in the family is known
3. Management
   a. Supporting care
   b. No treatment available for the underlying lethal disorder

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Fig. 1 (**a**–**e**) A neonate with hydrolethalus syndrome showing malformed skull, microcephaly, ocular hypertelorism, anomalous nose, micrognathia, left cleft lip and palate, a small tongue, low-set and malformed ears, short neck, postaxial polydactyly of the hands, and preaxial polydactyly of the feet

Hydrops Fetalis

Hydrops fetalis is a condition in which fluid accumulates in the serous cavities and/or in the soft tissues of the fetus. It is classified as immune if there is an indication of a fetomaternal blood group incompatibility, otherwise classified as nonimmune. The incidence of nonimmune hydrops fetalis is estimated to be approximately 1 in 2,500 to 1 in 3,500 neonates.

Synonyms and Related Disorders

Hydrops fetalis syndrome; Immune hydrops; Nonimmune hydrops

Genetics/Basic Defects

1. Causes of immune hydrops (IH)
   a. Rh-D disease (approximately 90% of immune hydrops)
      i. Prior to 1960s, this is the most common cause (up to 80%) of all cases with hydrops fetalis. The incidence of rhesus isoimmunization has declined steadily because of the widespread use of anti-D gamma globulin. The majority of hydrops is now of the nonimmune type (Holzgreve et al. 1985).
      ii. Mother (Rh−), father (Rh+), and fetus (Rh+)
      iii. After sensitization, maternal Rh antibody (IgG anti-D) crosses the placenta and destroys the Rh-positive fetal red blood cells. It results in fetal anemia.
      iv. Previous pregnancy, including maternal-fetal blood mixing
      v. Previous abortion (spontaneous, missed, therapeutic)
      vi. First trimester bleeding
      vii. Trauma
      viii. Blood transfusion
   b. ABO incompatibility (rare, overall incidence about 1%)
      i. ABO incompatible pregnancies (about 20%) in which only 5% of these cases lead to hydrops
      ii. Mother (nearly always O+ with antibodies to A, B, or both)
      iii. Fetus (A, B, or AB)
   c. Other autoimmune causes (targeting other RBC antigens)
      i. Anti-Lewis antibodies: benign ("Lewis lives")
      ii. Anti-Kell antibodies (the second most common type accounting for about 10% of antibody mediated severe fetal anemia): mild to severe hydrops ("Kell kills")
      iii. Anti-Duffy antibodies: mild to severe hydrops ("Duffy dies")
2. Pathophysiology of immune hydrops
   a. Sensitization of the mother to an antigen (usually Rh-D)
      i. Presence of antigen on fetal RBC but not on mother's RBC
      ii. Primary response generally a maternal IgM anti-RBC response
   b. Production of IgG antibodies by the mother on the secondary exposure. The IgG antibodies can cross the placenta.

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c. Destruction of fetal RBC by maternal anti-fetal RBC antibodies
   i. A Coombs' positive process
   ii. Destruction most likely mediated by complement and macrophages
   iii. Jaundice frequently observed secondary to increased bilirubin production
d. Compensatory increase in fetal cardiac output due to decreased fetal hematocrit
e. Heart failure resulting from high cardiac output by the fetal heart
   i. Edema
   ii. Ascites
   iii. Circulatory failure with fetal death *in utero*

3. Conditions associated with nonimmune hydrops fetalis (NIHF). Nonimmune type now represents majority of hydrops fetalis after the practice of anti-D gammaglobulin prophylaxis since 1960s (Holzgreve et al. 1985).
   a. Cardiovascular disorders (5.3–26%, the most frequent underlying cause of NIHF) (Bukowski and Saade 2000)
      i. Tachyarrhythmia (supraventricular tachycardia, atrial flutter)
      ii. Bradyarrhythmias (complete heart block)
      iii. Congenital heart block
      iv. Hypoplastic left heart syndrome (31%)
      v. Endocardial cushion defects (13%)
      vi. Agenesis of the ductus venosus
      vii. Other anatomic defects of the heart
      viii. Premature closure of the ductus arteriosus
      ix. Generalized arterial calcification
      x. Cardiomyopathy
      xi. Myocarditis (Coxsackie virus or CMV)
      xii. Cardiac rhabdomyoma
      xiii. Intracardiac teratoma
   b. Chromosome abnormalities (7.5–77.8%, the second most frequent underlying causes of NIH)
      i. Trisomies
         a) Trisomy 21
         b) Trisomy 18
         c) Trisomy 13
      ii. Turner syndrome (most common chromosome anomaly)
      iii. Triploidies
      iv. Deletions
      v. Others
   c. Recognizable syndromes (2.2–27.6%)
      i. Skeletal dysplasias
         a) Thanatophoric dysplasia
         b) Arthrogryposis multiplex congenita
         c) Asphyxiating thoracic dystrophy
         d) Hypophosphatasia
         e) Osteogenesis imperfecta
         f) Achondrogenesis
         g) Saldino–Noonan syndrome
         h) McKusick–Kaufman syndrome
         i) Klippel–Trenaunay–Weber syndrome
         j) Conradi syndrome
         k) Other types of skeletal dysplasias
      ii. Metabolic diseases
         a) Mucopolysaccharidosis type IV Morquio disease (β-galactosidase deficiency)
         b) Mucopolysaccharidosis Type VII (β-glucuronidase deficiency)
         c) I-cell disease
         d) Niemann–Pick disease
         e) Gaucher disease
         f) Sialidosis
         g) Galactosialidosis
         h) Salla disease (Finnish type sialuria)
         i) Wolman disease
         j) Farber disease
         k) Carnitine deficiency
         l) Disorder of glycosylation (Léticée et al. 2010)
      iii. Other genetic syndromes
         a) Pena–Shokeir syndrome
         b) Neu–Laxova syndrome
         c) Recessive cystic hygroma
         d) Multiple pterygium syndrome
         e) Meckel syndrome
         f) Caudal regression syndrome
         g) Noonan syndrome
         h) Tuberous sclerosis
         i) Myotonic dystrophy
         j) X-linked dominant disorders with male lethality (e.g., hypomelanosis of Ito)
         k) Other single gene disorders
   d. Twin pregnancy (twin-twin transfusion syndrome) (3–8%)
   e. Hematologic disorders (10–27%)
      i. Intrinsic hemolysis
         a) α-thalassemia syndromes (Homozygous α-thalassemia-1 is the most common

cause of hydrops fetalis in Southeast Asia) (Lam et al. 1999)
b) G6PD deficiency
c) Pyruvate kinase deficiency
d) Glucosephosphate isomerase deficiency
e) Spectin abnormalities
ii. Extrinsic hemolysis (Kasabach–Merritt syndrome)
iii. Hemorrhage
a) Fetomaternal hemorrhage
b) Twin-twin transfusion syndrome
c) Fetal hemorrhage
iv. Fetal liver and bone marrow replacement syndromes
a) Transient myeloproliferative disorder
b) Congenital leukemia
v. Red cell aplasia and dyserythropoiesis
a) Parvovirus B19 infection
b) Blackfan–Diamond syndrome
c) Congenital dyserythropoiesis

f. Thoracic abnormalities (2.5–13%)
i. Diaphragmatic hernia
ii. Congenital cystic adenomatous malformation of the lung
iii. Extralobar pulmonary sequestration
iv. Congenital hydrothorax or chylothorax
v. Mediastinal teratoma
vi. Laryngeal atresia
vii. Pulmonary hypoplasia

g. Genitourinary malformations (2.5–3.5%)
i. Urethral obstruction
ii. Posterior urethral valves
iii. Neurogenic bladder with reflux
iv. Ureterocele
v. Prune-belly syndrome
vi. Upper urinary tract obstruction
vii. Renal dysplasia
viii. Cloacal malformations

h. Gastrointestinal anomalies
i. Jejunal atresia
ii. Midgut volvulus
iii. Malrotation of the intestine
iv. Duplication of the intestinal tract
v. Meconium peritonitis
vi. Gastroschisis
vii. Tracheoesophageal fistula

i. Hepatic diseases
i. Polycystic disease of the liver
ii. Hepatic fibrosis
iii. Cholestasis
iv. Biliary atresia
v. Hepatic vascular malformations
vi. Familial cirrhosis

j. Neurological abnormalities
i. Encephalocele
ii. Intracranial hemorrhage
iii. Cerebral aneurysm
iv. Intracranial arteriovenous malformation

k. Maternal diseases/complications
i. Medications (indomethacin taken to stop premature labor causing fetal ductus closure and secondary nonimmune hydrops fetalis)
ii. Mirror syndrome
a) Maternal edema
b) Preeclampsia
iii. Systemic diseases
a) Severe diabetes mellitus
b) Severe anemia
c) Hypoproteinemia
iv. Antepartum/postpartum hemorrhage
v. Theca lutein cysts development

l. Placenta-umbilical cord abnormalities
i. Chorioangioma
ii. Chorionic vein thrombosis
iii. Fetomaternal transfusion
iv. Placental and umbilical vein thrombosis
v. Umbilical cord torsion
vi. True cord knots
vii. Angiomyxoma of the umbilical cord
viii. Aneurysm of umbilical artery

m. Intrauterine infections (2–17.5%)
i. Viruses
a) Parvovirus B19
b) CMV
c) Rubella
d) Adenovirus
e) Enteroviruses
f) Coxsackie virus
g) Polio
h) Influenza B
i) Respiratory syncytial virus
j) Congenital hepatitis
k) Herpes simplex, type I
ii. Bacteria/spirochetes
a) *Treponema pallidum*
b) *Listeria monocytogenes*
c) *Leptospira interogans*

iii. Parasites
a) *Toxoplasma gondii*
b) *Trypanosoma cruzii*
iv. Other
a) Chlamydia
b) *Ureaplasma urealyticum*
n. Miscellaneous conditions
i. Congenital lymphedema
ii. Congenital hydrothorax or chylothorax
iii. Polysplenia syndrome
iv. Amniotic band syndrome
v. Congenital neuroblastoma
vi. Tuberous sclerosis
vii. Ovarian cyst torsion
viii. Fetal trauma
ix. Large fetal angioma
x. Sacrococcygeal teratoma
xi. Cloacal malformation
o. Idiopathic (without an identifiable cause)

4. Pathophysiology of nonimmune fetal hydrops
a. Cardiac failure directly involving the heart
i. Arrhythmias
ii. Malformations
iii. Myocarditis
iv. Infarction
v. Cardiomyopathy
b. Abnormal vascularization causing high output cardiac failure
i. Twin-twin transfusion syndrome
ii. Acardiac twinning
iii. Tumors
iv. AV fistulas
v. Placental vascular anomalies
c. Profound anemia
i. Hemolytic anemias
ii. Parvovirus B19 (fifth disease)
iii. Fetal-maternal hemorrhage
iv. Alpha-thalassemia, hemoglobin Bart's
v. G6PD deficiency
vi. Glucose-6-phosphate isomerase deficiency
vii. Pyruvate kinase deficiency
viii. Defects of red cell membrane
d. Decreased plasma oncotic pressure
i. Congenital nephrosis
ii. Hepatic necrosis
e. Fetal infections
i. Increased capillary permeability (anoxia due to congenital infection)
ii. Infection of erythroid progenitor cells (e.g., parvovirus B19)
iii. Myocarditis (e.g., adenovirus, Coxsackie virus)
iv. Hepatic destruction (e.g., syphilis)
f. Obstruction of venous return
i. Congenital cystic adenomatoid malformation
ii. Fetal closure or restriction in the size of the ductus arteriosus, foramen ovale or ductus venosus
iii. Diaphragmatic hernia
iv. Pulmonary sequestration
v. Tumors of the heart, lungs, abdomen or pelvis
vi. Umbilical cord lesions
g. Obstruction of lymphatic flow (e.g., Turner syndrome)

Clinical Features

1. Maternal history associated with hydropic infants
a. Previous history of hydrops
b. Severe maternal anemia
c. Associated polyhydramnios in at least 50% of hydropic fetuses
d. Size-date discrepancy
e. Twin gestation
f. Maternal diabetes mellitus
g. Maternal pregnancy induced hypertension/preeclampsia
h. Fetal arrhythmia
i. Placentomegaly
j. Positive antibody screen
k. Syphilis or other TORCH infections
2. Edema due to right-sided heart failure
a. Circulatory failure
b. Ascites
i. First sign of fetal hydrops caused by anemia
ii. Hypertension
iii. Hypoalbuminemia
iv. Prune belly secondary to marked fetal ascites
c. Pleural effusions
d. Pericardial effusions
e. Jaundice (hyperbilirubinemia)
3. Hemolysis with extramedullary hematopoiesis

4. Hepatosplenomegaly
   a. A hallmark for immune hydrops
   b. Absent in nonimmune hydrops fetalis
5. Fetal prognosis: presence of fetal hydrops often indicating fetal compromise with a significant risk of mobility and death
   a. Cardiovascular disorders
      i. Best prognosis among abnormalities underlying nonimmune hydrops
      ii. Cumulative survival rate: 29%
      iii. Treatment of tachycardia improves prognosis.
   b. Chromosome abnormalities: 2% survival rate
   c. Syndromes: 5% survival rate
   d. Fetal infections: 19% cumulative survival rate
   e. Thoracic lesions: one of the best cumulative prognosis, 26%
   f. Fetofetal transfusion syndrome: 20% survival rate
   g. Extremely poor prognosis
      i. Anemia secondary to parvovirus infection
      ii. Anemia resulting from fetomaternal hemorrhage
      iii. α-thalassemia: All fetuses with the Hb Bart's hydrops fetalis syndrome succumb to severe fetal hypoxia in utero during the third trimester of gestation or within hours after birth (Chui and Waye 1998).
   h. Good prognosis for psychomotor development in survivors with nonimmune hydrops fetalis (Haverkamp et al. 2000)
6. Morbidity (Bukowski and Saade 2000)
   a. Morbidity depending on the underlying disorder
   b. Short-term morbidity high (neonate requires difficult resuscitation, long and intensive hospitalization, and multiple invasive procedures)
   c. Relatively low long-term morbidity in NIHF in children diagnosed prenatally
7. Mortality
   a. Mortality rate: 50–98%
   b. Contribute to 3% of perinatal mortality
   c. Mortality depending on the underlying disorder

Diagnostic Investigations

1. Diagnostic evaluation of immune hydrops
   a. ABO and Rh typing and a serum antibody screen (positive indirect Coombs' test) for every pregnant woman as early as possible during each pregnancy
   b. Spectrophotometric estimation of bilirubin pigments in the amniotic fluid, obtained by amniocentesis in selected patients, to estimate the risk of severe hemolytic disease while the fetus is still in utero
   c. Direct Coombs' test on cord blood
      i. Nearly always positive in Rh-induced hemolytic disease of newborns (HDN)
      ii. Frequently but not always positive in ABO-induced HDN
   d. Usually increased cord blood bilirubin and decreased cord blood hemoglobin in severe HDN
2. Diagnostic evaluation of newborn babies with nonimmune hydrops (Carlton et al. 1989)
   a. Cardiovascular disorders
      i. Echocardiogram
      ii. Electrocardiogram
   b. Thoracic abnormalities
      i. Chest radiographs
      ii. Pleural fluid examination
   c. Hematologic disorders
      i. Complete blood cell count
      ii. Differential
      iii. Platelet count
      iv. Blood type
      v. Coombs' test
      vi. Blood smear for morphology
      vii. Hemoglobin electrophoresis
   d. Gastrointestinal abnormalities
      i. Abdominal radiographs
      ii. Abdominal ultrasound
      iii. Liver function tests
      iv. Peritoneal fluid examination
      v. Total protein
      vi. Albumin
   e. Renal malformations
      i. Urinalysis
      ii. BUN
      iii. Creatinine
   f. Genetics
      i. Chromosome analysis
      ii. Skeletal radiographs
   g. Congenital infections viral cultures or serology (Barron and Pass 1995)
      i. Parvovirus B19
         a) Maternal infection: specific IgM and IgG
         b) Fetal/neonatal infection: specific IgM, virus detection by PCR

ii. Syphilis
  a) Maternal infection: RPR or VDRL
  b) Fetal/neonatal infection: RPR or VDRL, dark-field examination of material from lesions
iii. CMV
  a) Maternal infection: CMV-IgM or IgG seroconversion
  b) Fetal/neonatal infection: isolation of virus from amniotic fluid, fetal, or neonatal body fluid
iv. HSV
  a) Maternal infection: HSV culture of lesion
  b) Fetal/neonatal infection: HSV culture of amniotic fluid, fetal tissue, or neonate
v. Toxoplasmosis
  a) Maternal infection: capture IgM, specific IgG
  b) Fetal/neonatal infection: capture IgM ELISA
vi. Rubella
  a) Maternal infection: specific IgM and IgG or proven exposure plus compatible illness
  b) Fetal/neonatal infection: isolation of virus from fetal or neonatal body fluid, rubella IgM

h. Autopsy indicated for stillbirth or perinatal death including examination of the placenta and babygram

Genetic Counseling

1. Recurrence risk
  a. Patient's sib
    i. Immune hydrops fetalis: will be affected unless sensitization is prevented
    ii. Nonimmune hydrops fetalis
      a) Sporadic: no increased risk
      b) Autosomal recessive disorder: 25%
      c) Autosomal dominant disorder: not increased unless a parent is affected
      d) Chromosome disorder: increased especially when a parent is a translocation carrier
  b. Patient's offspring
    i. Immune hydrops fetalis: recurrence risk not increased
    ii. Nonimmune hydrops fetalis
      a) Sporadic: no increased risk
      b) Autosomal recessive disorder: not increased unless the spouse is a carrier
      c) Autosomal dominant disorder: 50%
      d) Chromosome disorder: increased if the patient survives to reproductive age
2. Prenatal evaluation of immune hydrops fetalis
  a. Rh testing and ABO typing indicated for all pregnancies
  b. Positive maternal antibody screen (indirect Coombs test)
  c. Suspicious for immune hydrops
    i. Cord blood for testing of hemolysis and hematocrit
    ii. Amniocentesis for bilirubin
  d. Specific testing for antibodies in women with previous pregnancy losses
  e. Doppler ultrasonography
    i. Used to measure peak velocity of systolic blood flow in fetus
    ii. Increased peak systolic blood flow velocity in fetuses with anemia
    iii. Increased systolic velocity: 100% sensitive to fetal anemia
  f. Prenatal diagnosis of fetal Rh-D status by molecular analysis
3. Maternal evaluation of nonimmune hydrops fetalis (Holzgreve et al. 1985)
  a. Complete blood count and indices for hematological disorders
  b. Hemoglobin electrophoresis (α-thalassemia)
  c. Kleihauer–Betke stain for evidence of fetomaternal hemorrhage
  d. Maternal blood chemistry for fetal red cell enzyme deficiency
    i. Glucose-6-phosphate deficiency screen
    ii. Pyruvate kinase carrier status
  e. Infection screening
    i. Syphilis by VDRL
    ii. TORCH titers
    iii. Parvovirus titers
    iv. Group B streptococcus
    v. Listeria monocytogenes
  f. Autoantibody screen
    i. Systemic lupus erythematosus
    ii. Anti-Ro (anti-SS-A) and Anti-La (anti-SS-B) antibody titers for Sjogren syndrome
  g. Fetal echocardiography for presence of congenital heart defects

4. Prenatal ultrasonography
   a. Immune hydrops secondary to α-thalassemia (Tongsong et al. 1996)
      i. Hepatosplenomegaly (>95%)
      ii. Cardiomegaly (>95%)
      iii. Edematous placenta (>95%)
      iv. Ascites (>95%)
      v. Oligohydramnios (82%)
      vi. Subcutaneous edema (75%)
      vii. Decreased fetal movement (74%)
      viii. Cord edema (63%)
      ix. Enlarged umbilical vessel (62%)
      x. Pericardial/pleural effusion (15%)
   b. Nonimmune hydrops
      i. Fetal ascites
      ii. Fetal pleural effusion
      iii. Fetal pericardial effusion (the earliest finding)
      iv. Fetal skin thickening
      v. Maternal polyhydramnios
      vi. Placentomegaly, especially Rh disease or chorioangioma
      vii. Cystic hygroma as early as 13 weeks of gestation
5. Fetal evaluation of nonimmune hydrops fetalis
   a. Fetal echocardiography, M-mode, pulsed, and color flow Doppler
      i. Congenital heart defects
      ii. Fetal rhythmic abnormalities
      iii. Cardiac biometry
   b. Doppler flow velocity studies
      i. Umbilical artery
      ii. Middle cerebral artery
      iii. Tricuspid ejection velocity
   c. Amniocentesis
      i. Amniotic fluid index
      ii. Fetal karyotype (chromosome abnormality)
      iii. Amniotic fluid viral cultures
      iv. Alpha-fetoprotein (congenital nephrosis, sacrococcygeal teratomas)
      v. Isolation of CMV virus for identification of CMV DNA by PCR
      vi. Specific metabolic tests
         a) Tay–Sachs disease
         b) Gaucher disease
         c) GM_1 gangliosidosis
      vii. Metabolic disease screening panel
         a) Acid sphingomyelinase deficiency
         b) Deficient cholesterol esterification
         c) Acid β-glucosidase deficiency
         d) Acid β-galactosidase deficiency
         e) Acid sialidase deficiency
         f) Sialidase deficiency
         g) β-galactosidase deficiency
         h) Ceramidase deficiency
         i) Glucose phosphate isomerase deficiency
         j) N-acetylglucosamine phosphotransferase deficiency
      viii. Restriction endonucleases tests (e.g., thalassemias)
   d. Fetal blood sampling
      i. Rapid karyotype (chromosome abnormality)
      ii. Fetal complete blood count (fetal anemia)
      iii. Blood group and Coombs' test
      iv. Hemoglobin electrophoresis (α-thalassemia)
      v. Fetal plasma analysis for specific IgM (e.g., CMV-specific IgM antibody, PCR)
      vi. G6PD in male fetuses
      vii. Fetal plasma albumin (fetal hypoalbuminemia)
      viii. Metabolic testing
         a) Tay–Sachs disease
         b) Gaucher disease
         c) GM_1 gangliosidosis
   e. Fluid aspirated for biochemistry and viral screen
      i. Pleural effusion
      ii. Ascites
      iii. Amniotic fluid
   f. Placenta
      i. Morphology
      ii. Thickness
6. Management
   a. Immune hydrops fetalis
      i. Prevent sensitization by Rhogam or Rh immune globulin
      ii. Prevent fetal heart failure when mother has sensitization reaction
      iii. Fetal transfusion for fetal anemia via cordocentesis
      iv. Induction of labor
      v. Postpartum exchange blood transfusion to prevent kernicterus, the most feared complication of Rh-induced HDN
   b. Nonimmune hydrops fetalis
      i. Screen tests to detect couples at risk for having a fetus with the Hb Bart's hydrops fetalis by simple blood counts and hemoglobin electrophoresis

ii. Neonatal resuscitation
iii. Intrauterine or immediate post-delivery transfusions to babies (e.g., homozygous α-thalassemia, Parvovirus B19 infection)
iv. Fetal cardiac arrhythmias treated by transplacental antiarrhythmic therapy
v. Flecainide acetate for fetal supraventricular tachycardia with hydrops fetalis
vi. Continuous arteriovenous hemodilution for fluid overload in newborns with hydrops fetalis
vii. Pleurocentesis in utero to drain pleural effusion to minimize pulmonary hypoplasia
viii. Treatment of maternal infection (Barron and Pass 1995)
   a) Parvovirus B19: intrauterine transfusion
   b) Syphilis: IV penicillin
   c) CMV: No pharmaceutic regimens available for treatment of maternal and fetal CMV infections. Treatment with antiviral agents (ganciclovir, foscarnet) is limited to severe infections (CMV retinitis) in immunocompromised patients and not currently used in pregnancy.
   d) HSV: acyclovir warranted in disseminated disease; fetal effect unknown
   e) Toxoplasmosis: spiramycin and/or pyrimethamine, sulfadiazine, and folinic acid
ix. Fetal surgery attempted for congenital cystic adenomatoid malformation, pulmonary sequestration, fetal pleural effusions, and sacrococcygeal teratoma

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Fig. 1 An 18-week gestation fetus with hydropic change of the scalp and chest

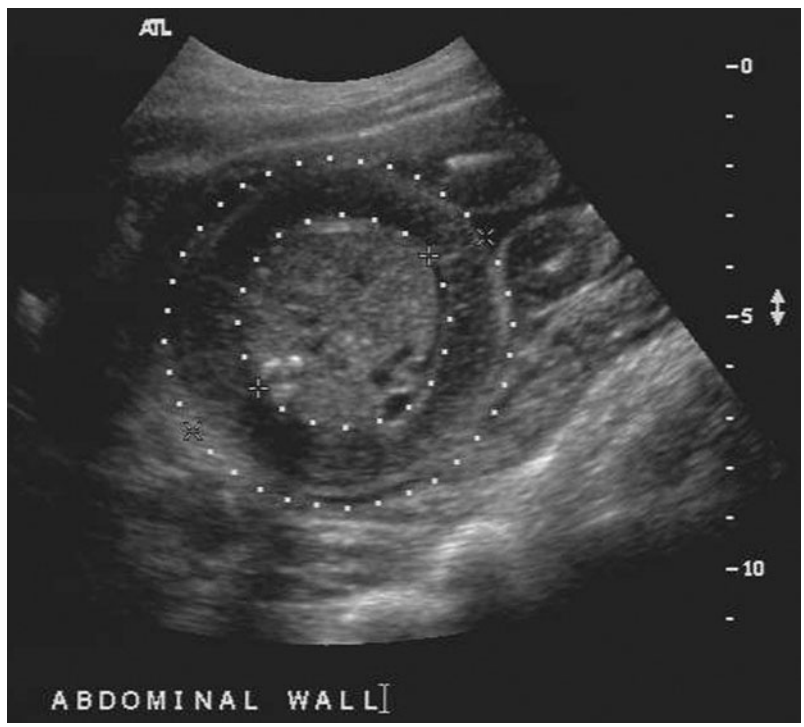

Fig. 2 A fetus showing hydropic change of the abdominal wall

Fig. 3 (**a**–**c**) A macerated fetus, a newborn, and an infant with nonimmune hydrops fetalis

Hyper-IgE Syndrome

Hyper-IgE syndrome (HIES) is a rare, hereditary multisystem disorder characterized clinically by hyperimmunoglobulinemia E, recurrent infections, and eczematoid dermatitis. In 1966, Job reported two patients with eczematous dermatitis, recurrent staphylococcal boils, hyperextensible joints, and distinctive coarse facies. In 1972, Buckley et al. expanded the clinical picture by adding elevated immunoglobulin E (IgE).

Synonyms and Related Disorders

Job syndrome

Genetics/Basic Defects

1. Inheritance (Erlewyn-Lajeunnesse 2000)
   a. Autosomal dominant with variable penetrance and expressivity
   b. Linkage to a region on chromosome 4q21demonstrated in several affected families
   c. An upregulating mutation in the interleukin-4 receptor gene on chromosome 16, demonstrated in some patients with hyper-IgE syndrome
   d. Autosomal recessive hyper-IgE syndrome: a similar but distinct syndrome reported by Renner et al. (2004)
2. Autosomal dominant hyper-IgE syndrome (AD-HIES): caused by dominant-negative mutations in signal transducer and activator of transcription 3 (*STAT3*) in most cases of autosomal dominant HIES (Holland et al. 2007; Minegishi et al. 2007; Jiao et al. 2008; Renner et al. 2008)
   a. Most cases are sporadic.
   b. When familial, all individuals carrying the mutation have the HIES phenotype.
3. Autosomal recessive hyper-IgE syndrome (AR-HIES) (Freeman and Holland 2009; Engelhardt et al. 2009)
   a. Homozygous mutation of *Tyk2* with a four nucleotide deletion resulting in a premature stop codon reported in one patient (Minegishi et al. 2006). This patient had the following common features of AR-HIES:
      i. Eczema
      ii. Viral infections
      iii. Recurrent sinopulmonary infections
      iv. Bacille Calmette–Guerin and *Salmonella* infections, classic for IL-12/IFN-gamma defects
   b. Mutations of Tyk2 have been absent in the other reported cases of AR-HIES (Woellner et al. 2007).
   c. Homozygous mutations (large deletions and point mutations) in the dedicator of cytokinesis 8 (*DOCK8*) identified recently in most patients with AR-HIES (Engelhardt et al. 2009)

Clinical Features

1. Classic triad (77%) (Grimbacher et al. 1999a; Erlewyn-Lajeunnesse 2000)
   a. Abscesses
   b. Pneumonia
   c. An elevated IgE

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2. Skin manifestations
   a. Onset with distinctive neonatal rash
      i. Typically pruritic, secondary to intradermal mast cell histamine release triggered by the elevation of available IgE
      ii. Often lichenified
      iii. A distribution atypical for true atopic dermatitis
   b. Chronic eczema and dermatitis
   c. Skin infections
      i. Frequent presentation in infancy
         a) Furuncles
         b) Occasional "cold" abscesses
         c) Cellulitis
      ii. Multiple staphylococcal abscesses on the skin (furunculosis)
         a) Most common around the face
         b) Tender and warm to touch
      iii. Cold abscesses
         a) A large fluctuant mass that feels like a tumor or cyst
         b) Neither hot or tender
         c) Not associated with systemic symptoms, fever, or other signs of local or generalized inflammation
         d) Filled with pus that always grows *Staphylococcus aureus*
         e) Pathognomic to hyper-IgE syndrome
         f) Not essential to the diagnosis
   d. Skin abscesses
   e. Candidiasis
3. Infections
   a. Pulmonary infections
      i. Recurrent and severe
      ii. Most common infecting organism: *Staphylococcus aureus*
      iii. Chronic infections
         a) Sinusitis
         b) Discharging otitis media
         c) Otitis externa
         d) Mastoiditis
      iv. Long-term complications
         a) Bronchiectasis
         b) Bronchopleural fistulae
         c) Pneumatocele secondary to staphylococcal pneumonia
   b. Mucocutaneous candidiasis and fungal infection
      i. Chronic candidiasis (83%)
         a) Mucosa sites (oral moniliasis)
         b) Nail fungal infection and dystrophy secondary to *Candida albicans*
      ii. *Aspergillus* infection
      iii. Cryptococcal infection
   c. Other serious infections
      i. Skin, sinopulmonary, and bone infections: most common
      ii. Staphylococcus: the most frequently infecting organisms
      iii. Encapsulated organisms
         a) Haemophilus
         b) *Streptococcus pneumoniae*
      iv. Opportunistic infections: *Pneumocystis carinii*
4. Facial and dental abnormalities
   a. Characteristic coarse facies
      i. Frontal bossing
      ii. Wide alar base of the nose
      iii. Wide outer canthal distance
      iv. Rare craniosynostosis
      v. Midline facial defects
      vi. High-arched palate
   b. Red hair: uncommon finding
   c. Retained primary teeth (72%): failure or delay of shedding of the primary teeth secondary to lack of root resorption
5. Skeletal abnormalities
   a. Scoliosis (76%)
   b. Pathological fractures
      i. Secondary to minor trauma
      ii. Associated with osteopenia
      iii. Frequent recurrent fractures (57%)
      iv. Systemic infections at fracture sites
         a) Recurrent bacterial arthritis
         b) Staphylococcal osteomyelitis
   c. Generalized joint hyperextensibility (68%)
      i. Fingers
      ii. Wrists
      iii. Shoulders
      iv. Hips
      v. Knees
      vi. Genu valgum
6. Vascular features (Yavuz and Chee 2009): constitute one of the major clinical characteristics in HIES
   a. Types of vascular abnormalities
      i. Aneurysms (coronary, aortic, carotid, and cerebral)
      ii. Pseudoaneurysms
      iii. Congenital patent ductus venosus

iv. Superior vena cava syndrome
v. Vasculitides
vi. Vascular ectasia
vii. Thrombosis
viii. Others

b. May be congenital or acquired, in the veins and arteries, affecting both sexes
c. Can be seen in all subtypes of HIES
d. Can be fatal in children and adults
e. Limited pathological investigations revealed the presence of vasculitis.
f. Presence of hypereosinophilia, vasculitis, and defective angiogenesis in HIES may contribute to the formation of vascular abnormalities in HIES.

7. Association with isolated reports of autoimmune disease
   a. Systemic lupus erythematosus
   b. Dermatomyositis
   c. Membranoproliferative glomerulonephritis
8. Malignant changes
   a. Hodgkin disease
   b. Lymphoma
   c. Leukemias
   d. Cancers of the vulva, liver, and lung
9. Autosomal recessive hyper-IgE syndrome (AR-HIES) (Renner et al. 2004)
   a. Similar features
      i. Extremely elevated serum IgE
      ii. Severe eczema
      iii. Recurrent skin bacterial and viral infections as well as sinopulmonary infection
   b. Distinctive features
      i. Lack the somatic features, such as the characteristic facies, scoliosis, and the failure of baby teeth to exfoliate
      ii. Although pneumonias occur in AR-HIES, pneumatoceles do not form.
      iii. Has a much higher rate of cutaneous viral infections such as *Molluscum contagiosum*, Herpes simplex, and varicella infections
      iv. Has frequent neurologic disease, ranging from facial paralysis to hemiplegia, in some cases due to CNS vasculitis
      v. Mortality: high at a young age in AR-HIES with sepsis more frequent than in AD-HIES
      vi. Eosinophilia and elevated serum IgE: the most consistent laboratory findings and may be more dramatic than in AD-HIES
      vii. Autoimmune cytopenias may occur.

Diagnostic Investigations

1. Routine laboratory workup
   a. Grossly elevated serum polyclonal IgE: at least ten times normal (peak serum IgE >2,000 IU/mL)
   b. Accompanying eosinophilia
2. Radiographs, CT scan, and MRI imaging
   a. Pulmonary abnormalities
      i. Recurrent alveolar lung infections
      ii. Pneumatoceles
      iii. Occasional pneumothorax
   b. Skeletal abnormalities
      i. Full evaluations and monitor vigilantly for fractures after even minor trauma
      ii. Scoliosis
   c. CNS abnormalities on brain MRI (Freeman et al. 2007)
      i. Remarkably common and previously unrecognized aspect of HIES
      ii. Several patients with lacunar infarcts in addition to focal hyperintensities suggest possible small vessel disease.
3. Skin biopsy (Chamlin et al. 2002)
   a. An eosinophilic infiltrate similar to that seen in eosinophilic pustular folliculitis
   b. Spongiosis
   c. Perivascular dermatitis
4. Molecular genetic diagnosis
   a. AD-HIES: investigate *STAT3* mutations
   b. AR-HIES: investigate *DOCK8* mutations in patients with a phenotype of elevated IgE, eosinophilia, and recurrent skin boils, pneumonia, and viral infections (especially molluscum contagiosum and herpes) (Engelhardt et al. 2009)

Genetic Counseling

1. Recurrence risk
   a. Autosomal recessive inheritance
      i. Patient's sib: 25%
      ii. Patient's offspring: not increased unless the spouse is a carrier
   b. Autosomal dominant inheritance
      i. Patient's sib: not increased unless one of the parents is affected, in which case, there will be 50% risk of sibling affected
      ii. Patient's offspring: 50%

2. Prenatal diagnosis for AD-HIES (Freeman et al. 2010)
   a. Possible for pregnancies at increased risk by analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling (CVS):The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.
   b. Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified previously.
3. Management (Erlewyn-Lajeunnesse 2000; Freeman and Holland 2009)
   a. Largely supportive
   b. Prompt treatment of infection with prolonged intravenous antibiotics
   c. Treatment of eczema and prevention of *S. aureus* abscesses are most successfully accomplished with antiseptics such as bathing in bleach (120 mL of bleach in tub of water for 15 min three times weekly) or swimming in chlorinated pools.
   d. Active suspicion of pneumonia is necessary because systemic symptoms of illness are often lacking.
   e. Antimicrobial prophylaxis
      i. Prevents recurrent sinopulmonary infections with trimethoprim–sulfamethoxazole, a frequent choice
      ii. Pneumonias should be treated aggressively to try to prevent parenchymal damage.
      iii. If pneumatocoeles and bronchiectasis are present, antimicrobial prophylaxis often needs to be broadened to cover Gram-negative bacteria and fungi.
      iv. Management of pneumatocoeles is complex, as these cysts when secondarily infected carry significant risk for morbidity and mortality; however, surgery is not without risk, as HIES patients may have trouble re-expanding their lungs and soilage of the pleural space can occur.
   f. Cimetidine, the histamine receptor-2 (H2) antagonist
      i. Shown to reverse the hyper-IgE syndrome neutrophil chemotactic defect in vitro
      ii. A single patient showed a clinical improvement on treatment with improved neutrophil chemotaxis in spite of a clinical relapse.
      iii. Another seven patients treated with H2 antagonist with benefit.
   g. Cyclosporine may be helpful.
   h. Bronchoscopy may help isolate causative pathogens and clear pus.
   i. Dental extraction of primary teeth
   j. Surgical intervention by incision and drainage of abscesses
   k. Chest tube drainage and lobectomy for complications of pneumonias
   l. Orthopedic cares for fractures and scoliosis
   m. Dermatitis
      i. Topical steroid
      ii. Topical antifungals
      iii. Emollient creams
   n. Isotretinoin used to improve dermatitis
   o. High-dose intravenous γ-globulin for patients with aberrant humoral immunity: Intravenous immunoglobulin (IVIG) may decrease the number of infections for some individuals and is the most frequent immunomodulator used.
   p. Invasive approach with plasmapheresis with temporary improvement of skin condition and free of infections
   q. Bone marrow transplantation: only hope of cure at present, likely not fully corrective
   r. A single report of a peripheral stem cell transplantation
      i. Serum IgE returned to normal
      ii. Disappearance of symptoms
      iii. Unfortunately, patient died of interstitial pneumonia
   s. Hematopoietic cell transplantation (Gatz et al. 2010)
      i. Curative in patients with AR-HIES
      ii. Should be considered early before life-threatening complications develop, which include malignancies

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Fig. 1 (**a**–**d**) A 3-year-9-month-old patient with hyperimmunoglobulin E syndrome showing skin scars on his arm and bowing of the legs. Facial features included frontal bossing, wide alar basis of the nose, and wide outer canthal distance. He had history of recurrent pneumonias, otitis media, asthma, and fractures of the leg bones. At 2 years and 10 months of age, IgE was 15,610 ($\leq$93 KU/L). He is currently on intravenous immunoglobulin therapy with antibiotic prophylaxis

Fig. 2 A 13-year-old boy had a history of recurrent pneumonias, a right hip infection, and significant atopic dermatitis. Facial features included frontal bossing, wide alar basis of the nose, and wide outer canthal distance. Laboratory tests showed hyperimmunoglobulin E

Hypochondroplasia

Hypochondroplasia is a disproportionate short stature disorder resembling achondroplasia but with less severe phenotype.

Genetics/Basic Defects

1. Inheritance (Le Merrer et al. 1994).
   a. Autosomal dominant with full penetrance
   b. Sporadic in 90% of cases
   c. Observation of an increased paternal age effect at the time of conception, suggesting involvement of de novo mutations of paternal origin
   d. Presence of locus heterogeneity
2. Evidence supporting the view that hypochondroplasia and achondroplasia are allelic disorders (McKusick et al. 1973; Le Merrer et al. 1994)
   a. A remarkable inter- and intrafamilial variation in expression of hypochondroplasia with some cases resembling minor forms of achondroplasia
   b. Offspring of an achondroplastic parent and hypochondroplastic parent with severe neonatal achondroplasia resembling homozygous achondroplasia
   c. Similar histopathological aspects of the growth cartilage for the two disorders
3. Molecular defect.
   a. About 70% of affected individuals who are heterozygous for a mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene, which is mapped on chromosome 4p16.3 (Francomano 2005)
   b. *FGFR3* mutations reported in hypochondroplasia
      i. 1620C-A (Asn540Lys): two thirds of cases
      ii. 1620C-G (Asn540Lys): one third of cases
      iii. 1658A-C (Asn540Thr) and other *FGFR3* mutations: rare
   c. FGFR3 mutation reported in hypochondroplasia association with acanthosis nigricans (Castro-Feijóo et al. 2008) and acanthosis nigricans and hyperinsulinemia (Blomberg et al. 2010): p.Lys650Thr mutation
4. Hypochondroplasia-achondroplasia compound heterozygote
   a. Born to a hypochondroplastic parent and an achondroplastic parent
   b. The severity of the child: clinical and radiographic findings more severe than achondroplasia or hypochondroplasia alone but less severe than homozygous achondroplasia (Huggins et al. 1999)
   c. Demonstration of both the hypochondroplasia (Asn540Lys) and achondroplasia (Gly380Arg) mutations at the FGFR3 locus in a patient with the genetic compound

Clinical Features

1. Short stature (Francomano 2005)
   a. Evident by school age
   b. Adult height: 128–165 cm
2. Stocky build
3. Facial appearance
   a. Usually normal
   b. Mild macrocephaly may be present.

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4. Skeletal features
   a. General features: usually similar but milder to achondroplasia
   b. Limbs
      i. Disproportionately short compared with the length of the trunk
      ii. Shortening of the proximal (rhizomelia) or middle (mesomelia) segments of the extremities
      iii. Mild limitation of elbow extension
      iv. Broad and short hands and feet (brachydactyly)
      v. Absence of trident hand deformity
      vi. Bow legs (genu varum): usually mild
      vii. Adult onset osteoarthritis: less common
   c. Spine
      i. Scoliosis
      ii. Slight lumbar lordosis with a sacral tilt
5. Rare association with acanthosis nigricans
6. Medical complication
   a. Following complications: less frequent compared to achondroplasia
      i. Spinal stenosis with neurologic complications
      ii. Tibial bowing
      iii. Obstructive apnea
   b. Deficits in mental capacity and/or function: may be more prevalent than achondroplasia

Diagnostic Investigations

1. Radiography (Francomano 2005)
   a. The most common features
      i. Short proximal (rhizomelic) and/or middle (mesomelic) segments of the long bones with mild metaphyseal flare, especially femora and tibiae
      ii. Caudal narrowing or unchanged lumbar interpedicular distance
      iii. Mild to moderate brachydactyly
      iv. Short and broad femoral neck
      v. Squared and shortened ilia
   b. The less common but significant features
      i. Elongation of the distal fibula
      ii. Anterior-posterior shortening of the lumbar vertebrae
      iii. Dorsal concavity of the lumbar vertebral bodies
      iv. Shortening of the distal ulna
      v. Long ulnar styloid in adults
      vi. Prominence of muscle insertions on the long bones
      vii. Shallow "chevron" deformity of distal femur metaphysis
      viii. Low articulation of sacrum on pelvis with a horizontal orientation
      ix. Flattened acetabular roof
2. Molecular genetic testing
   a. Mutation analysis
      i. 1620C-A (Asn540Lys)
      ii. 1620C-G (Asn540Lys)
      iii. Other *FGFR3* mutations
   b. Sequence analysis of mutations in *FGFR3* exons 10, 13, and 15

Genetic Counseling

1. Recurrence risk (Francomano 2005)
   a. Patient's sib: an extremely low risk (<0.01%) of having an affected sib if parents are not affected (germline mosaicism has not been reported for hypochondroplasia)
   b. Patient's offspring
      i. 50% risk of having an affected offspring if the spouse is normal
      ii. If the spouse is an achondroplastic
         a) Twenty-five percent chance of having an affected offspring with hypochondroplasia
         b) Twenty-five percent chance of having an affected offspring with achondroplasia
         c) Twenty-five percent chance of having an affected offspring with achondroplasia-hypochondroplasia genetic compound
         d) Twenty-five percentchance of having a normal offspring
      iii. If the spouse also has hypochondroplasia or other dominant form of skeletal dysplasia: genetic counseling becoming more complicated due to the high incidence of genetic heterogeneity and the lack of medical literature addressing these circumstances
2. Prenatal diagnosis
   a. Prenatal diagnosis by amniocentesis or CVS for family with high-risk pregnancy with a parent who has hypochondroplasia

i. When the spouse is normal: testing for disease-causing FGFR3 mutation in the fetus
ii. When the spouse is affected with another dominantly inherited skeletal dysplasia caused by a known gene mutation: testing for the known mutation for that skeletal dysplasia and the mutation for the hypochondroplasia in the fetus

b. Prenatal diagnosis by ultrasonography, amniocentesis, or CVS in low-risk pregnancy without family history of affected individual
i. Ultrasonography: short limbs detected by routine ultrasound examination late in pregnancy
ii. DNA-based diagnosis of *FGFR3* mutations to confirm the diagnosis of hypochondroplasia

3. Management
a. Follow closely developmental milestones and signs of learning disability or mental retardation
b. Treatment of short stature
i. Trials of growth hormone therapy with mixed results
ii. Surgical limb lengthening for severe case of hypochondroplasia
a) An invasive procedure
b) Entails considerable disability and discomfort over a long period of time
c) Prefer postponement of the procedure until adolescence when the patient can make an informed decision

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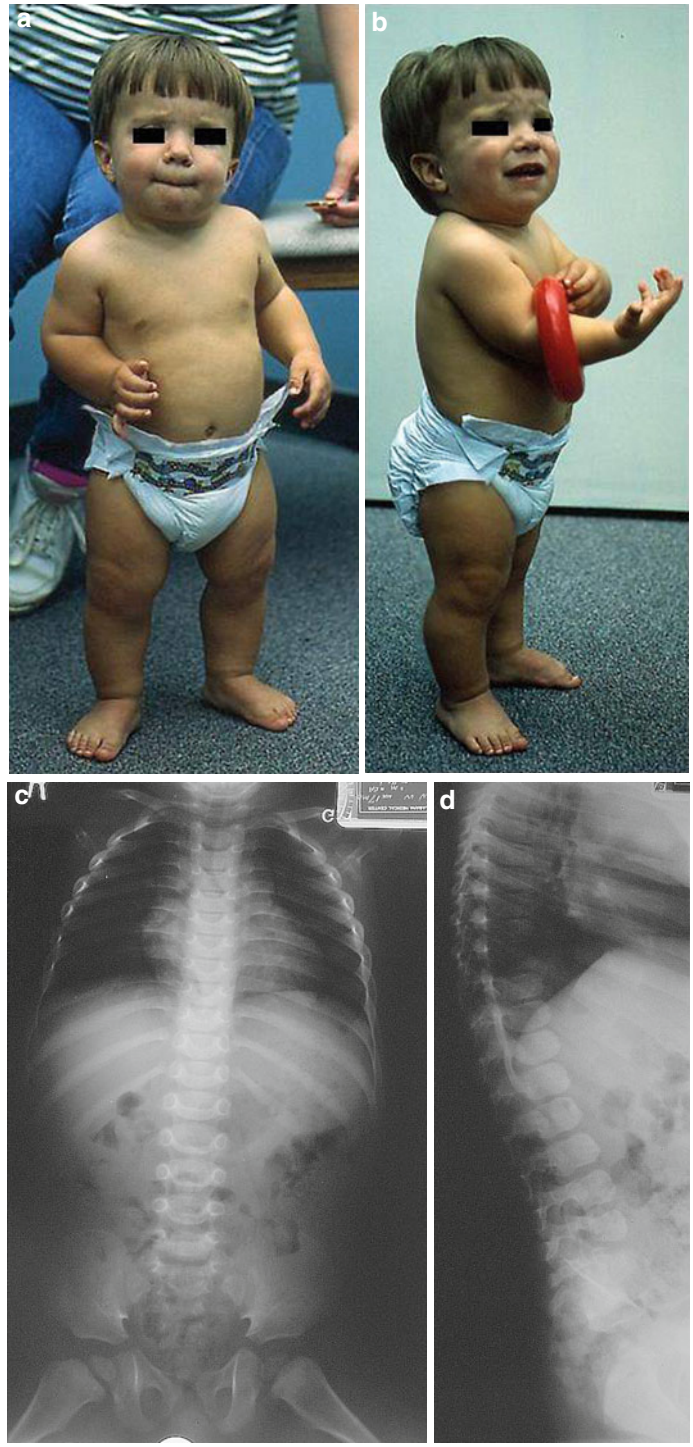

Fig. 1 (**a**–**d**) A young child affected with hypochondroplasia showing mild short stature and mild rhizomelic shortening of the extremities. Radiographs showed unchanged lumbar interpedicular distance

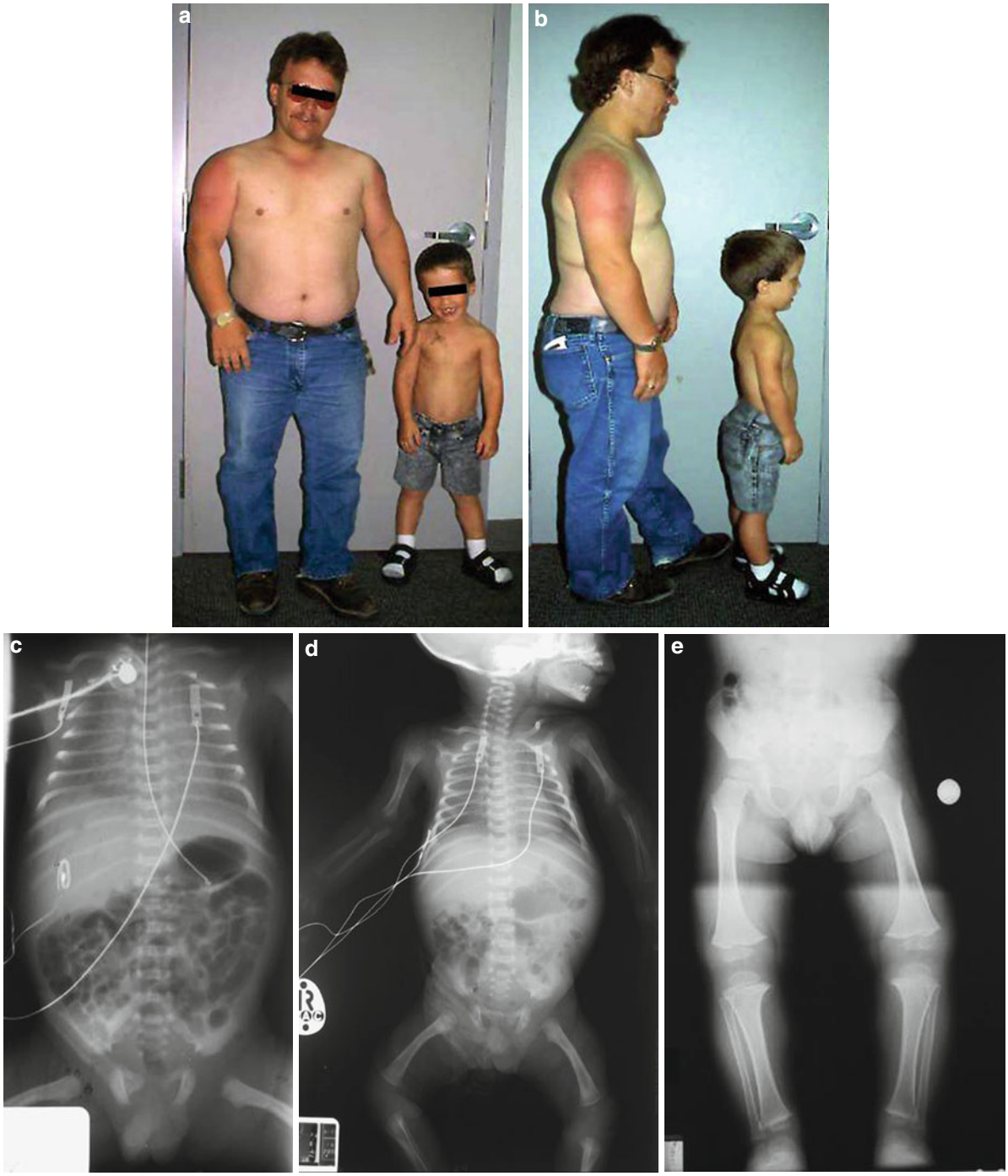

Fig. 2 (**a**–**e**) Father and son showing typical features of hypochondroplasia. The son's radiographs at birth, 17 days, and 2 years and 6 months showing unchanged lumbar interpedicular distance, mild shortening of long bones, and short, squared ilia

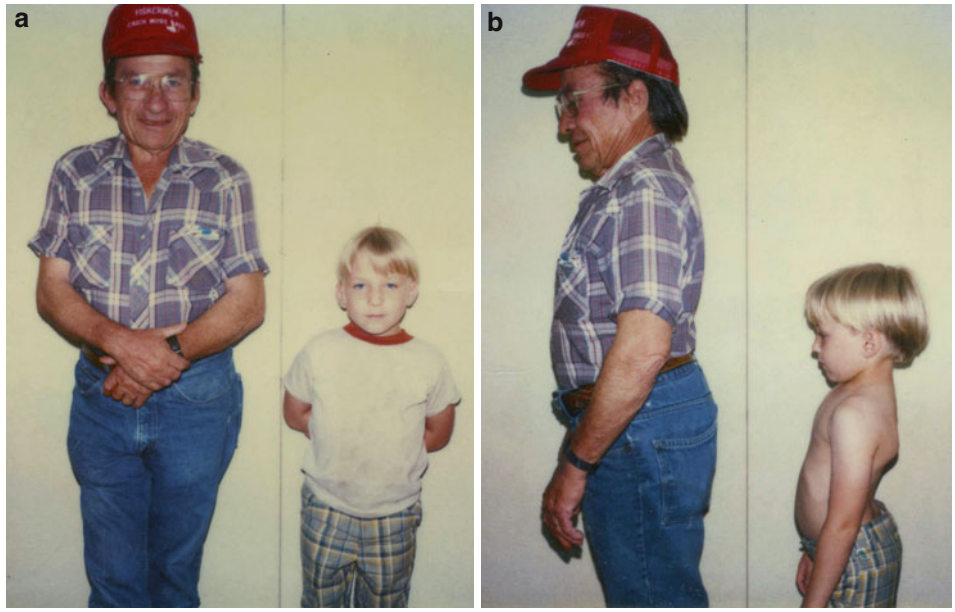

Fig. 3 (**a**, **b**) Father and son with clinical features of hypochondroplasia

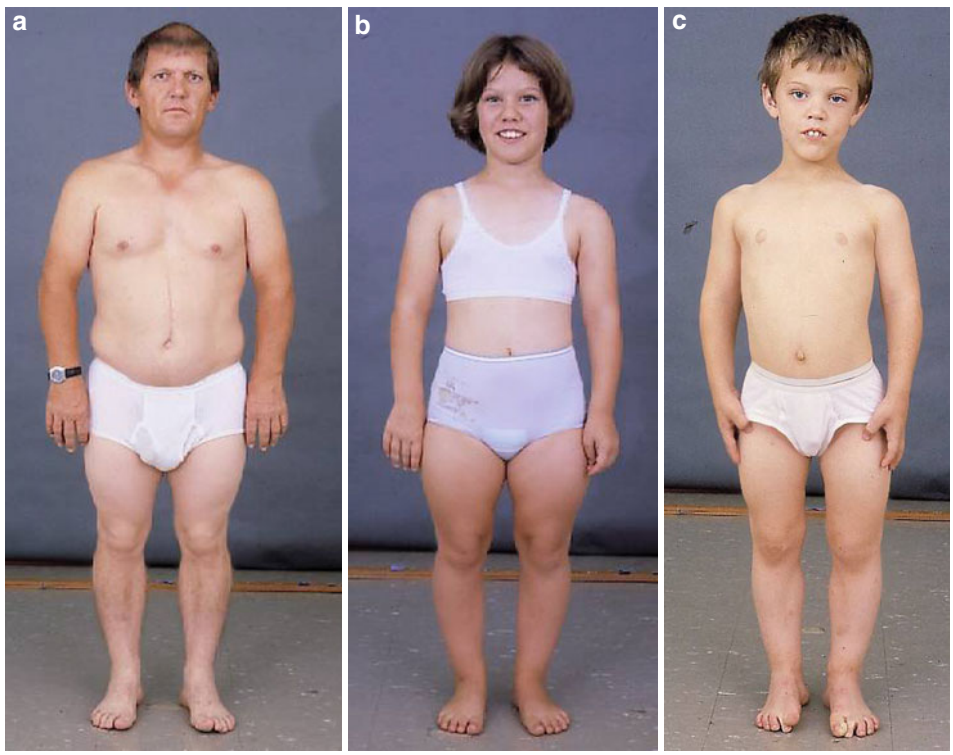

Fig. 4 (**a**–**c**) Father, daughter, and son affected with hypochondroplasia showing stocky build, mild short stature, normal facial appearance, rhizomelic shortening of the extremities, and absence of trident hands

Fig. 5 A 2-year-old boy with disproportional short stature with relatively short upper arms and thighs and mild lumbar gibbus. Molecular testing identified the presence of a C > A transversion at nucleotide 1620 (c.1620 C > A) of the fibroblast growth factor receptor 3 (*FGFR3*) gene. The presence of this mutation is consistent with a clinical diagnosis of hypochondroplasia

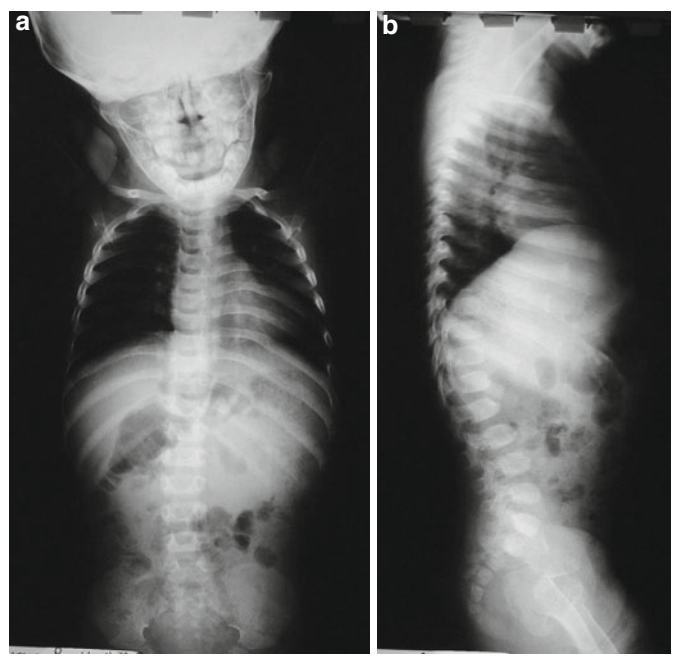

Fig. 6 (**a**, **b**) Radiographs of the spine (AP and lateral views) show caudal narrowing of lumbar interpedicular distance and the dorsal convexity of the lumbar vertebral bodies

Hypoglossia-Hypodactylia Syndrome

Hypoglossia-hypodactylia syndrome is an extremely rare condition characterized by a small tongue associated with distal limb deficiency. The syndrome is also called aglossia-adactylia syndrome, which is a misnomer since the tongue is never completely absent and the term "adactylia" does not convey the variation in limb defects of affected individuals. The syndrome is also known as oromandibular limb hypogenesis syndrome, a spectrum of congenital anomalies that affect the tongue, oromandibular region, and the limbs.

Synonyms and Related Disorders

Aglossia-adactylia syndrome; Oromandibular limb hypogenesis syndrome

Genetics/Basic Defects

1. Inheritance
   a. Sporadic in all reported cases.
   b. Autosomal dominant inheritance cannot be ruled out.
2. Pathogenesis (Yasuda et al. 2003)
   a. Impairments or insults to fetus during the early fetal life (fourth to seventh week) may be responsible for the findings of tongue and limb abnormalities seen in hypoglossia-hypodactylia syndrome because of the close chronological relationship between the development of the tongue and the limbs.
   b. A hypoplastic mandible with concurrent hypoglossia could be explained by the fact that the mandible originates from the same visceral arch as the tongue.
   c. Vascular mechanism (either hemorrhage or vasoocclusion) may be responsible for defects that are asymmetric and always distal.

Clinical Features

1. Mouth
   a. Mandible
      i. Micro-/retrognathia
         a) Minor feeding problems in infancy
         b) Minor speech impairment
      ii. Oligodontia
      iii. Absent mandibular incisors with concomitant hypoplasia of the associated alveolar ridge
      iv. Other features
         a) Mild lower lip defect
         b) Microstomia (markedly reduced mouth opening)
         c) Intraoral bands
         d) Oral frenula
         e) Oral syngnathia
   b. Tongue
      i. Varying degrees of hypoglossia
      ii. Ankyloglossia
      iii. Marked enlargement of the sublingual muscular ridges
      iv. Hypertrophy of the sublingual and submandibular glands
2. Variable limb anomalies
   a. May involve any limb

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   b. Distal reduction anomalies
      i. Oligodactyly (absence of some fingers and toes)
      ii. Adactylia (congenital absence of the fingers and toes)
      iii. Peromelia (severe congenital malformation of the extremity, including absence of hand and foot)
   c. Syndactyly
3. Other associated anomalies
   a. Moebius syndrome
   b. Fused labia majora
   c. Unilateral renal agenesis
   d. Imperforate anus
4. Normal intelligence
5. Classification of syndromes of oromandibular and limb hypogenesis (Hall 1971)
   a. Type I
      i. Hypoglossia
      ii. Aglossia
   b. Type II
      i. Hypoglossia-hypodactylia
      ii. Hypoglossia-hypomelia (peromelia)
      iii. Hypoglossia-hypodactylomelia
   c. Type III
      i. Glossopalatine ankylosis
      ii. With hypoglossia
      iii. With hypoglossia-hypodactylia
      iv. With hypoglossia-hypomelia
      v. With hypoglossia-hypodactylomelia
   d. Type IV
      i. Intraoral bands and fusion
      ii. With hypoglossia
      iii. With hypoglossia-hypodactylia
      iv. With hypoglossia-hypomelia
      v. With hypoglossia-hypodactylomelia
   e. Type V
      i. The Hanhart syndrome
      ii. Charlie M syndrome
      iii. Pierre Robin syndrome
      iv. Moebius syndrome
      v. Amniotic band syndrome
6. Differential diagnosis with other oromandibular limb hypogenesis syndromes (Bonneau et al. 1999)
   a. Hanhart syndrome
      i. Micrognathia
         a) Microglossia
         b) Hypodontia
      ii. Limb anomalies
         a) Ranging from stunted digits, oligodactyly, to more severe peromelia
         b) May affect any limb
   b. Glossopalatine and ankylosis syndrome
      i. Tongue.
         a) Usually attached to the hard palate
         b) May adhere to the maxillary alveolar ridge
         c) Mildly cleft tongue tip
      ii. High-arched or cleft palate.
      iii. Hypoplastic mandible.
      iv. Hypodontia principally affects the incisor teeth.
      v. Ankylosis of the temporomandibular joint.
      vi. Facial paralysis.
      vii. Extremely variable limb anomalies.
         a) Oligodactyly
         b) Syndactyly
         c) Polydactyly
         d) Peromelia
   c. Limb deficiency-splenogonadal fusion syndrome (Bonneau et al. 1999)
      i. Splenogonadal fusion
         a) A rare malformation in which the spleen is abnormally connected to the gonad, or, more rarely, to a derivative of the mesonephros
         b) May occur as a rare malformation
      ii. Association with other malformations, especially with terminal limb defects
   d. Moebius syndrome (please refer to the chapter of Moebius Syndrome)

Diagnostic Investigations

1. Radiography
   a. Fusion of the temporomandibular joints
   b. Micro-/retrognathia
   c. Hypodontia
   d. Limb defects
      i. Variable distal limb deficiency
      ii. Asymmetric reduction deformities of the distal extremities
      iii. Severity ranging from hypoplastic digits to peromelia

   e. Other rare anomalies
      i. Dextrocardia
      ii. Transposition of abdominal organs
      iii. Jejunal atresia
      iv. Short bowel
      v. "Apple peel" bowel
2. Reconstructed 3D CT imaging of the craniofacial skeletal structures (Yasuda et al. 2003)
   a. Retruded and reduced mandible
   b. Steep inclination of the anterior surface of the mandible in relation to the lower mandibular plane
   c. Bone defect of the alveolar ridge at the midline area of the mandible
3. MRI of the tongue and the floor of the mouth (Yasuda et al. 2003)
   a. Degree of the hypoglossia
   b. Space between the tongue and the inferior surface of the palate
   c. Hypertrophy of the floor of the mouth

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: not increased unless the condition represents an autosomal dominant inheritance, in which case there will be 50% risk to have an affected offspring
2. Prenatal diagnosis: not been reported
3. Management (Yasuda et al. 2003)
   a. Early surgical intervention for presence of severe anomalies that are life-threatening and interfere swallowing, breathing, and eating
   b. Extraction of the supernumerary tooth
   c. Orthodontic expansion appliance for widening the mandibular dental arch
   d. Distraction osteogenesis to improve the size and shape of the hypoplastic mandible
   e. Mandibular advancement

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Fig. 1 (**a**–**c**) A 2-month-old female infant with hypoglossia-hypodactylia syndrome showing antimongoloid slant of the palpebral fissures, facial palsy, micro-/retrognathia, microstomia, hypoglossia, and limb anomalies with adactylia of the right hand and both feet and oligodactyly of the left hand

Fig. 2 (**a**, **b**) Another infant with hypoglossia-hypodactylia syndrome showing extreme micro-/retrognathia, hypoglossia, microstomia, and adactylia of both hands

Fig. 3 (**a**–**c**) A 3-month-old girl with hypoglossia-hypodactylia syndrome showing extreme micro-/retrognathia, hypoglossia, microstomia, and adactylia of both hands (*right upper* extremity showed a transverse growth arrest beyond the wrist and *left upper* extremity showed a transverse arrest beyond the proximal one third of the forearm)

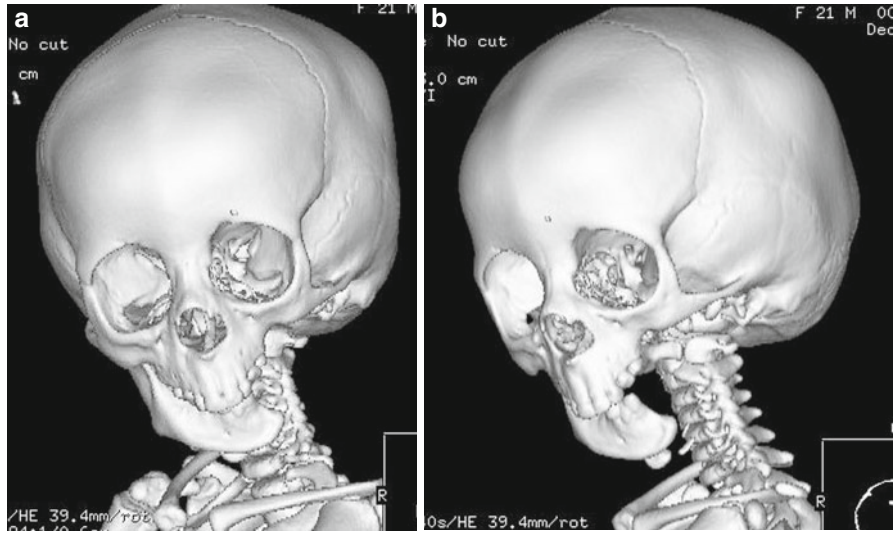

Fig. 4 (**a**, **b**) CT of the face (AP and lateral views) show left hemimandibular agenesis (complete absence of the body, angle, ramus, and condyle) and a significant aplasia of posterior maxilla on the left

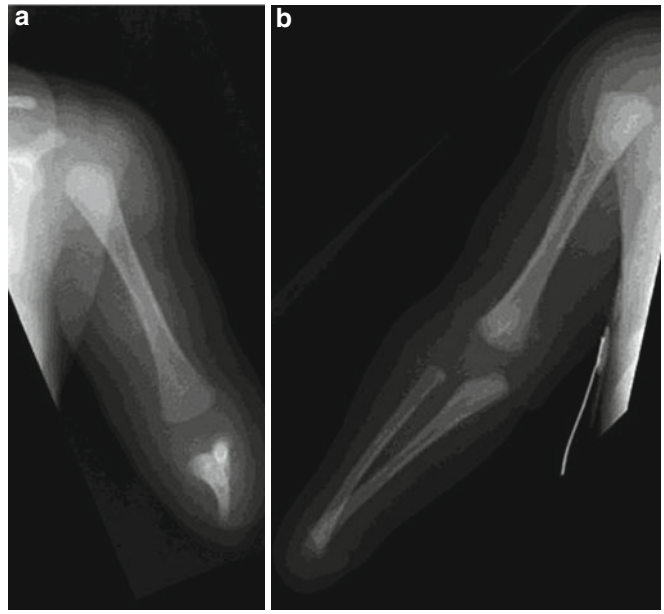

Fig. 5 (**a**, **b**) Plain radiographs show transverse growth arrest past the proximal one third of the left forearm and V-shaped formation of the radius and ulna with growth arrest past the right wrist

Fig. 6 The previous girl was seen at 3 years of age

Fig. 7 (**a**, **b**) Preoperative photos at 5 years of age

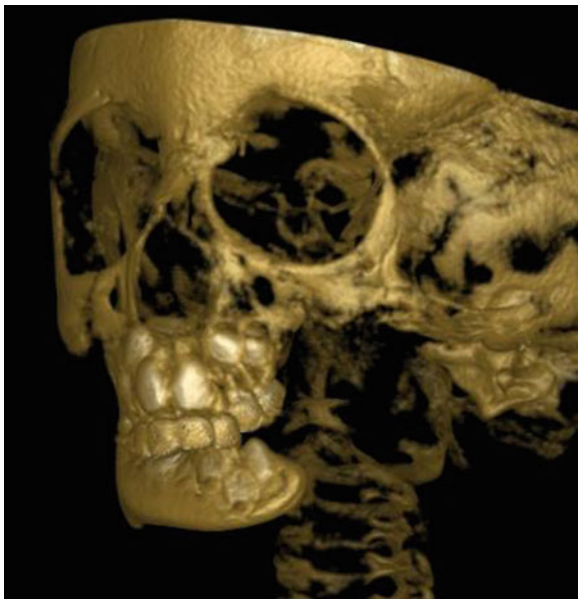

Fig. 8 Preoperative CT at the age of 5

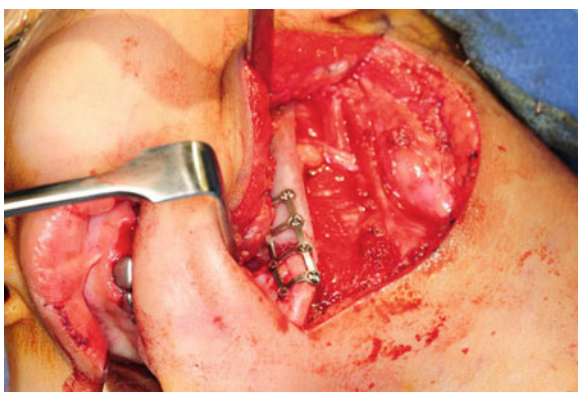

Fig. 9 Intraoperative photo. Costochondral graft fixated to the adjacent mandible. Cartilaginous cap seated in the glenoid fossa

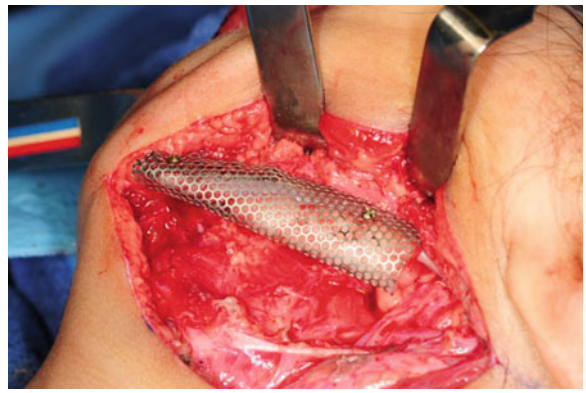

Fig. 10 Titanium mesh used as a crib for BMP at the inferior border of the rib graft

Fig. 11 (**a**, **b**) Postoperative photos at age 5. She was reconstructed with a right costochondral rib graft to replace the condyle and ramus region and established continuity of her mandible. This was combined with the use of a titanium mesh crib and some bone morphogenetic proteins (BMP) at the junction of the native mandible and the costochondral graft. Note the improved facial profile on the left. Despite improved result, the patient will require further surgery as she grows to correct her facial profile

Fig. 12 Three-month postoperative cone beam CT. Cartilaginous cap not apparent on this view

Fig. 13 Note the broad intraoral band extending from the left subglossal region to the soft palate. This band also attaches to the left lower lip causing retraction of the lip

Fig. 14 The patient protruding her tongue past the intraoral band. Maximum protrusion. Based on the hypoglossia, the oral band extending from the floor of mouth and left cheek to the soft palate, and the limb abnormalities (hypodactylomelia), the patient would fit best as Hall's type IVD (intraoral bands and fusion with hypoglossia-hypodactylomelia. Thus, the patient is classified as a type IVD with hemimandibular agenesis (Qaisi et al. 2010)

Hypohidrotic Ectodermal Dysplasia

Hypohidrotic ectodermal dysplasia (HED) is a common form of ectodermal dysplasia characterized by a defect in the hair, in the teeth, and in mucosal and sweat glands. It is also known as anhidrotic ectodermal dysplasia. The incidence is estimated to be 1 in 10,000 to 1 in 100,000 male live births (Crawford et al. 1991).

Synonyms and Related Disorders

Anhidrotic ectodermal dysplasia; Christ-Siemens-Touraine syndrome

Genetics/Basic Defects

1. Inheritance: genetically heterogeneous
   a. X-linked recessive type: the most common form of over 170 different ectodermal dysplasias
   b. Autosomal dominant type: less common
   c. Autosomal recessive type: less common
2. X-linked HED: the most common form
   a. Caused by mutations in the ectodysplasin-A gene (*EDA1*) which (Doffinger et al. 2001):
      i. Codes for the tumor necrosis factor (TNF) family member ectodysplasin-A (EDA)
      ii. Maps to chromosome Xq12-q13.1 by X autosome translocations of female EDA patients
      iii. Affects a transmembrane protein expressed by keratinocytes, hair follicles, and sweat glands
      iv. Possibly has a key role in epithelial-mesenchymal signaling
   b. Over 94% of patients with X-linked HED carry mutations in the *EDA1* gene.
   c. Tabby phenotype is caused by mutation in mouse homolog of the human *EDA* gene (Priolo et al. 2000).
   d. Hemizygous males show severe forms of the disease while heterozygous females often manifest mild to moderate symptoms because of X-chromosome inactivation.
3. Autosomal dominant form and some familial cases of autosomal recessive form of HED caused by at least two genes:
   a. *EDAR* (*EDA* receptor) gene (2q11-q13)
      i. Cause either dominant or recessive forms
      ii. Mutated in approximately 25% of non-EDA-related HED
   b. *EDARADD* (*EDAR*-associated death domain) gene (1q42-q43)
      i. Encodes a protein that interacts with the EDA receptor
      ii. Known to cause either autosomal recessive or dominant HED
      iii. Implicated in a very small number of HED patients (Chassaing et al. 2010)

Clinical Features

1. General features
   a. Characterized by a triad of symptoms
      i. Atrichosis or hypotrichosis (missing or sparse hair)
      ii. Anodontia, hypodontia, or misshapen teeth
      iii. Absent or reduced sweating
   b. Variable clinical features
   c. Short stature

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d. Recurrent benign infectious disease seen in most patients with HED
e. Unusually severe infections observed in:
   i. Anhidrotic ectodermal dysplasia with immunodeficiency: a distinct syndrome
   ii. Ectodermal dysplasia with cleft lip/palate
   iii. Ectrodactyly-ectodermal dysplasia-cleft lip/palate
f. Otitis media
g. Infantile fever of unknown etiology
h. Hyperthermia
i. Hoarse voice

2. Clinical features in X-linked recessive hypohidrotic ectodermal dysplasia
   a. Affected individuals
      i. Hemizygous males: affected
      ii. Heterozygous female carriers: variable clinical symptoms (normal, or mild or partially affected)
         a) Dental abnormalities, such as hypodontia
         b) Mild hypohidrosis
         c) Mild hypotrichosis
   b. Clinical evidence of the distribution of normal and abnormal skin along Blaschko lines in heterozygous and postzygotic mutation carriers of X-linked hypohidrotic ectodermal dysplasia
      i. Presence of two different cell lines in a female heterozygous for the XHED due to random inactivation of one of the two X chromosomes during embryogenesis, reflected by the presence of different skin areas, some normal and some showing the result of the genetic abnormality.
      ii. These abnormal areas, disposed along Blaschko lines, reflect the lines of embryonal development of the epidermis and epidermal derivatives.
      iii. This clonal inactivation ("lyonization") of the X chromosome results in variable degree of clinical expression of the disorder.
   c. Clinically differentiating X-linked HED from autosomal forms of HED
      i. Finding heterozygous females with XHED
      ii. Finding parents with partial manifestations of the disorder due to a postzygotic mutation
   d. Clinical features
      i. Scalp hair
         a) Sparse
         b) Thin
         c) Light pigmented
         d) Slow growing
         e) Excessive fragility of the shafts, breaking easily with the usual wear and tear of childhood
      ii. Body hair
         a) Sparse
         b) Normal sexual hair (beard, pubic hair)
      iii. Sweating
         a) Greatly deficient sweating (hypohidrosis)
         b) Leading to hyperthermia
      iv. Teeth
         a) Congenital absence of teeth (hypodontia)
         b) Teeth that are present (smaller than average and have conical crowns)
      v. Facial features
         a) Frontal bossing
         b) A saddle nose (depressed nasal bridge)
         c) Thick lips
         d) Periorbital hyperpigmentation
      vi. Other features
         a) Normal growth and psychomotor development
         b) Atopic dermatitis
         c) Bronchial asthma
         d) Fever of unknown reason
         e) Sudden death during infancy and early childhood

3. Clinical features in autosomal recessive hypohidrotic ectodermal dysplasia
   a. Similar to (but indistinguishable from) the hemizygous form of X-linked hypohidrotic ectodermal dysplasia
      i. Decreased sweating
      ii. Hypodontia
      iii. Conical teeth
      iv. Hypotrichosis of the scalp
      v. Sparse or absent eyebrows and eyelashes
      vi. Sparse or absent body hair
      vii. Dry skin or eczema
      viii. Hypoplastic nails
      ix. Hypoplastic breasts
      x. Atrophic rhinitis
      xi. Depressed nasal bridge
      xii. Hyperpigmented and wrinkled periorbital skin
   b. Males and females equally affected

4. Clinical features in autosomal dominant hypohidrotic ectodermal dysplasia: milder in expression
   a. Hypodontia, anodontia, microdontia, or other dental anomalies (100%)
   b. Sparse eyelashes (100%)
   c. Sparse eyebrows (96%)
   d. Sparse, fine, slow-growing hair (89%)
   e. Decreased sweating (85%)
   f. Thin skin (78%)
   g. Sparse body hair (62%)
   h. Decrease heat tolerance (50%)
   i. Onychodysplasia (39%)

Diagnostic Investigations

1. Radiography
   a. Hypodontia and adontia
      i. Essential to determine the extent of hypodontia and adontia
      ii. Useful in the diagnosis of mildly affected individuals
   b. Recurrent respiratory infections
2. Normal hair morphology under electron microscopy
3. Starch-iodine test to confirm a mosaic distribution of functional sweat glands in a heterozygous female carrier of X-linked HED (Cambiaghi et al. 2000)
4. Molecular analysis: clinically available
   a. Sequence analysis
      i. Mutation in *EDA* gene for the X-linked form
      ii. Mutations in *EDAR* and *EDARADD* genes for the autosomal dominant or recessive forms
   b. Duplication/deletion testing: to detect exonic, multiexonic, or whole gene deletions in females which sequence analysis of *EDA* cannot detect

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. X-linked recessive: 50% of affected brothers if the mother is a carrier, otherwise the risk to sibs is low
      ii. Autosomal dominant: not increased unless a parent is affected, in which case the risk to the sibs is 50%
      iii. Autosomal recessive: 25% of the sibs affected
   b. Patient's offspring
      i. X-linked recessive
         a) Offspring of a male proband: none of the sons will be affected; 50% of the daughters will be carriers
         b) Offspring of a female proband: 50% of her son will be affected and 50% of her daughters will be carriers and may show minimal manifestations
      ii. Autosomal dominant: 50% risk to each child
      iii. Autosomal recessive: not increased unless the spouse is also a carrier, in which case the risk to offspring is 50%
2. Prenatal diagnosis
   a. Analysis of fetal skin obtained from fetoscopy-guided skin biopsy in the second trimester
   b. Three-dimensional ultrasonography to identify the distinct facial features during the third trimester
   c. Identification of the disease-causing mutation in the fetus
   d. Preimplantation genetic diagnosis for at-risk pregnancies is possible, provided disease-causing mutations have been identified
3. Management
   a. Environmental modification to control temperature
      i. Air condition for home, school, and work
      ii. Adequate supply of water during the hot weather
   b. Control body temperature
      i. Tepid sponging
      ii. Showers
      iii. Cold drink
      iv. Antipyretics
      v. Wet clothing
   c. Use moisturizers to prevent xerosis or eczema for dry skin
   d. Use artificial tears (eye drops) to prevent damage to the cornea in patients with defective tearing
   e. Remove nasal and aural concretions with suction devices or forceps and humidification of the ambient air to prevent their formation
   f. Treatment and prophylaxis for infections

g. Dental evaluation and intervention
   i. Early dental treatment
      a) Simple restoration
      b) Dentures
      c) Orthodontics
   ii. Dental implants
   iii. Orthodontic treatment
h. Wear wigs to improve appearance for patients with severe alopecia
i. Avoid vigorous physical activities for patients with hypohidrosis
j. Monitor growth

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Fig. 1 Three boys (**a**–**d**) with X-linked hypohidrotic ectodermal dysplasia showing sparse scalp hair, frontal bossing, sparse eyebrows and eyelashes, saddle nose, hypodontia, and irregularly shaped conical and pointed primary incisors

Fig. 2 Two brothers with X-linked hypohidrotic ectodermal dysplasia showing sparse eyebrows, hypodontia, and conical permanent teeth

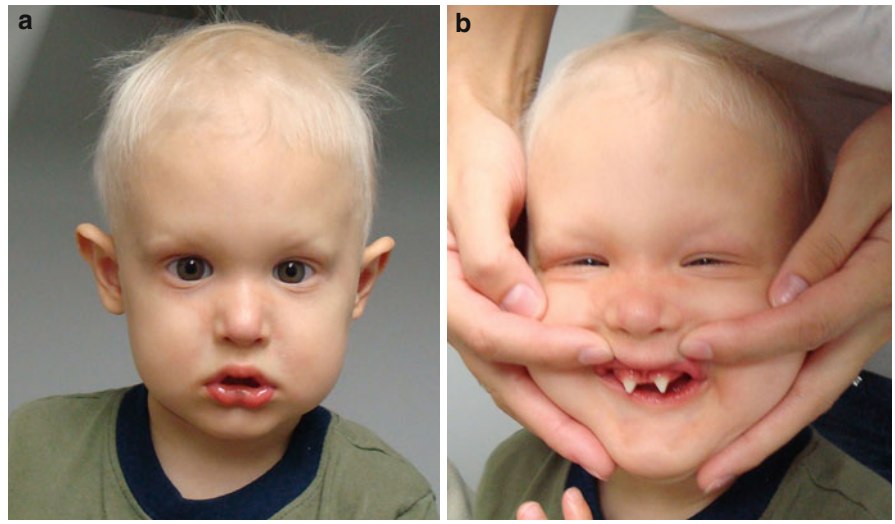

Fig. 3 (**a**, **b**) A boy with hypohidrotic ectodermal dysplasia showing sparse scalp hairs and eyebrows, hypodontia, and conical permanent teeth

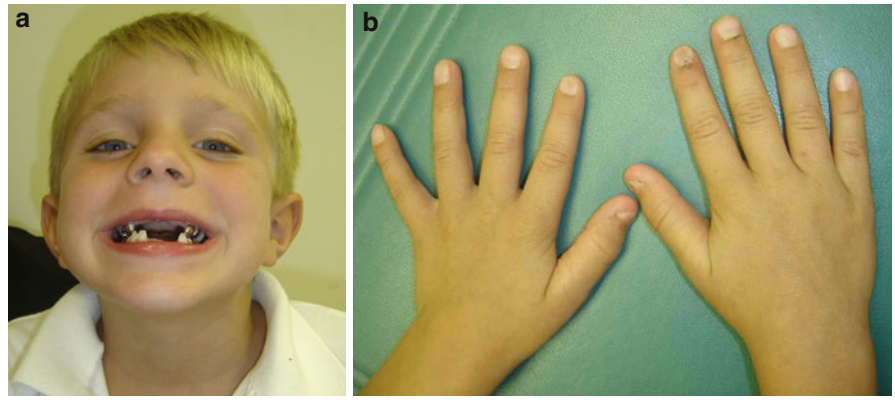

Fig. 4 (**a**, **b**) A boy with hypohidrotic ectodermal dysplasia showing sparse scalp hairs and eyebrows, hypodontia, and nail hypoplasia of the thumbs

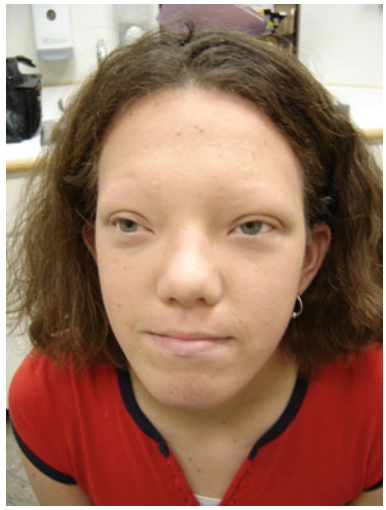

Fig. 5 A 15-year-old girl with hypohidrotic ectodermal dysplasia showing sparse eyebrows and ocular hypertelorism

Hypomelanosis of Ito

In 1952, Ito reported a female patient with a widespread, symmetric pattern of depigmented whorls and streaks, naming it incontinentia pigmenti achromians because the distribution of the depigmented lesions is the negative image of the hyperpigmented streaks of incontinentia pigment. Hypomelanosis of Ito (HI) is a relatively common disorder with a frequency of 1 in 8,000–10,000 patients in a general pediatric hospital and 1 in 1,000 patients in a pediatric neurology service (Küster and Konig 1999).

Synonyms and Related Disorders

Incontinentia pigmenti achromians

Genetics/Basic Defects

1. Inheritance
   a. Sporadic occurrence in nearly all cases with no affected sibs or parents (Küster and Konig 1999)
      i. Result of a de novo postzygotic mutation
      ii. Mutation can only survive in a mosaic state
   b. Only a few cases with possible genetic inheritance reported
      i. X-linked dominant inheritance
      ii. Autosomal dominant
      iii. Autosomal recessive
2. Pathogenesis
   a. Chromosome abnormalities (52%)
      i. Mosaicism leading to generation of two cell lineages producing patterns of hypopigmented and hyperpigmented skin
      ii. Balanced X/autosome translocations
      iii. Supernumerary X chromosome/ring fragment
      iv. Ring chromosomes (10, 14, 22)
      v. Mosaic triploidy
      vi. Mosaic diploidy/tetraploidy
      vii. Mosaic trisomies (2, 8, 13, 14, 18, 20, 22)
      viii. Mosaic tetrasomy 13q
      ix. Mosaic translocations
      x. Mosaic deletions
      xi. Autosomal deletions and duplications involving chromosomes 7, 12, 13, 14, 15, and 18
      xii. Dup(Xp)
   b. X chromosome abnormalities
      i. Inactivation
      ii. Activation
      iii. Mosaicism
3. "Pigmentary mosaicism" (Taibjee et al. 2004)
   a. Hypomelanosis of Ito and related disorders such as linear and whorled nevoid hypermelanosis are due to mosaicism for a variety of chromosomal abnormalities.
   b. Classification of chromosome mosaicism
      i. Mosaicism with two or more different karyotypes, involving structural abnormalities of chromosomes
      ii. Mosaicism involving structural abnormalities of chromosomes, where the chromosome was undetermined
      iii. Chromosomal abnormality apparently affecting all cells, but where undetected mosaicism remains a possibility
      iv. Balanced X/autosome translocations affecting all cells, with functional mosaicism due to lionization

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v. Polyploidy mosaicism (cells having different multiples of 23 chromosomes): can be associated with mosaic trisomy such as chromosome18
vi. Chimaerism

4. A descriptive term rather than a true syndrome
   a. Suggested by the pattern of chromosomal aberrations and the polymorphic nature of the disease
   b. A term used for a phenotype
      i. Presence of linear streaks lighter than the patient's background skin color, extending around the trunk and down the long axes of the extremities, roughly following the lines of Blaschko
      ii. Association with systemic findings

Clinical Features

1. Cutaneous symptoms (Küster and Konig 1999)
   a. Onset
      i. Recognizable at birth (54%)
      ii. Visible during childhood (70%)
   b. No signs of inflammation or verrucous changes characteristically seen in incontinentia pigmenti
   c. Hypopigmented lesions
      i. Typical phenotype
         a) Cutaneous pattern: essentially the reverse of the third stage of incontinentia pigmenti
         b) Bilateral or unilateral whirls, patches, and streaks corresponding to the lines of Blaschko, often showing a midline cutoff
         c) Eruption not preceded by any inflammatory lesions (unlike incontinentia pigmenti)
      ii. Unilateral skin lesions contralateral to the side of brain malformation in patients with HI and hemimegalencephaly
      iii. Wood lamp useful in demonstrating hypopigmented lesions in persons with fair skin
      iv. Atypical phenotype: checkerboard pattern zosteriform, dermatomal, or plaque-like arrangement
   d. Nonspecific skin lesions (20–40%)
      i. café-au-lait spots
      ii. Persistent Mongolian blue spots
      iii. Nevus of Ota
      iv. Nevus marmoratus and angiomatous nevi
      v. Soft fibroma
      vi. Pilomatrixoma
      vii. Aplasia cutis
      viii. Atopic dermatitis
2. Hair/nail/sweat gland anomalies
   a. Focal hypertrichosis
   b. Slow growth
   c. Diffuse alopecia
   d. Coarse, curly hair
   e. Trichorrhexis
   f. Widow's peak
   g. Generalized hirsutism
   h. Facial hypertrichosis
   i. Low hairline
   j. Ungual hypoplasia
   k. Hypohidrosis corresponding to hypopigmented areas
3. Associated extracutaneous anomalies (75%)
   a. CNS anomalies
      i. Mental retardation (50–75%)
      ii. Seizures (50%)
      iii. Autistic behavior (11%)
      iv. Microcephaly
      v. Hypotonia
      vi. Hyperkinesia
      vii. Ataxia
      viii. Deafness
      ix. Hemimegalencephaly
      x. Brain tumors (medulloblastoma, choroid plexus papilloma)
   b. Ophthalmological abnormalities (20%)
      i. Microphthalmia
      ii. Ptosis
      iii. Nonclosure of the upper lid
      iv. Symblepharon
      v. Dacryostenosis
      vi. Strabismus
      vii. Nystagmus
      viii. Myopia
      ix. Hyperopia
      x. Astigmatism
      xi. Amblyopia
      xii. Megalocornea
      xiii. Corneal opacification
      xiv. Cataracts
      xv. Iridal heterochromia
      xvi. Scleral melanosis

xvii. Heterochromia of the iris
xviii. Optic atrophy
xix. Striated patchy hypopigmented fundi
xx. Retinal detachment

c. Dental abnormalities
i. Defective dental implantation
ii. Conical teeth
iii. Partial anodontia
iv. Dental dysplasia/hypoplasia
v. Defective enamel
vi. Hamartomatous dental cusps

d. Skeletal defects
i. Short stature
ii. Facial and limb asymmetry (hemihypertrophy)
iii. Pectus carinatum or excavatum
iv. Scoliosis
v. Syndactyly
vi. Polydactyly
vii. Brachydactyly
viii. Clinodactyly

e. Congenital heart defect
i. Tetralogy of Fallot
ii. Pulmonary stenosis
iii. Ventricular septal defect
iv. Atrial septal defect
v. Incomplete right bundle branch block
vi. Cardiomegaly of unknown etiology

f. Abdomen/gastrointestinal anomalies
i. Diastasis recti
ii. Hepatomegaly
iii. Segmental dilation of the colon
iv. Diaphragmatic, umbilical, and inguinal hernias

g. Genitourinary anomalies
i. Hypospadias
ii. Micropenis
iii. Single kidney
iv. Urethral duplication
v. Cryptorchidism
vi. Precocious puberty
vii. Gynecomastia
viii. Asymmetrical breasts
ix. Nephritis

4. Diagnostic criteria (Ruiz-Maldonado et al. 1992)
a. Sine qua non criterion: congenital or early acquired nonhereditary cutaneous hypopigmentation in linear streaks or patches involving more than two body segments
b. Major criterion
i. One or more nervous system anomalies
ii. One or more musculoskeletal anomalies
c. Minor criterion
i. Two or more congenital malformations other than nervous system or musculoskeletal anomalies
ii. Chromosomal anomalies
d. Definitive diagnosis: sine qua non criterion plus one or more major criteria or two or more minor criteria
e. Presumptive diagnosis: sine qua non criterion alone or in association with one minor criterion

5. Classification of linear pigmentary disorders distributed along the Blaschko lines (Di Lernia 2007)
a. Linear and whorled hypermelanosis
i. Hyperpigmentation
ii. Diffuse distribution
iii. Presence of mosaicism
iv. Associated abnormalities ($\leq$30%)
b. Hypomelanosis of Ito
i. Hypopigmentation
ii. Diffuse distribution
iii. Presence of mosaicism
iv. Associated abnormalities ($\geq$30%)
c. Progressive cribriform and zosteriform hyperpigmentation
i. Hyperpigmentation
ii. Segmental distribution
iii. Associated abnormalities: very low incidence
d. Segmental nevus depigmentosus
i. Hyperpigmentation
ii. Segmental distribution
iii. Associated abnormalities: very low incidence

Diagnostic Investigations

1. Cytogenetic investigation
a. Peripheral blood karyotyping indicated especially when systemic manifestations are present
b. Fibroblast karyotyping by sampling the dark and light skin for demonstrating mosaicism or chromosomal abnormalities
c. Presence of a wide variety of karyotypic abnormalities

2. Histopathology
   a. Decreased numbers of melanocytes
   b. Decreased numbers and size of pigmented melanosomes
   c. Neuropathological features
      i. Polymicrogyria
      ii. Disarray of cortical lamination
      iii. Heterotopic neurons in the white matter
      iv. Giant cells
3. CT and MRI of the brain
   a. White matter abnormalities somewhat predictive of a poor neurological outcome
   b. Neuroblast migration
      i. Heterotopia
      ii. Pachygyria
      iii. Polymicrogyria
   c. Localized or generalized cerebral atrophy
   d. Cerebral hemiatrophy
   e. Hemimegalencephaly
   f. Other rare anomalies
      i. Noncommunicating hydrocephalus
      ii. Megacisterna magna
      iii. Arteriovenous malformation
      iv. Cerebellar hypoplasia (hemispheres and vermis)
      v. Brainstem hypoplasia
      vi. Brain tumors
4. Radiography for musculoskeletal anomalies
5. EEG for seizures

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased unless a parent shows chromosomal abnormalities
   b. Patient's offspring
      i. Not increased unless the patient has chromosomal abnormalities
      ii. Guarded counseling in women with a phenotype similar to HI who have nonmosaic balanced X/autosome translocations
2. Prenatal diagnosis: undetermined for affected mother who has a specific type of chromosome abnormality
3. Management
   a. Early intervention programs including physical, occupational, and speech therapies
   b. Special education
   c. Seizure control
   d. Surgical treatment of cataracts and retinal detachment

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Fig. 1 (**a**–**c**) Three children with hypomelanosis of Ito showing hypopigmented skin lesions in a characteristic distribution of whirls and streaks on the trunk and limbs. The first patient has 49,XXXXY

Hypophosphatasia

Hypophosphatasia is a heritable metabolic disease, characterized by impaired ossification of the bones, reduction in tissue and plasma levels of alkaline phosphatase, and the presence of phosphoethanolamine in the urine. The incidence is estimated to be about 1 in 100,000 live births (Fraser 1957). The incidence of severe disease is especially high in Canadian Mennonites (1 in 2,500 newborns) (Gehring et al. 1999).

Synonyms and Related Disorders

Adult hypophosphatasia (mild hypophosphatasia, odontohypophosphatasia); Childhood hypophosphatasia; Perinatal lethal hypophosphatasia; Phosphoethanolaminuria

Genetics/Basic Defects

1. Genetic heterogeneity
   a. Perinatal lethal hypophosphatasia form: autosomal recessive
   b. Prenatal benign hypophosphatasia form: autosomal dominant
   c. Infantile hypophosphatasia form: autosomal recessive
   d. Childhood hypophosphatasia form: autosomal recessive (frequent) and dominant (rare)
   e. Adult hypophosphatasia form: autosomal recessive and dominant with variable penetrance
   f. Odontohypophosphatasia form: autosomal recessive and dominant
2. Cause
   a. Caused by mutations in the alkaline phosphatase gene (*ALPL*) which (Barcia et al. 1997):
      i. Codes for tissue nonspecific ("liver/bone/kidney") alkaline phosphatase (TNSALP)
      ii. Is mapped on chromosome 1p36.1–p34
   b. Typically, the other isoenzymes (placental and intestinal forms) are not affected (Gehring et al. 1999).
3. Pathophysiology
   a. Defects in mineralization.
      i. Caused by deficiency in TNSALP
      ii. Resulting in increased urinary excretion of phosphoethanolamine and inorganic pyrophosphate and an increase in serum pyridoxal 5'-phosphate
   b. Osteoclasts, although morphologically normal, lack membrane-associated alkaline phosphatase activity on histochemical analysis (Barcia et al. 1997).
      i. Impede the proper incorporation of calcium into newly formed bone matrix
      ii. Result in bone demineralization and hypercalcemia when the impaired matrix calcification process occurs with a rapid rate of bone resorption
4. Genotype-phenotype correlations
   a. A number of different mutations account for the clinical heterogeneity.
      i. Individuals with recessive hypophosphatasia with both defective TNSALP alleles.
         a) In general, manifest more severe symptoms, with many of those affected being stillborn or expiring shortly after birth.

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b) Exception when consanguineous marriage is a factor: the two defective alleles tend to have distinct point mutations resulting in different amino acid substitutions in the alkaline phosphatase protein.

ii. Individuals with dominant hypophosphatasia with only one defective TNSALP allele: usually manifest moderate symptoms, such as the premature exfoliation of fully rooted primary teeth.

iii. Division between dominant and recessive hypophosphatasia sometimes is not well defined because the heterozygous siblings with one defective TNSALP allele in kindreds with recessive hypophosphatasia may show mild or moderate symptoms of the disease.

b. Missense mutations in the TNSALP gene have been observed in some hypophosphatasia kindreds, particularly those families with the more severe perinatal and infantile forms of the disease.

c. Autosomal recessive inheritance has been observed in most cases of hypophosphatasia with affected individuals being compound heterozygotes for two different mutant hypophosphatasia alleles.

d. Autosomal dominant alleles cause a few relatively mild cases of hypophosphatasia.

e. Mild hypophosphatasia (Fauvert et al. 2009).

i. Can result from either compound heterozygosity for severe and moderate mutations but also in a large part from heterozygous mutations with a dominant negative effect.

ii. A sequence variation in linkage disequilibrium with haplotype E could in addition play the role of an aggravating factor resulting in loss of haplosufficiency.

Clinical Features

1. Presence of a wide phenotypic variability ranging from intrauterine death and extreme hypomineralization of the skeleton to lifelong absence of clinical symptoms (Gehring et al. 1999)
   a. The following four different forms of the hypophosphatasia have been defined:
      i. Perinatal lethal form
      ii. Infantile form
      iii. Childhood form
      iv. Adult form
   b. In general, the earlier the age of presentation, the more severe the presenting features.
2. Perinatal lethal form
   a. Often stillborn
   b. Skeletal deformities: presenting features
      i. A profound lack of skeletal mineralization in utero.
      ii. Skin-covered spurs extending from the forearms or legs (skin dimples) (Shohat et al. 1991): these spurs are often diagnostic for hypophosphatasia.
      iii. Markedly shortening and bowing of the long bones (short-limbed dwarfism).
      iv. Fractures (perinatal).
      v. Rickety rosary.
      vi. Metaphyseal swelling.
      vii. Soft, pliable cranial bones ("vault like a balloon").
      viii. Bulging anterior fontanelle.
   c. Respiratory distress due to hypoplastic lungs and rachitic deformities of the chest
   d. Other features
      i. Hypotonia
      ii. High-pitched cry
      iii. Vomiting
      iv. Constipation
      v. Unexplained fever
      vi. Apnea
      vii. Cyanosis
      viii. Irritability
      ix. Seizures
   e. Prognosis
      i. Lethal in utero or within a few days of birth.
      ii. In the rare prenatal benign form, despite prenatal symptoms, there is a spontaneous improvement of skeletal defects (Pauli et al. 1999; Moore et al. 1999; Wenkert et al. 2007).
3. Infantile form
   a. Appears normal at birth
   b. Onset of symptoms
      i. Before 6 months of age
      ii. Poor feeding
      iii. Failure to thrive (growth failure)
      iv. Hypotonia
      v. Convulsions

c. Associated with progressive bony demineralization
   i. Abnormal skull with apparent wide separation of the cranial sutures and a wide, bulging anterior fontanelle
   ii. Tendency toward developing craniosynostosis
      a) Formation of a sagittal ridge
      b) A bony prominence at the position of the anterior fontanelle
   iii. Rachitic skeletal deformities manifesting by age 6 months
   iv. Flail chest
   v. Pulmonary insufficiency
d. Late in walking
e. Development of genu valgum
f. Short stature
g. Complications
   i. Recurrent pneumonia
   ii. Increased intracranial pressure
   iii. Renal compromise secondary to:
      a) Hypercalcemia
      b) Hypercalcinuria
      c) Nephrocalcinosis
h. Prognosis:
   i. Fatal in approximately 50% of cases by the age of 1 year
   ii. Survivors
      a) Tend to improve symptomatically.
      b) Deformities persist and often become worse.

4. Childhood form
   a. Appears normal at birth.
   b. Often present after 6 months of age.
   c. History of delayed walking and waddling gait.
   d. Early loss of deciduous teeth (before age of 5 years): the most consistent clinical sign.
   e. Frequent bone pain.
   f. Defective bone mineralization presenting clinically as rickets in children.
   g. Respiratory complications due to rachitic deformities of the chest.
   h. Premature craniosynostosis despite open fontanelle resulting in increased intracranial pressure.
   i. Dolichocephalic skull.
   j. Enlarged joints.
   k. Short stature.
   l. Bone fractures.
   m. Presence of hypercalcemia causes increased excretion of calcium resulting in renal damage.
   n. Prognosis: improving both clinically and radiographically with age in some childhood hypophosphatasia patients.
5. Adult form
   a. Variable age of onset and severity.
   b. Onset usually during middle age.
   c. Defective bone mineralization presents clinically as osteomalacia in adults.
   d. Premature loss of deciduous teeth.
   e. Usually presents clinically with loss of adult teeth.
   f. Multiple fractures secondary to osteomalacia, often after minimal fractures.
   g. Foot pain due to stress fractures of the metatarsals.
   h. Thigh pain due to pseudofractures of the femur.
   i. Delay in healing after a fracture.
   j. Joint pain due to deposition of calcium pyrophosphate dihydrate (chondrocalcinosis).
6. Odontohypophosphatasic form: premature loss of adult teeth; the only physical finding in this form
7. Craniosynostosis
   a. Considered a known feature in the infantile and childhood types of hypophosphatasia (Whyte 1995; Mornet 2007; Collmann et al. 2009), while it is missed in the adult and odontohypophosphatasia forms
   b. Often progressively involves all cranial sutures and poses significant functional risks to the optic nerves, as well as the spinal cord

Diagnostic Investigations

1. Laboratory tests.
   a. Low serum alkaline phosphatase levels in all types of hypophosphatasia
   b. Increased levels of urinary phosphoethanolamine levels
   c. Elevated plasma levels of pyridoxal 5'-phosphate
   d. Normal serum calcium, except in infantile cases where hypercalcemia can be seen due to renal failure
   e. Normal serum phosphate: hyperphosphatemia in various forms of hypophosphatasia reported

2. Skeletal survey (Kozlowski et al. 1976).
   a. Lethal perinatal form
      i. Near absence of skeletal mineralization
      ii. Skull: tiny ossification of occipital and/or frontal bones or complete absence of ossification
      iii. Teeth: very poorly formed
      iv. Spine
         a) Some vertebrae frequently unossified
         b) Occasionally unossified vertebrae
         c) Abnormally shaped vertebrae: rectangular, round, flattened, sagittally cleft, or butterfly-shaped vertebrae
      v. Shortening and bowing of the long and tubular bones
      vi. Diaphyseal spurs
      vii. Skin-covered spurs extending from the medial and lateral aspects of the knee and elbow joints
      viii. Fractures
      ix. Rachitic changes
         a) Pathology most evident at metaphyses as in rickets where growth is most rapid, namely the wrists, knees, hips, and proximal humeri.
         b) Defective, irregular ossification of the metaphysis: the most diagnostic feature of the disease.
         c) Nearly absent provisional zone of calcification.
         d) Irregular widening of the epiphyseal plate.
         e) Grossly irregular ossification of metaphysis giving a "frayed" or "tufted" appearance: a distinguished feature in hypophosphatasia. In rickets, the decalcification is usually regular and may give a "ground glass" effect to the affected metaphysis (metaphyseal cupping).
   b. Infantile form
      i. Deficient skeletal mineralization.
      ii. Congenital bowing of the long bones.
      iii. Bands of decreased density in metaphyses.
      iv. Widened cranial sutures.
      v. Later craniosynostosis: premature craniosynostosis occurs despite an open fontanelle.
      vi. Asymmetrical, moderate to severe rickets-like metaphyseal changes.
      vii. Metaphyseal and epiphyseal ossification defects.
      viii. Distorted bone trabeculation with areas of decreased and increased transradiancy.
      ix. Thin cortical bone.
      x. Diaphyseal spurs.
   c. Childhood form
      i. Mild, asymmetrical, metaphyseal changes resembling rickets or metaphyseal dysplasia
      ii. Distorted bone trabeculation with areas of decreased and increased transradiancy
      iii. Thin cortical bone
      iv. Hypotubulation and bowing of long bones
      v. Stress fractures
      vi. Radiolucent projections from the epiphyseal plate into the metaphysis
   d. Adult form
      i. Pseudofractures often occur in the lateral aspect of the proximal femur: a hallmark of this form
      ii. Osteomalacia
      iii. An increased incidence of poorly healing stress fractures, especially of the metatarsals
   e. Odontohypophosphatasic form: normal radiographic findings
3. Radiography and ultrasound screening for nephrocalcinosis.
4. Histology.
   a. Growth plates
      i. Rachitic abnormalities
      ii. Poorly mineralized and ossified columns with broad osteoid seams in metaphysis
      iii. Osteoblasts lacking membrane-associated alkaline phosphatase activity on histochemical testing, disrupting incorporation of calcium into the matrix
   b. Teeth
      i. A decrease in cementum
      ii. Enlarged pulp chamber
      iii. Incisors tend to be affected
5. Molecular genetic diagnosis: ALPL, the gene-encoding alkaline phosphatase, tissue nonspecific isozyme (TNASALP), is the only gene known to be associated with hypophosphatasia.
   a. Targeted mutation analysis
   b. Sequence analysis

Genetic Counseling

1. Recurrence risk: genetic counseling is complicated by the inheritance that may be autosomal dominant or autosomal recessive, the existence of the uncommon prenatal benign form, and the variable expression of the disease (Simon-Bouy et al. 2008).
   a. Patient's sib
      i. Autosomal recessive: 25%
      ii. Autosomal dominant: not increased unless a parent is affected in which case the recurrence risk is 50%
   b. Patient's offspring
      i. Autosomal recessive: not increased unless a spouse is a carrier in which case the recurrence risk is 50%
      ii. Autosomal dominant: 50%
2. Prenatal diagnosis.
   a. Fetal radiography
   b. Prenatal ultrasonography
      i. 2D-ultrasonography
         a) Failure to visualize a well-defined skull
         b) Other fetal skeletal structures not readily discernable
      ii. 3D-ultrasonography: can demonstrate specific osseous spurs in a lethal form (Sinico et al. 2007)
   c. Assay of the alkaline phosphatase activity: a useful complementary and independent method, especially when a mutation is unidentified and DNA from the index case is unavailable
      i. Assay of the tissue nonspecific alkaline phosphatase activity in chorionic villus samples in the first trimester
      ii. Absent alkaline phosphatase activity in the amniotic fluid and cultured amniotic fluid cells in the second trimester
   d. Prenatal diagnosis and preimplantation genetic diagnosis: mutation analysis of fetal DNA from amniocentesis or CVS where the disease-causing mutation has been identified in the family
3. Management.
   a. No specific treatment available: efforts to effect improved mineralization in patients with hypophosphatasia have not been successful (Barcia et al. 1997).
      i. Nonsteroidal anti-inflammatory drugs for control of the bone pain.
      ii. Dietary phosphate restriction may be helpful (Wenkert et al. 2007).
      iii. Large dose of vitamin D: reversal of improvement in the bony architecture upon withdrawal of the drug (Anderton 1979).
      iv. Oral cortisone: reversal of improvement in serum alkaline phosphatase level and radiographic appearance of the bones upon withdrawal of the drug (Anderton 1979).
      v. Avoid saline solution, furosemide diuresis, steroid therapy, or a low-calcium diet because these approaches may actually worsen bone mineralization and nephrocalcinosis.
      vi. Inhibition of osteoclastic activity with calcitonin: continued demineralization despite returning of normal serum calcium concentration.
      vii. Plasma infusions designed to supplement alkaline phosphatase activity or induce alkaline phosphatase production: not consistently improve bone mineralization.
      viii. Pyridoxine and/or pyridoxal phosphate in neonates with intractable seizures (Balasubramaniam et al. 2010).
   b. A clinical trial of marrow cell transplantation for infantile hypophosphatasia.
      i. A significant, prolonged clinical and radiographic improvement followed soon after receiving a boost of donor marrow cells.
      ii. Biochemical features of hypophosphatasia, however, remain unchanged to date.
      iii. The most plausible hypothesis for the patient's survival and progress: transient and long-term engraftment of sufficient numbers of donor marrow mesenchymal cells forms functional osteoblasts and perhaps chondrocytes, to ameliorate the skeletal disease.
   c. Surgical care.
      i. Rachitic deformities
      ii. Gait abnormalities
      iii. Adult form
         a) Rod placement for pseudofractures of the adult type results in the union and relief of the pain.
         b) Primary bone grafting and plating for midshaft fractures.
         c) Anticipate delayed union of fractures.

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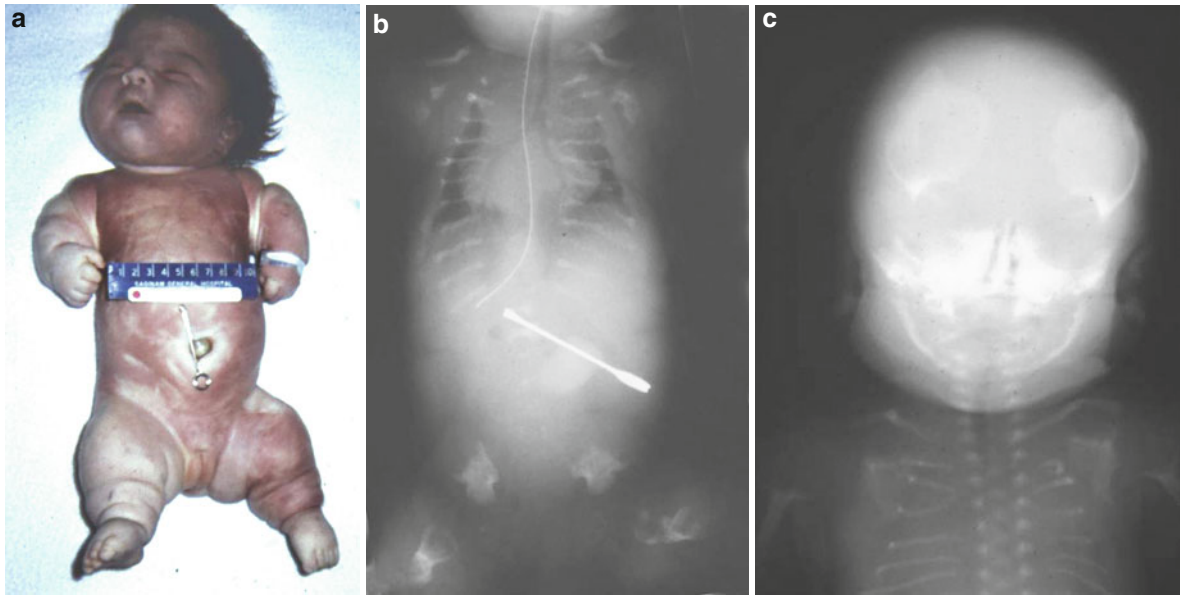

Fig. 1 (**a**–**c**) A neonate with perinatal lethal form of hypophosphatasia showing severe shortening of limbs. Radiograph shows markedly deficient ossification and abnormal bone development similar to achondrogenesis type I

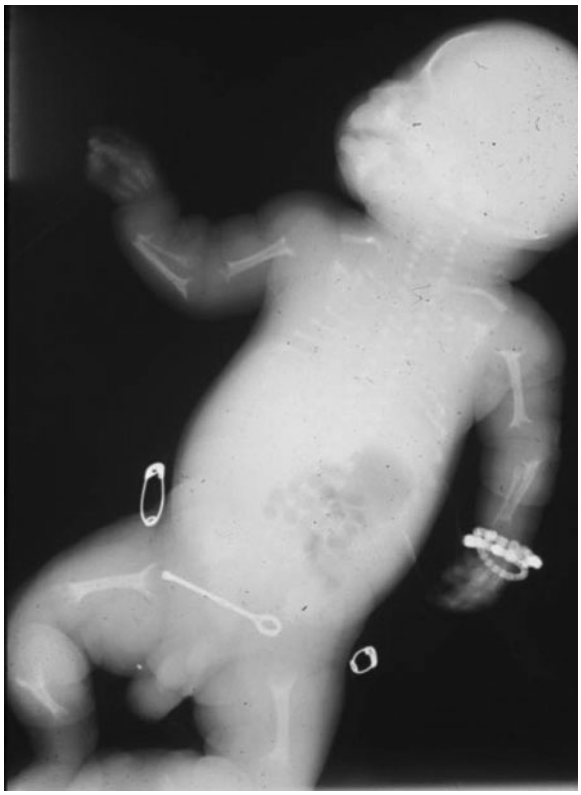

Fig. 2 Radiograph of another neonate with hypophosphatasia shows rickets-like metaphyseal cupping (spurs) and poor mineralization of cranial bones

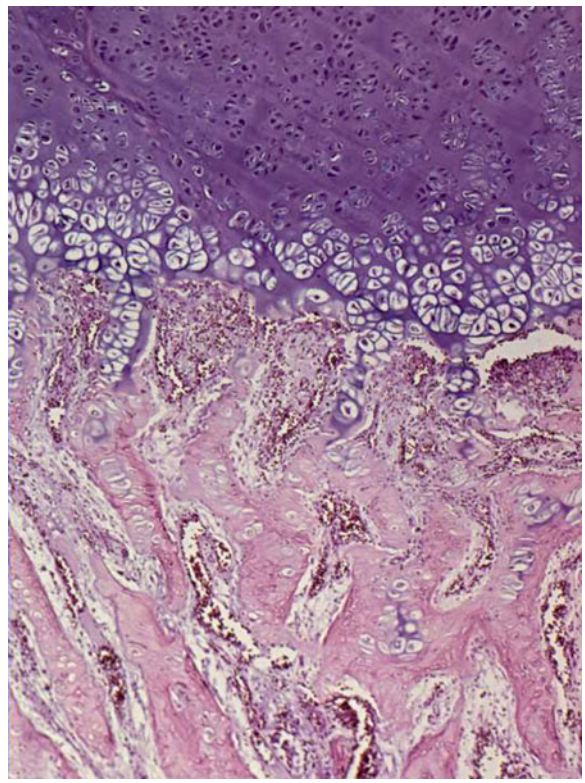

Fig. 3 Photomicrograph of a rib. Broad columns of hypertrophic chondrocytes with osteoid seams are present in the metaphysis. These columns are poorly mineralized and ossified

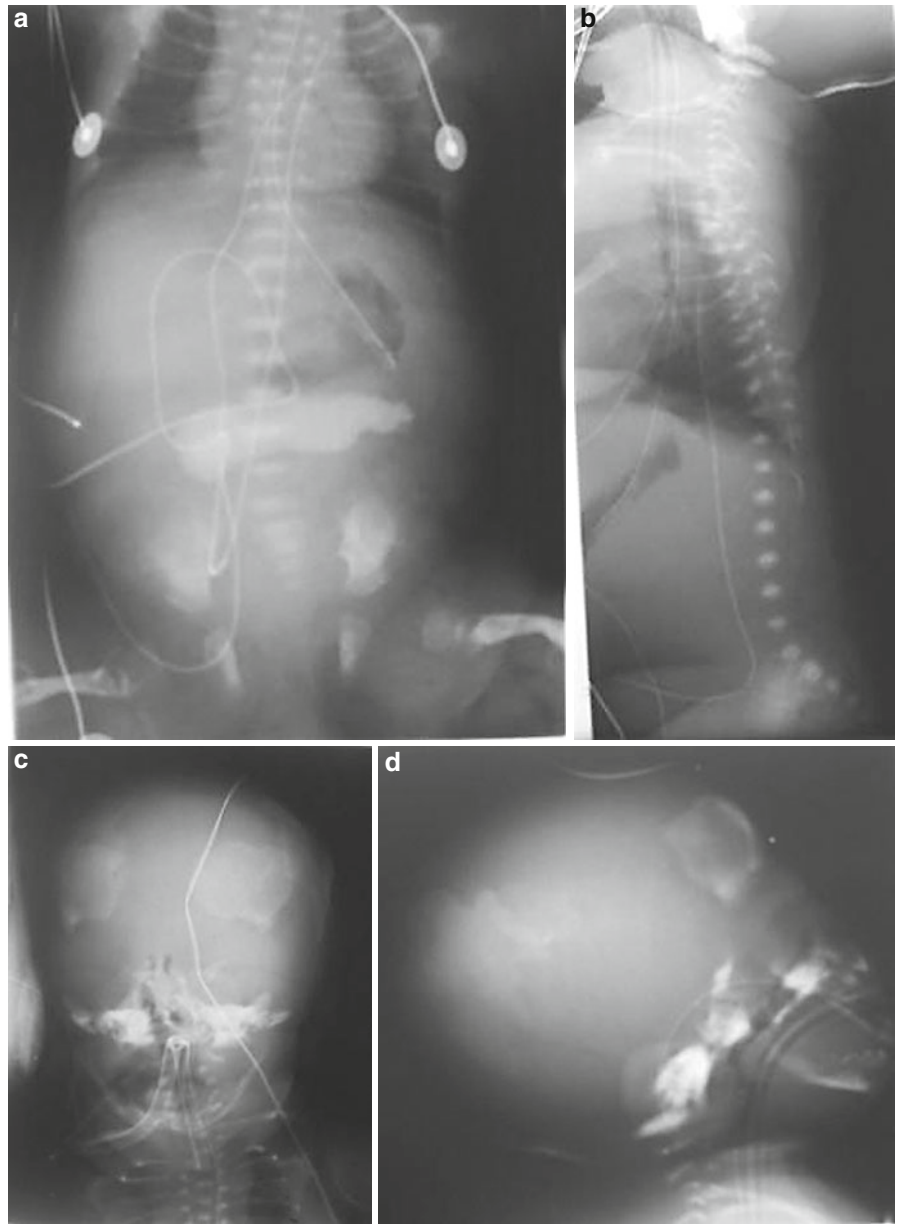

Fig. 4 (**a**–**d**) Radiographs of another neonate with perinatal lethal form of hypophosphatasia showing marked deficient skeletal mineralization, prenatal fracture of the left femur, and abnormal metaphyseal ossification of the proximal femurs

Fig. 5 Childhood hypophosphatasia in two brothers showing short stature and bowed legs

Hypopituitarism

Hypopituitarism is a term used to describe the deficiency of one or more of the hormones of the anterior or posterior pituitary gland. It can vary in severity and age at presentation. These hormonal deficits can also be present as part of a syndrome, with patients manifesting extrapituitary abnormalities such as in the eye and forebrain.

In clinical practice, panhypopituitarism is used to describe patients deficient in growth hormone (GH), gonadotropins, corticotropin, and thyrotropin in whom posterior pituitary function remains intact.

Hypopituitarism is rare, with an estimated annual incidence rate of 4.2 cases per 100,000 and with a prevalence rate of 45.5 per 100,000 (Regal et al. 2001).

Synonyms and Related Disorders

Adrenocorticotropin deficiency; Gonadotropin deficiency; Growth hormone deficiency; Pituitary hormone deficiency; Prolactin deficiency; Thyrotropin deficiency

Genetics/Basic Defects

1. Heterogeneous causes (Schneider et al. 2007; Kelberman and Dattani 2007; Toogood and Stewart 2008)
   a. Brain damage
      i. Traumatic brain injury (trauma to hypophysis)
      ii. Subarachnoid hemorrhage
      iii. Neurosurgery
      iv. Radiation
      v. Stroke
   b. Pituitary tumors
      i. Adenomas
      ii. Others
   c. Non-pituitary tumors
      i. Craniopharyngiomas
      ii. Meningiomas
      iii. Gliomas
      iv. Chordomas
      v. Ependymomas
      vi. Metastases
   d. Infections
      i. Abscess
      ii. Hypophysitis
      iii. Meningitis
      iv. Encephalitis
      v. Tuberculosis
      vi. Syphilis
   e. Infarction
      i. Anoplexia
      ii. Sheehan syndrome
   f. Autoimmune disorders: lymphocytic hypophysitis
   g. Infiltrative processes
      i. Hemochromatosis
      ii. Granulomatous diseases
      iii. Histiocytosis X
   h. Empty sella syndrome
   i. Perinatal insults
   j. Pituitary hypoplasia or aplasia
   k. Genetic causes
   l. Idiopathic causes
2. Genetic causes (mutations) of multiple pituitary hormone deficiencies
   a. *POU1F1* (*PIT-1*) (Andersen and Rosenfeld 2001): genetic combined pituitary hormone

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deficiency (CPHD) caused by mutations within the pituitary-specific transcription factor 1
   i. Hormone deficiencies
      a) GH
      b) Thyrotropin (TSH)
      c) Prolactin
   ii. Inheritance
      a) Autosomal dominant
      b) Autosomal recessive
   iii. Phenotypes
      a) Hormone deficiencies: severe
      b) Thyrotropin secretion: initially normal, but secondary hypothyroidism inevitable
      c) Pituitary size: variable
b. *PROP1* (Sornson et al. 1996): the most common cause of CPHD caused by mutations of *Prophet of PIT1*
   i. Hormone deficiencies
      a) GH
      b) TSH
      c) LH
      d) FSH
      e) Prolactin
      f) Occasionally adrenocorticotropic hormone (ACTH)
   ii. Inheritance: autosomal recessive (AR)
   iii. Phenotypes
      a) Deficiencies tend to be milder than in *POU1F1* mutations
      b) Evolving corticotropin deficiency with increasing age
      c) Enlarged pituitary size with later involution
      d) Can be associated with a mass lesion (Turton et al. 2005)
c. *HESX1* (Dattani et al. 1998)
   i. Hormone deficiencies: range from isolated GH deficiency to panhypopituitarism, including diabetes insipidus
   ii. Inheritance: autosomal dominant (AD), AR
   iii. Phenotypes
      a) May be associated with septo-optic dysplasia, combined pituitary hormone deficiency (CPHD), and isolated growth hormone deficiency.
      b) Mutations result in a variable phenotype: anterior pituitary hypoplasia, ectopic posterior pituitary, and midline forebrain abnormalities.
      c) Environmental factors, such as drugs and alcohol, are implicated.
d. *LHX3* (Netchine et al. 2000)
   i. Hormone deficiencies
      a) GH
      b) TSH
      c) LH
      d) FSH
      e) Prolactin
   ii. Inheritance: AR
   iii. Phenotypes
      a) Elevated and anteverted shoulders giving the appearance of a stubby neck with limited rotation of the head (short rigid cervical spine)
      b) Hypoplasia of anterior pituitary gland
      c) Preservation of corticotropin secretion
(e) *LHX4* (Machinis et al. 2001)
   i. Hormone deficiencies
      a) GH
      b) TSH
      c) Cortisol
   ii. Inheritance: AD
   iii. Phenotypes (MRI of the brain)
      a) Small sella
      b) Persistent craniopharyngeal canal
      c) Hypoplastic anterior pituitary and ectopic posterior pituitary
      d) Pointed cerebellar tonsils
3. Genetic causes (mutations) of isolated pituitary hormone deficiencies
   a. *TBX19* (*TPIT*) (Pulichino et al. 2003)
      i. Hormone deficiencies: corticotropin
      ii. Inheritance: AR
      iii. Phenotypes
         a) Presentation in neonatal period with severe hypoglycemia and prolonged cholestatic jaundice
         b) Undetectable corticotropin and cortisol levels
         c) Failure to respond to corticotropin-releasing hormone
         d) High incidence of neonatal death in affected families
   b. *SOX2* (Maheshwari et al. 1998)
      i. Hormone deficiencies: hypogonadotropic hypogonadism
      ii. Inheritance: de novo mutation reported
      iii. Phenotypes

a) Anophthalmia or microphthalmia
b) Learning difficulties
c) Developmental delay
d) Genital abnormalities
e) Esophageal atresia
f) Sensorineural hearing loss

c. *SOX3* (Hamel et al. 1996; Laumonnier et al. 2002)
i. Hormone deficiencies: isolated growth hormone deficiency
ii. Inheritance: XL recessive
iii. Phenotypes
a) Mental retardation
b) Anterior pituitary hypoplasia
c) Infandibular hypoplasia
d) Midline abnormalities

d. *GHRHR* (Maheshwari et al. 1998)
i. Hormone deficiencies: GH
ii. Inheritance: AR
iii. Phenotypes
a) Short stature
b) Proportionate growth
c) Anterior pituitary hypoplasia

e. *GH1* (Cogan et al. 1993)
i. Hormone deficiencies: GH
ii. Inheritance: AR
iii. Phenotypes
a) Short stature
b) Abnormal facies
c) Respond to exogenous GH treatment, but may develop antibodies

f. *KAL-1* (Legouis et al. 1991; Franco et al. 1991)
i. Hormone deficiencies
a) GnRH
b) FSH
c) LH
ii. Inheritance: X-linked
iii. Phenotypes
a) Failed or arrested puberty
b) Anosmia
c) Synkinesis
d) Unilateral renal agenesis

g. *FGFR-1* (*KAL-2*) (Dode et al. 2003)
i. Hormone deficiencies
a) GnRH
b) FSH
c) LH
ii. Inheritance: AD
iii. Phenotypes: failed or arrested puberty

h. *GNRHR1* (Beranova et al. 2001)
i. Hormone deficiencies
a) FSH
b) LH
ii. Inheritance: AR
iii. Phenotypes: variable, determined by the sensitivity of the mutant receptor to GnRH

i. *DAX1* (Lin et al. 2006)
i. Hormone deficiencies
a) FSH
b) LH
ii. Inheritance: AR, X-linked
iii. Phenotypes
a) Presents initially with severe neonatal hypoadrenalism
b) Subsequently fail to enter puberty or suffer delayed or arrested puberty

j. *GPR54* (de Roux et al. 2003)
i. Hormone deficiencies
a) FSH
b) LH
ii. Inheritance: AR
iii. Phenotypes: presents with absent or delayed puberty

k. *POMC* (Krude et al. 1998)
i. Hormone deficiencies: corticotropin
ii. Inheritance: AR
iii. Phenotypes (clinical triad)
a) Early-onset obesity
b) Adrenal hypoplasia
c) Cortisol deficiency

l. *Thyrotropin-β* (Vuissoz et al. 2001)
i. Hormone deficiencies: thyrotropin
ii. Inheritance: AR
iii. Phenotypes: severe congenital hypothyroidism if not detected and treated early on

Clinical Features

1. Nonspecific symptoms (Toogood and Stewart 2008)
a. Feeling of general ill health
b. Being abnormally tired
c. Increased lethargy
d. Feeling cold
e. Weight loss
f. Reduced appetite
g. Abdominal pain

2. Symptoms related to local effects of any underlying tumor
   a. Headaches
   b. Visual disturbance (typically a bitemporal hemianopia)
   c. Cerebrospinal fluid rhinorrhea
3. GH deficiency
   a. Neonates with congenital GH deficiency (or hypopituitarism)
      i. Severe neonatal hypoglycemia often associated with convulsions, presenting most frequently in the first 24 h of life (birth trauma)
      ii. Prolonged conjugated hyperbilirubinemia
      iii. Hypothermia
      iv. Possibly a micropenis (Ogilvy-Stuart 2003)
   b. Neonates with midline birth defects should be considered at risk for isolated or multiple pituitary hormone deficiencies
   c. Older babies who escape early diagnosis may present with failure to thrive and poor weight gain
   d. Older children
      i. Proportional short stature with height more than 2–3 standard deviations (SD) below the mean for the age
      ii. Reduced growth velocity for their age
      iii. Delayed bone maturation in the absence of an inherited skeletal dysplasia or chronic disease
      iv. Characteristic craniofacial appearance in patients with severe GH deficiency: a prominent forehead and depressed midface development caused by the lack of GH effect on endochondrial growth at the base of the skull, occiput, and sphenoid
      v. Delayed dentition
      vi. Presence of other features attributable to the underlying etiology of the GH deficiency
   e. Adults
      i. Multiple symptoms and pathophysiologic changes affecting a variety of biologic systems (none are pathognomonic) are attributed to GH deficiency in adult life (Molitch et al. 2006).
      ii. Impaired quality of life (Burman et al. 1995; Holmes and Shalet 1995)
         a) Complaining of tiredness
         b) Lack of energy
         c) Emotional lability
         d) Reduced sleep quality
         e) A degree of disability consistent with psychiatric illness requiring treatment (up to 30% of patients) (McGauley et al. 1990)
         f) Patients who have childhood-onset GH deficiency do not seem to suffer the same degree of impairment in quality of life as those who have adult-onset GH deficiency (Attanasio et al. 1997)
4. Gonadotropin (LH, FSH) deficiency
   a. Male infants with congenital hypogonadotropic hypogonadism: effect of relative androgen deficiency occurring during the third trimester
      i. Unilateral or bilateral cryptorchidism
      ii. Microphallus
   b. Adolescent boys
      i. Pubertal development
         a) Fail to initiate, or abnormal with failure to progress normally
         b) Testicular volumes vary between prepubertal boys (<4 cm^3) and normal adult size
         c) Pubic hair (mediated by testicular or adrenal androgens): present but unlikely to be normal
   c. Adolescent girls
      i. Gonadotropin deficiency becoming apparent in teenage years
      ii. Delayed breast development
      iii. Primary amenorrhea
   d. Isolated gonadotropin deficiency
      i. Normal growth during childhood
      ii. Slow growth during adolescence when the growth spurt fails to occur
      iii. Epiphyses, however, fail to fuse at the usual age, and the long bones continue to grow, ultimately resulting in tall stature and a eunuchoid habitus
   e. Men with acquired gonadotropin deficiency during adult life
      i. Usually achieve a normal height with proportionate growth.
      ii. Adult secondary sexual characteristics are present, although the testes may become soft and reduced in size because the FSH deficiency causes atrophy of the seminiferous tubules.

iii. Slowing of beard growth with less frequent shaving.
iv. Loss of body hair.
v. Skin becoming thin with development of thin wrinkles if the gonadotropin deficiency is severe and prolonged.
vi. Libido may be reduced, and the ability to achieve and maintain an erection may be compromised.
vii. Testosterone deficiency can lead to nonspecific symptoms, e.g.:
a) Tiredness
b) Reduced muscle bulk
c) Reduced exercise capacity
viii. Decreased bone mineral density with a risk for:
a) Osteopenia or osteoporosis
b) Increased fractures
ix. Azoospermia: usually present in prolonged gonadotropin deficiency, although there are exceptions.
x. Symptoms of hypogonadotropism: nonspecific and may not become evident for many years, particularly if fertility is not an issue.

f. Women with secondary gonadotropin deficiency
i. Diagnosed quickly when oligomenorrhea or amenorrhea develops.
ii. Symptoms of estrogen deficiency.
a) Vaginal dryness
b) Dyspareunia
c) Hot flashes
d) Breast atrophy
iii. Pubic and axillary hair remains unless there is coexistent corticotropin deficiency with adrenal androgen deficiency.

5. Adrenocorticotropin (ACTH) deficiency
a. Results in secondary hypoadrenalism.
b. The most serious of anterior pituitary hormone deficits.
c. During an intercurrent illness.
i. May develop an adrenal crisis with severe hyponatremia and hypovolemic shock
ii. Can result in death if not diagnosed and treated appropriately
d. Decompensation and shock occur during periods of illness or physical stress, such as surgery.
e. Other symptoms of cortisol deficiency.
i. Lethargy
ii. Fatigue
iii. Weight loss
iv. Nonspecific abdominal pain
v. Hypoglycemia
a) Feelings of hunger
b) Light-headedness
c) Sweating
d) Hypotension and complain of postural symptoms
vi. Absence of the pigmentation associated with primary adrenal failure in patients with corticotropin deficiency: the skin may be pale with an alabaster-like appearance (Arlt and Allolio 2003)
f. Patients who have hypopituitarism are protected somewhat from developing severe, acute hypoadrenalism compared with patients who have primary adrenal failure, as the angiotensin-aldosterone axis remains intact.

6. Thyrotropin (TSH) deficiency
a. Symptoms and signs
i. Similar to those of primary hypothyroidism but usually are less severe, as there often is some residual thyrotropin secretion
ii. Tiredness
iii. Cold intolerance
iv. Weight gain
v. Constipation
vi. Dry skin and hair are common features
b. With the exception of traumatic brain injury (TBI), thyrotropin deficiency usually occurs late in the evolution of hypopituitarism and often is seen with other anterior pituitary hormone deficits.
c. In children, secondary hypothyroidism contributes to poor growth, delayed bone age, and failure of secondary dentition.

7. Prolactin deficiency
a. Prolactin is inhibited predominately by dopamine; as a consequence, prolactin levels frequently are raised in the presence of hypothalamic-pituitary disease because of compression or transection of the pituitary stalk.
b. Hypoprolactinemia is found in patients who have mutations of the transcription factors, PIT1 and PROP1.
c. However, in patients with structural pituitary disease, prolactin deficiency is a marker of

severe pituitary damage (Mukherjee et al. 2003; Toledano et al. 2007).
   d. In women, prolactin deficiency can cause failure of lactation in the postpartum period.
   e. Although prolactin is an important hormone in the animal world with multiple identified roles in growth, water homeostasis, reproduction, behavior, and growth and immune modulation (Bole-Feysot et al. 1998), a phenotype attributable to prolactin deficiency in man has yet to be established.
8. *PROP1*-related combined pituitary hormone deficiency (Phillips et al. 2005)
   a. Most affected individuals are ascertained because of growth failure and failure to thrive starting in infancy or early childhood.
   b. Hypothyroidism
      i. Usually mild
      ii. Occurs in later infancy and childhood
   c. Absent or delayed and incomplete secondary sexual development with infertility
      i. Males: usually have a small penis and small testes
      ii. Females: some experience menarche, but subsequently require hormone replacement therapy
   d. GH deficiency
      i. Neonatal hypoglycemia
      ii. Proportionate short stature
      iii. Delayed bone age
   e. TSH deficiency
      i. Suspected in children with growth failure, poor weight gain, and delayed bone maturation
      ii. Large posterior fontanelle
      iii. Jaundice lasting more than 1 week after birth
      iv. Macroglossia
      v. Hoarse cry
      vi. Distended abdomen
      vii. Umbilical hernia
      viii. Hypotonia
   f. LH and FSH deficiency
      i. Newborn males
         a) Micropenis without hypospadias
         b) With or without cryptorchidism
      ii. Adolescent males
         a) Delayed onset of puberty (after age 14)
         b) Cessation of secondary sexual development
      iii. Adolescent females: lack of breast development or menses by age 14
   g. Prolactin deficiency: suspected in females with impaired lactation
   h. ACTH deficiency
      i. Less common
      ii. Usually occurs in adolescence or adulthood
      iii. Suspected in children with persistent weakness, abdominal pain, anorexia, and weight loss
      iv. Signs of acute ACTH deficiency
         a) Acute hypotension
         b) Dehydration
         c) Shock accompanied by hyponatremia, hyperkalemia, and hypoglycemia
9. *POU1F1* combined pituitary hormone deficiency (Phillips et al. 2005)
   a. Normal birth weight and birth length and uncomplicated perinatal course
   b. Growth failure in early infancy in most affected individuals
   c. Growth hormone deficiency: usually severe
   d. Proportional short stature
   e. Hypothyroidism
      i. Can be congenital
      ii. Can be mild and later onset
      iii. Progressive loss of TSH occurring over time
   f. Distinctive facies (Aarskog et al. 1997)
      i. Prominent forehead
      ii. Marked midface hypoplasia
      iii. Depressed nasal bridge
      iv. Deep-set eyes
      v. Short nose with anteverted nostrils
   g. MRI of the brain: pituitary usually appears hypoplastic

Diagnostic Investigations

1. Brain MRI (Toogood and Stewart 2008)
   a. To exclude tumors and other lesions of the sellar and parasellar region after confirmation of hypopituitarism.
   b. Normal MRI of the sellar and parasellar region cannot exclude hypopituitarism.
2. Growth hormone deficiency
   a. The definition of GH deficiency in adulthood differs from that in childhood.

i. In children, the diagnosis of GH deficiency is made in the presence of a reduced growth velocity.
ii. In adults, the clinical features attributed to GH deficiency are numerous and nonspecific; there is no single pathognomonic feature that alerts clinicians to the diagnosis.
iii. Diagnosis of GH deficiency should be considered only in adults who have a history of pituitary disease, secondary to neoplastic disease, surgery, or cranial radiation or in those who have had a history of treatment with GH during childhood and adolescence (Growth Hormone Research Society 1998).
iv. Results of dynamic tests of GH status are affected by obesity (all stimuli) (Shalet et al. 1998) and age (Toogood et al. 1998) and could lead to an inappropriate diagnosis.

b. The insulin tolerance test (ITT)
i. Considered the gold standard used to diagnose GH deficiency in adults, using a diagnostic threshold of 3 mg/L.
ii. Not suitable for use in all patients and is contraindicated in patients who have a history of seizures or ischemic heart disease.
iii. Consequently, the majority of endocrinologists do not use the ITT in patients over 65 in case undiagnosed heart disease is present.

c. Insulin-like growth factor (IGF-1)
i. A GH-dependent peptide, although the level of dependence seems to diminish with increasing age.
ii. In young adults who have childhood-onset GH deficiency, 95% (de Boer et al. 1994) have serum IGF-1 below the normal range, whereas 82% of GH-deficient patients over 60 years old have a normal IGF-1 (Toogood et al. 1998).

3. Gonadotropin deficiency
a. Women with gonadotropin deficiency
i. In women of postmenopausal age, low or undetectable levels of FSH and LH are sufficient to make a diagnosis.
ii. In younger women, amenorrhea with low estradiol levels and low or normal gonadotropins is consistent with the diagnosis of gonadotropin deficiency.
iii. Failure to induce a withdrawal bleed after a progesterone challenge confirms the presence of a hypoestrogenic state.

b. Men with gonadotropin deficiency
i. Diagnosed in the presence of low or normal serum gonadotropin levels and a low serum testosterone.
ii. Semen analysis is useful when considering fertility and may demonstrate oligospermia or azoospermia.

4. Adrenocorticotropin deficiency
a. The activity of the hypothalamic-pituitary-adrenal (HPA) axis exhibits a diurnal rhythm; serum cortisol levels often are undetectable at midnight during sleep, rising and reaching peak at approximately 5:00 AM, and declining gradually over the course of the day
b. The insulin tolerance test (ITT)
i. A peak response to hypoglycemia (blood glucose 2.2 mmol/L) of greater than 20 mg/dL: considered a normal response (Tuchelt et al. 2000; Nelson and Tindall 1978)
ii. Tests the integrity of the whole HPA axis and has the advantage of simultaneously assessing the GH status of patients
c. Short Synacthen test (SST): an alternative test to ITT
i. Measures the serum cortisol response after an intramuscular injection of cosyntropin (Synacthen) (250 mg) (Stewart et al. 1988; Clayton 1996; Kane et al. 1995)
ii. Based on the premise that corticotropin deficiency results in atrophy of the adrenal cortex and subsequently becomes unresponsive to a single pulse of corticotropin
iii. A serum cortisol value of 22 mg/dL (550 nmol/L) or higher 30 min after administration of Synacthen: consistent with normal corticotropin reserve
iv. Risk for a false negative result (a perception that patients have normal corticotropin reserve): the SST should not be performed until at least 6 weeks after surgery or an apoplectic event

5. Thyroid-stimulating hormone deficiency
a. Diagnosed based on the presence of a low or normal serum thyrotropin measurement with a low serum free thyroxine (fT4) level.

b. Measurement of serum fT3: not required but may be low or normal.
c. In patients treated with radiotherapy, sequential falls in the serum fT4 toward the lower end of the normal range associated with evolving symptoms of hypothyroidism may be sufficient to warrant instigation of levothyroxine.
d. The thyrotropin response to thyrotropin-releasing hormone: used less frequently since the introduction of sensitive thyrotropin assays.

6. *PROP1*-related combined pituitary hormone deficiency (CPHD) (Phillips et al. 2005)
   a. Testing for deficient secretion of GH, TSH, LH, FSH, prolactin, and ACTH: establishes the diagnosis
   b. *PROP1* is the only gene associated with *PROP1*-related CPHD
      i. Targeted mutation analysis for the common recurring deletion in which three AG repeats are reduced to two repeats: available clinically
      ii. This mutation accounts for 55% of familial cases and 12% of nonfamilial cases

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal dominant inheritance
         a) Recurrence risk of 50% if a parent is affected
         b) Low recurrence risk if both parents are normal
      ii. Autosomal recessive inheritance: risk of recurrence 25%
      iii. X-linked recessive: 50% of male sibs affected if the mother is a carrier
   b. Patient's offspring
      i. Autosomal dominant inheritance: a 50% risk of offspring affected.
      ii. Autosomal recessive inheritance: low recurrence risk unless the spouse is affected or a carrier.
      iii. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal.
2. Prenatal diagnosis
   a. Prenatal diagnosis is possible for pregnancies at increased risk for various conditions such as *PROP1* or *POU1F1* CPHD when the disease-causing mutation in the family is known.
   b. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified in an affected family member.
3. Management (Toogood and Stewart 2008)
   a. Pituitary hormone replacement therapy
      i. Growth hormone replacement
         a) GH replacement in children who have GH deficiency results in an increase in linear growth, and its use for that purpose is accepted universally.
         b) Recombinant human GH has allowed GH replacement to be used in adults.
         c) In the event of side effects (peripheral edema, arthralgia, and headaches) during the titration phase, the dose of GH should be reduced or, if severe, treatment should be withdrawn.
      ii. Sex steroid and gonadotropin replacement
         a) The aim of androgen replacement in men: to maintain secondary sexual characteristics, restore a sense of well-being, prevent loss of and optimize bone mass, and improve sexual function (Bhasin et al. 2006).
         b) Women who have gonadotropin deficiency require sex steroid replacement to alleviate the symptoms of estrogen deficiency and to optimize bone health.
         c) Induction of fertility can be achieved in men and women using exogenous gonadotropins. In men, human chorionic gonadotropin can be used initially to stimulate spermatogenesis (Vicari et al. 1992). In women, ovulation induction is initiated with FSH or human menopausal gonadotropin.
      iii. Adrenocorticosteroid replacement
         a) Cortisol: Hydrocortisone is the glucocorticoid of choice for patients who have secondary adrenal insufficiency

   b) Optimize and monitor glucocorticoid replacement therapy
  iv. Dehydroepiandrosterone
   a) In addition to cortisol, the adrenal cortex produces androgens regulated by corticotropin.
   b) Patients who have corticotropin deficiency also are deficient in dehydroepiandrosterone (DHEA) (Arlt et al. 1999).
  v. Thyroxine replacement
- b. Long-term consequences of hypopituitarism
  i. Patients who have hypothalamic-pituitary disease and are receiving a combination of sex steroids, glucocorticoids, and thyroxine, but not GH replacement, for a range of anterior pituitary hormone deficiencies have an approximately twofold increase in mortality compared with the general population (Rosen and Bengtsson 1990; Bates et al. 1996; Tomlinson et al. 2001).
  ii. In the largest study to date, there was an increase in deaths from cardiovascular, cerebrovascular, and respiratory disease (Tomlinson et al. 2001).
  iii. GH replacement therapy improves short-term individual cardiovascular risk profiles.
- c. Long-term follow-up of patients with hypopituitarism
  i. Continued follow-up under the care of a physician (endocrinologist) who has expertise in the field
  ii. Annual assessment to determine their cardiovascular risk once hormone replacement treatments are optimized
  iii. Attention to blood pressure and cholesterol levels and treatment with antihypertensives and cholesterol lowering agents instigated as appropriate

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Fig. 1 A 16-year-old female was evaluated for pituitary hormone deficiency. She had short stature for which she received growth hormone therapy since 3 years of age. MRI scan of the brain showed a very small (hypoplastic) pituitary gland. Endocrine investigations revealed the following: low serum IGF-1 (somatomedin-C): <10 ng/mL (normal 11–206 ng/mL); low free T4: 0.67 ng/dL (normal 0.71–1.85 ng/dL); low TSH: 0.02 μU/mL (normal 0.47–5.01 μU/mL); normal cortisol: 7.5 μg/dL (normal 3.0–21 μg/dL); low ACTH-ICMA: 9.0 pg/mL (normal 10.0–60.0 pg/mL); low estradiol: < 0.5 ng/dL (normal 0.7–6.0 ng/dL); low FSH: 1.3 mIU/mL (normal 1.5–12.8 mIU/mL); normal LH: 0.38 mIU/mL (normal 0.10–12.0 mIU/mL). Molecular genetic testing for *POU1F1* gene mutation revealed no sequence variants. However, a different genetic basis for combined pituitary hormone deficiency cannot be ruled out

Fig. 2 A 6-year-old boy was evaluated for pituitary hormone deficiency. He had a history of hypoglycemia and a micropenis. He was noted to be very short, for which he received growth hormone shots daily. He was also treated for hypothyroidism. Past lab results: TSH: 3.16 μU/mL; low free T4: 0.56 ng/dL; normal IGF-1: 66 ng/mL; low IGFBP-3: 0.7 mg/L; normal cortisol: 5.5 μg/dL; normal ACTH-ICMA: 17 pg/mL. Molecular genetic testing for *POU1F1* gene mutation showed no sequence variation

I(1p), I(1q) Syndrome

In 1999, Chen et al. first described uniparental (paternal) isodisomy, resulting from 46,XX,i(1p),i(1q) in a woman with short stature, ptosis, micro/retrognathia, myopathy, deafness, and sterility.

Synonyms and Related Disorders

I(1p), I(1q) uniparental (paternal) isodisomy; Isochromosome 1p, isochromosome 1q syndrome

Genetics/Basic Defects

1. Uniparental disomy (UPD): inheritance of both homologues from one parent. Several types of errors in chromosome segregation during gamete formation may be responsible for uniparental disomy (Spence et al. 1988).
2. Uniparental isodisomy: caused by isochromosome formation from misdivision of the centromere (Bernasconi et al. 1996; Eggerding et al. 1994; Lindenbaum et al. 1991; Shaffer et al. 1997). Although maternal UPD (Pulkkinen et al. 1997; Turner et al. 2007) and paternal UPD (Gelb et al. 1998; Takizawa et al. 2000) of chromosome 1 have been reported previously, none of these involved an isochromosome.
3. Cytogenetic analysis from the peripheral blood of the patient demonstrated one i(1p) and one i(1q) without normal chromosome 1 homologues (Figs. 2–4, Table 1).
4. The most likely mechanism of formation of the rearranged chromosomes in our patient (Fig. 5) is as follows:
   a. The zygote contained a chromosome 1 from the father and none from the mother due to nondisjunction resulting in a monosomy 1 conceptus.
   b. Subsequently, misdivision at the centromere may have occurred, leading to two isochromosomes, one of each chromosome arm.
   c. At the next mitotic division, both went into the same daughter cell.
   d. In the following cell cycle, normal replication took place. This would produce two isochromosomes, made up of one i(1p) and one i(1q), with uniparental isodisomy.
5. Additionally, many mechanisms could account for the finding of isochromosomes, as put forward by Bernasconi et al. (1996) regarding two isochromosomes and UPD 2. Except for the possibility of homozygosity for recessive mutations, maternal uniparental disomy 2 appears to have no adverse impact on the phenotype.
6. Mechanisms of formation of the two isochromosome, maternal i(2q) and paternal i(2p) (Baumer et al. 2007):
   a. The initial maternal meiotic I error may have been a nondisjunction event of chromosome 2.
   b. Trisomy rescue may have occurred during the recombination event that led to the isochromosomes or, alternatively, the formation

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of the maternal i(2q) preceded that of the paternal i(2p). In this case, the formation of the paternal i(2p) would rescue the trisomy 2q and monosomy 2p.

c. A third possibility: the initial meiotic I rearrangement consisted in the formation of the maternal isochromosome; rescue of the trisomy 2q/monosomy 2p would have occurred postzygotically through formation of a paternal i(2p).

7. To the best of our knowledge, our patient is the first case of uniparental isodisomy resulting from i(1p) and i(1q).
   a. Our patient, therefore, has allelic homozygosity for all paternal chromosome 1 loci, demonstrated in part by our molecular studies.
   b. However, the possibility of areas of heterodisomy through meiotic recombination likely exists.
   c. The patient's abnormal phenotype is most likely due to unmasking of rare recessive mutations through isodisomy, but the possibility of genomic imprinting and the presence of mosaicism cannot be ruled out.
   d. The presence of myopathy in this patient suggests the possibility that the potential gene(s) involved may be localized on chromosome 1.

Clinical Features

1. Short stature
2. Bilateral conductive hearing loss
3. Facial features
   a. Downward slant of palpebral fissures
   b. Bilateral ptosis
   c. Malar hypoplasia
   d. Severe micro/retrognathia
4. High-arched palate
5. Cervical vertebral anomaly
6. Slightly short fingers
7. Scoliosis
8. Normal intelligence
9. Normal secondary sex characteristics
10. Menarche at 11 years with regular menstruation but never conceived in three marriages with different partners.

Diagnostic Investigations

1. Cytogenetic analyses: to demonstrate one i(1p) and one i(1q) without normal chromosome 1 homologues by:
   a. GBG banding
   b. CBG banding
   c. FISH analysis using whole chromosome 1 probe
2. Molecular investigations to demonstrate isochromosomes with complete homozygosity of either paternal or maternal markers

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: The presence of two isochromosome 1s would virtually exclude viable offspring since either duplication of the long arm with deletion of the short arm or duplication of short arm with deletion of long arm would be lethal to the fetus.
2. Prenatal diagnosis: demonstration of i(1p), i(1q) without two normal chromosome 1s by either CVS or amniocentesis
3. Management: supportive

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Table 1 Genotype analysis of the patient and her parents with chromosome 1 markers*

Markers	Location	Mother	Patient	Father	Informative
D1S214	1p36.23-p36.33	13	24	24	*
D1S186	1p34	12	12	12	
D1S220	1p33-p31.3	24	13	13	*
D1S550	1p31	13	24	24	*
D1S162	1p32	24	13	13	*
D1S188	1p22	12	22	22	
D1S248	1p13-1p21	22	11	11	*
D1S514	1p13	13	24	24	*
D1S2347	1q21	13	24	24	*
D1S1589	1q25	12	12	12	
D1S422	1q31.3	12	12	12	
D1S103	1q32	12	12	12	
D1S102	1q32-q44	12	12	12	
D1S459	1q42.12	13	22	22	*

The polymorphic markers used in the analysis are shown on the left, with fully informative ones indicated by *asterisks* (*) on the right, and their cytogenetic locations noted in the second column

Fig. 1 (**a**, **b**) A 43-year-old woman was referred for evaluation because of minor facial anomalies, myopathy, sterility, short stature, hearing loss, downward slant of palpebral fissures, bilateral ptosis, severe micro/retrognathia, high-arched palate, and scoliosis

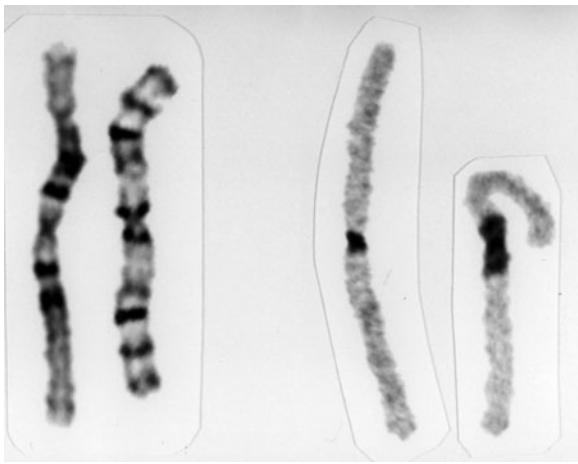

Fig. 2 Cytogenetic analyses utilizing GTG and CBG bandings showed presence of one i(1p) and one i(1q) without normal chromosome 1 homologues

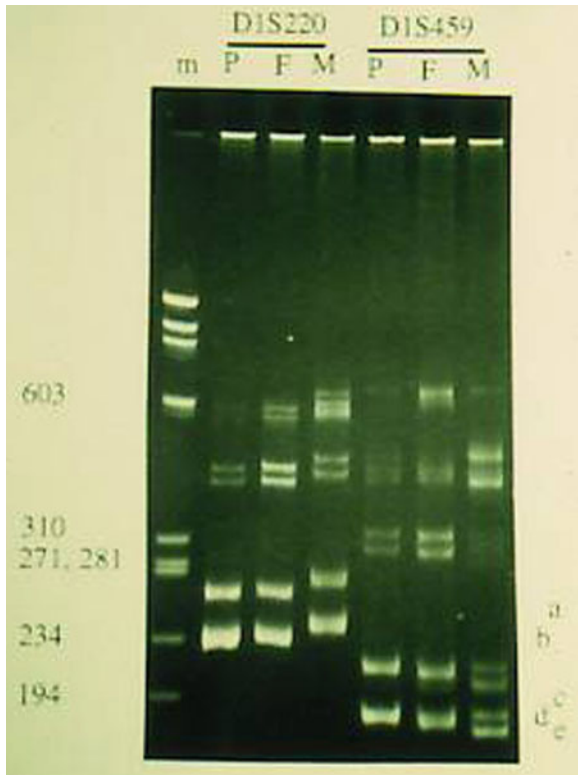

Fig. 4 PCR analyses of chromosome 1 markers (D1S220, D1S459) indicated that the patient (P) inherited b allele (using D1S220) and d allele (using D1S459) from the father (F) but none (a, c, or e alleles) from the mother (M) (D1S214, D1S550, D1S162, D1S188, D1S248, D1S514, and D1S2347 data not shown). The numbers on the left are standard marker size in bp

Fig. 3 Fluorescence in situ hybridization analysis showed hybridization to only two chromosomes, consistent with the G-banded interpretation of i(1p) and i(1q). To the best of our knowledge, this is the first case of isochromosomes 1p and 1q replacing the two normal chromosome 1s

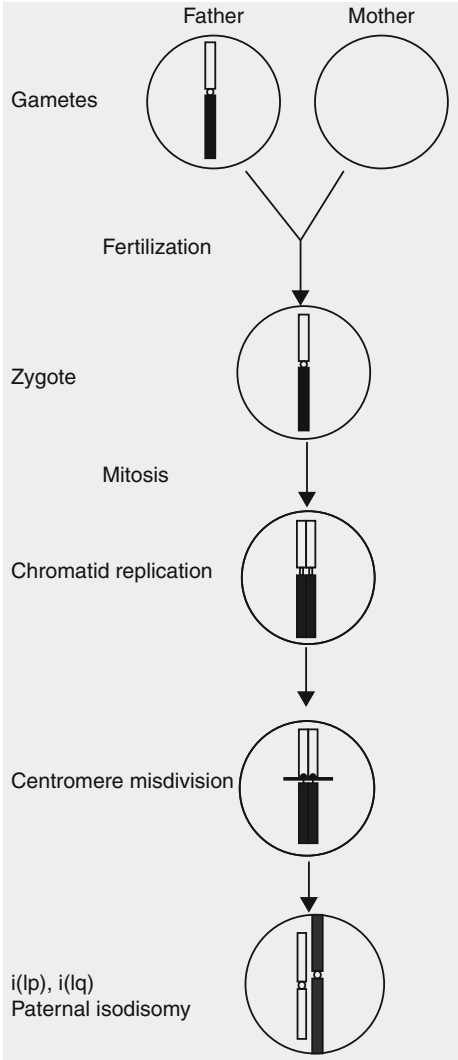

Fig. 5 Mechanism of i(1p) and i(1q) formation resulting in uniparental (paternal) isodisomy

Idic(Yq) Syndrome

Dicentric chromosomes are among the most common structural changes of the Y chromosome (deletions, rings, Y-autosomal or Y–X translocations, isochromosomes, and dicentrics). Among these structural abnormalities, dicentric Y chromosomes are the most commonly found (Hsu 1994; Yoshida et al. 1997).

The dicentric Y chromosomes have two different types: dic(Yq), resulting from the fusion between the short arms of two Y chromosomes in which some Yp material is maintained, and dic(Yp) in which only the Yq arms fuse (Codina-Pascual et al. 2004). If the dicentric has completely symmetric arms, it is considered an isodicentric chromosome. The sites of breakage and fusion at Yp and Yq are variable (Robinson et al. 1999).

Synonyms and Related Disorders

Isodicentric chromosome Yq syndrome

Genetics/Basic Defects

1. Isochromosome (DesGroseilliers et al. 2006)
   a. A chromosome with identical chromosome material in which two arms are mirror images and are of equal length.
   b. An isochromosome can be monocentric or dicentric.
2. Isodicentric chromosomes (dicentric isochromosomes)
   a. Likely resulting from a single break in the paracentric region followed by chromatid duplication and the joining of chromatids from one side of the break (Guevarra et al. 2009).
   b. Usually unstable during cell division and remain so until one of their centromeres is inactivated (Daniel et al. 1980; Therman et al. 1986), resulting in various types of cell lines (Kohn et al. 1997).
   c. Consequently, most reported patients have alternate cell lines, including 45,X (95% of cases) (Bouayed Abdelmoula and Amouri 2005a).
   d. The resulting phenotype depends on the proportion of each cell line and on the localization of the breakpoints (Alvarez-Nava et al. 2003; Bouayed Abdelmoula and Amouri 2005b).
   e. The most likely mechanism of formation of the isodicentric chromosome (Bouayed Abdelmoula and Amouri 2005a).
      i. An isochromatid break, followed by a U-type exchange.
      ii. Breakpoints in the short arm lead to a duplication of the entire long arm and a part of the short arm.
      iii. Breakpoints in the long arm lead to the duplication of the entire short arm and part of the long arm.
3. Isodicentric Y chromosome [idic(Y)]
   a. Isodicentric Y chromosome: formed by homologous crossing over between opposing arms of palindromes on sister chromatids (Lange et al. 2009).
      i. These ectopic recombination events occur at nearly all Y-linked palindromes.
      ii. Intrapalindrome sequence identity is maintained via noncrossover pathways of homologous recombination.
      iii. DNA double-strand breaks that initiate these pathways can be alternatively resolved

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by crossing over between sister chromatids to form idic(Y) chromosomes, with clinical consequences ranging from spermatogenic failure to sex reversal and Turner syndrome.

b. Isodicentric Yq (Guevarra et al. 2009).
   i. Refers to a dicentric Y chromosome with two complete long arms and two symmetric incomplete portions of the short arms, arranged in a mirror image.
   ii. The breakpoints in the short arm of Y.
   iii. When two centromeres are not closely located, only one is active; the other is suppressed.

c. Most dicentric Y chromosomes (90%) are present in mosaic form due to the instability of isodicentric chromosomes during cell division (Kohn et al. 1997).
   i. The mosaicism may be more or less complex depending on its meiotic or postzygotic origin and on its mitotic stability, and it usually includes a 45,X, in addition to idic(Y), idic(Y)*x*2, del(Y), or 46,XY cell lines (Ying and Ives 1971; Daniel et al. 1980; Chandley et al. 1986; Stankiewicz et al. 2001; Codina-Pascual et al. 2004; Bouayed Abdelmoula and Amouri 2005a).
   ii. Errors occurring during gametogenesis, before the spermatid stage, or in the first mitotic division after fertilization would result in a mosaicism without a normal 46, XY cell line.
   iii. Errors occurring after the first zygotic division, a normal 46,XY cell line can be present (Fernandez et al. 2002).
   iv. Patients carrying a dicentric Y chromosome have a wide range of somatic, genital, and gonadal phenotypic manifestations, depending on the structure of the dicentric Y chromosome, the Yp and Yq breakpoints, and the types of mosaicism (Tuck-Muller et al. 1995).
   v. Of affected individuals, 40.9% were phenotypical females, 31.8% were phenotypical males, and 27.3% had different degrees of intersexuality (Hsu 1994).

d. The absence or mutation of SRY (sex-determining region on the Y chromosome) gene on the isodicentric Y chromosome: another factor adding to diversity of the phenotype, illustrated by case studies by DesGroseilliers et al. (2006).
   i. In one case of idic(Y), the female phenotype and Turner stigmata can be explained by the localization of the breakpoint, which is proximal to the SRY gene, in Yp11.2 or p11.31.
   ii. In three patients, who do not have a predominant 45,X cell line but possess two copies of SRY (as breakpoints are in the long arm), usually develop as males: They are often infertile due to the absenceof one of the azoospermia factor (AZF) regions or the incorrect pairing between the rearranged Y and the X chromosome during meiosis I (Chandley et al. 1986).

e. Nonmosaic 46,X,idic(Y) with breakpoints in the long arm has been reported in rare cases of females: dicentric chromosome Y associated with Leydig cell agenesis and sex reversal (female phenotype) (Genuardi et al. 1995).

4. The putative gonadoblastoma locus (GBY) hypothesized by Page in 1987
   a. Thought to correspond to the TSPY (testis-specific protein, Y-linked) gene (Lau et al. 2003), which has clusters in several loci on both the short and the long arms of the Y chromosome (Tsuchiya et al. 1995; Rottger et al. 2002).
   b. Presence of multiple GBY loci on the Y chromosome could explain why such tumors have been reported in both idic with breakpoints in the long and short arms (Hsu 1994; Tuck-Muller et al. 1995).

Clinical Features

1. Extremely variable physical and genital features (52 cases with dicentric Yq, studied by Guevarra et al. 2009) (Hsu 1994; Tuck-Muller et al. 1995; Bouayed Abdelmoula and Amouri 2005b; DesGroseilliers et al. 2006)
   a. Twelve phenotypic males (23%)
      i. Age/presenting symptoms
         a) Six adults: infertility (5), short stature (1)
         b) Six children: short stature (6)
      ii. Gonads
         a) Normal testes (10)

b) Not reported (2)
c) Gonadoblastoma (0)
iii. Stature
a) Short (6)
b) Normal (3)
c) Borderline (1)
d) Not reported (2)
iv. Turner syndrome stigmata (3)
b. 17 phenotypic ambiguities (33%)
i. Age/presenting symptoms
a) Two adults: inguinal mass/gynecomastia (1), ambiguous genitalia (1)
b) 15 children: short stature (4), ambiguous genitalia (12)
ii. Gonads
a) Normal testes (2)
b) Abdominal testes (2)
c) Mixed gonadal dysgenesis (10)
d) Not reported (3)
e) Gonadoblastoma (3)
iii. Stature
a) Short (9)
b) Normal (3)
c) Not reported (5)
iv. Turner syndrome stigmata (2)
c. Twenty-three phenotypic females (44%)
i. Age/presenting symptoms
a) Six adults: short stature (1), primary amenorrhea (5)
b) Thirteen children: short stature (9), primary amenorrhea (3), not reported (1)
ii. Gonads
a) Normal ovaries (0), mixed gonadal dysgenesis (15)
b) Gonadoblastoma (6)
iii. Stature
a) Short (16)
b) Normal (3)
c) Not reported (4)
iv. Turner stigmata (10)

2. Karyotype–phenotype correlations
a. Sexual differentiation of patients: depends on the distribution of the 45,X cell line in various tissues, including gonads.
i. Three cases reported by Alvarez-Nava et al. (2003):
a) 45,X/46,X,idic(Y) positive for the same Y chromosome molecular markers, with various degrees of abnormal sexual differentiation.
b) A predominant 45,X cell line was found in the streak gonads of the female with Turner stigmata, while the dysgenetic testes of the male had a predominant 46,X,idic(Y) cell line.
c) The individual with sexual ambiguity had a streak gonad with a predominant 45,X cell line on one side and a dysgenetic testis with a predominant 46,X,idic(Y) cell line on the other side.
ii. Nine female patients studied by DesGroseilliers et al. (2006)
a) An increase in the proportion of 45,X cells in the gonads compared to blood in four patients (93% vs 64%, 80–100% vs 39%, 82% vs 60%, and 79% vs 8%), thus could explain their female or ambiguous phenotypes.
b) A similar increase of the 45,X cell line was found in fibroblasts compared to blood in three patients (96% vs 39%, 92% vs 8%, and 95% vs 23%).
b. Great phenotypic variations observed in patients with an isodicentric Y chromosome greatly limit the genotype–phenotype correlation.
i. The variability is explained by the degree of mosaicism in different tissues and the various locations of the breakpoints.
ii. To improve the genotype–phenotype correlation.
a) Analyze more than one tissue, as significantly different proportions of various cell lines can be found.
b) Perform histological studies of the gonads.
c) Molecular definition of the breakpoints will provide more information, allowing for a better genetic counseling.

3. Differential diagnosis of idic(Yp) (Bruyere et al. 2006)
a. Adult males with idic Yp invariably present with a history of infertility
i. Likely, a result of loss or disruption of all or part of the Yq11.2 AZF gene cluster, which is crucial for spermatogenesis

(Siffroi et al. 2000; Stankiewicz et al. 2001; Marrocco et al. 2003; Yoshitsugu et al. 2003; Patsalis et al. 2005).

ii. Pairing dysfunction between the X and Y chromosomes during meiosis: proposed as an alternate mechanism for azoospermia in these men (Yoshida et al. 1997).

iii. All idic Yp cases in which paternal chromosome testing has been performed have been de novo (Schintzel 2001; Bruyere et al. 2006). This further supports the concept that males with an idic Yp are usually infertile. With the exception of cases, whose mosaicism included the presence of a structurally normal Y chromosome in a significant proportion of cells, normal fertility in these boys is unlikely.

b. Phenotype

i. Normal male phenotype with sterility with rare exception

ii. Rare ambiguous genitalia

Diagnostic Investigations

1. Cytogenetic analysis by high-resolution banding techniques (Q-, G-, and C-bandings).
   a. Blood
   b. Skin fibroblasts
   c. Gonadal tissues
2. Fluorescence in situ hybridization (FISH) and SKY (spectral karyotyping), using DNA probes specific for Y chromosome sequences present in Yp, in Yq, and in the centromeric Y region, allow the structural characterization of abnormal Y chromosomes (Robinson et al. 1999).
3. Molecular studies.
   a. Use of PCR to determine the presence or absence of specific Y chromosome sequences: may not provide enough information to determine the structure of the abnormal Y chromosome
      i. Amplify genes or chromosome regions (SRY, ZFY, DYZ1) which are needed for the male development
      ii. Y centromere sequence (DYZ3) (Tuck-Muller et al. 1995; Robinson et al. 1999)
   b. Comparative genomic hybridization (CGH)
4. Hormonal investigations.
   a. Estradiol level
   b. Follicle-stimulating hormone level
   c. Luteinizing hormone level
   d. Testosterone level
5. Abdominal ultrasonography and MRI (Mizuno et al. 2009): suspect the presence of a testicular component and the possibility of mixed gonadal dysgenesis or true hermaphroditism in a phenotypic girl without gonad (especially with a history of a high testosterone level, enlargement of the clitoris, response to human chorionic gonadotropin stimulation test, and the presence of SRY), followed by laparoscopic evaluation and biopsy of the specimen: laparoscopic bilateral gonadectomy when dysgenetic gonad is found.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Since reported cases so far have been de novo, recurrence risk to sib is not likely increased.
      ii. However, several sets of affected identical twins have been reported.
         a) Monozygotic twins with 47,X,idic(Y)(q11.2),idic(Y)(q11.2)/46,X,idic(Y)(q11.2)/45,X from peripheral blood: twin A (phenotypic female with 42% of Y-containing cells); twin B (phenotypic male with 94% of Y-containing cells) (Nonomura et al. 2002)
         b) Monozygotic twins with 45,X/46,X,idic(Y)(p11) from peripheral blood and skin fibroblasts: twin A (phenotypic female with 0–57% Y-containing cells); twin B (phenotypic male with 22–60% Y-containing cells) (Fujimoto et al. 1991)
   b. Patient's offspring: not likely increased since affected individuals are infertile
2. Prenatal diagnosis: possible via amniocentesis or CVS
   a. Cytogenetic analysis
   b. FISH
   c. SKY
   d. Molecular studies using specific Y chromosome sequence
3. Management
   a. Gender assignment after careful evaluation of the patient when there is a genital ambiguity.

b. Advise surgery to remove gonads in women with gonadal dysgenesis and Y material at young age since they are at higher risk (15–20%) of developing gonadoblastoma and seminoma (Verp et al. 1987; Fallat and Donahoe 2006).
c. A boy with 45,X/46,XidicY(p11) mosaicism and short stature who has shown an improved final adult height as a result of long-term growth hormone treatment (Guevarra et al. 2009).

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Fig. 1 (**a**, **b**) An 18-year-old female was evaluated for primary amenorrhea and short stature (Tuck-Muller et al. 1995). She was noted to be obese. Laboratory findings included prepubertal female levels of estradiol (below 10 pg/mL) and high levels of luteinizing hormone (72 mU/mL with normal of 4–30 mU/mL), follicle-stimulating hormone (53 mU/mL with normal of 4–30 mU/mL) and testosterone (103 ng/dL with normal adult female value of 6.0–86 ng/dL). Laparoscopic exploration revealed an infantile uterus, a left streak gonad, and a right gonadal enlargement. Histological examination of the right gonad showed gonadoblastoma merged with a diffuse germ cell component diagnosed as dysgerminoma. The specimen leveled as left streak ovary consisted of vestigial Wolffian ducts. The analysis of genomic DNA from the patient indicated that sequences derived from the short arm (using SRY and ZFY mapped at Yp11.32), centromere (using Y97 mapped at Y centromere), and the middle and terminal portions of the long arm of the Y chromosome (using eD6 mapped at Yq11; 1 F5 mapped at Yq11.2; pY3.4 mapped at Yq12) were present

Fig. 2 Her external genitalia was characterized by clitoromegaly, rudimentary labia minora, hypoplastic labia major, and a narrow but patent vagina

Fig. 3 The predominant cell line in the patient's blood (29 of 40 cells), skin (33 of 35 cells), and right (31 of 33 cells) and left (25 of 25 cells) gonadal tissues had monosomy X. The second cell line had 46 chromosomes with one X and one abnormal Y chromosome, illustrated in this Q-banded spread showing isodicentric Y chromosome. Brightly fluorescent bands were present at the terminus of both arms of the abnormal chromosome, which stained darkly by C-banding (Fig. 4). The abnormal chromosome was interpreted to be a dicentric isochromosome composed of two copies of the long arm, centromere, and proximal portion of the short arm of the Y chromosome. Both parents were karyotypically normal

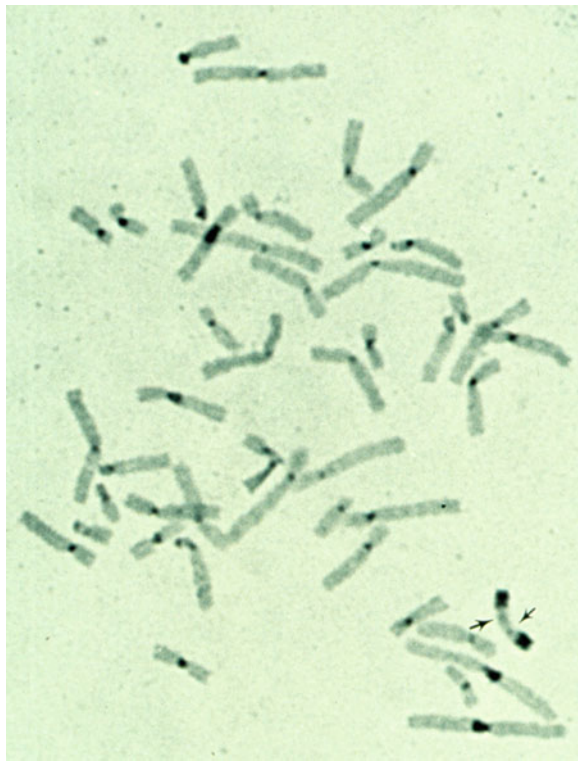

Fig. 4 The isodicentric Y chromosome (arrows) is illustrated in this C-banded spread

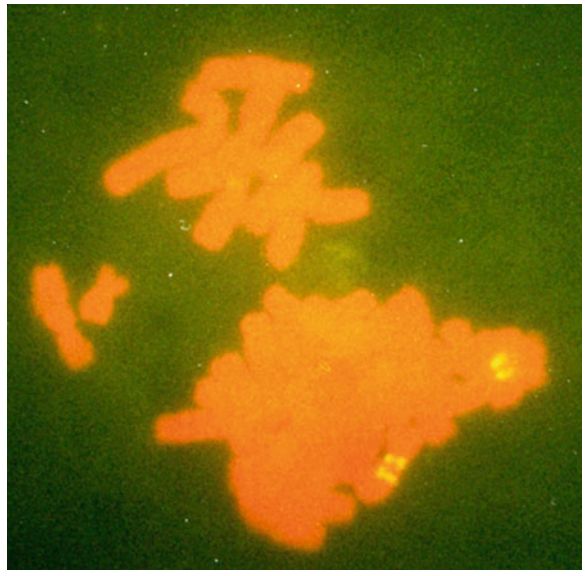

Fig. 5 The Y-specific α-satellite probe hybridized to the two centromeric regions of the abnormal Y chromosomes. The chromosome spread illustrates the presence of two idic(Y)

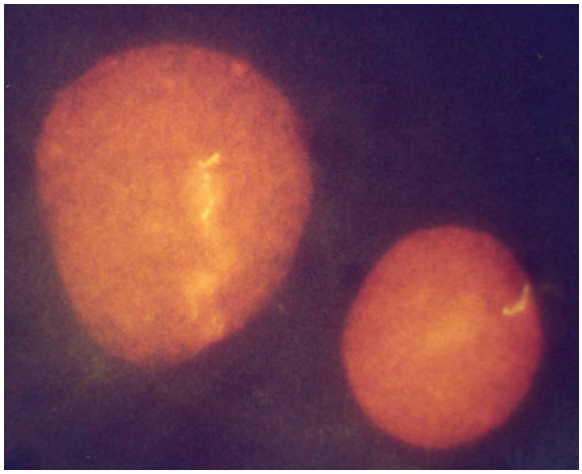

Fig. 6 FISH on interphase cells using Y probe shows idic(Yq) signals

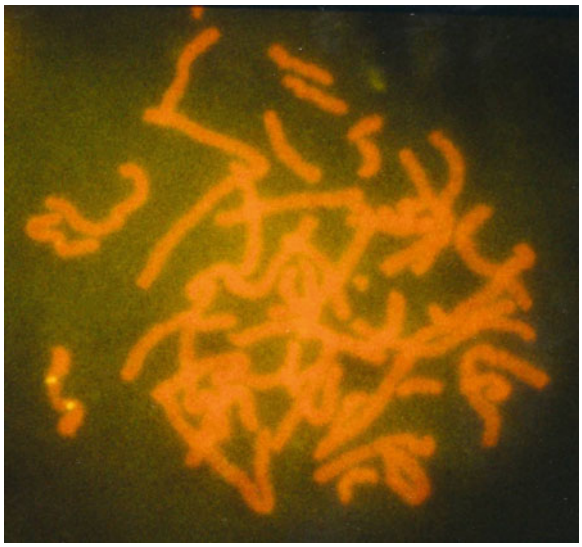

Fig. 7 FISH on a metaphase spread using Y centromeric probe shows idic(Yq) chromosome

Incontinentia Pigmenti

Bloch and Sulzberger, in 1926 and 1928, respectively (Bloch 1926; Sulzberger 1928), were credited for the first description of the clinical syndrome of incontinentia pigmenti (IP), known as Bloch–Sulzberger syndrome. It is a rare genodermatoses occurring in approximately 1 in 50,000 newborns (Aradhya et al. 2001).

Synonyms and Related Disorders

Bloch–Sulzberger Syndrome

Genetics/Basic Defects

1. Inheritance (Berlin et al. 2002).
   a. X-linked dominant transmission, usually prenatally lethal in males, suggested by pedigree analyses
   b. A high affected female/affected male ratio
   c. Instances of female-to-female transmission
   d. 1:1:1 affected female/normal female/normal male ratio in the offspring of an affected mother
   e. Increased incidence of miscarriages in patients with incontinentia pigmenti, presumably representing affected male conceptuses that typically fail to survive past the second trimester
2. Female patients with IP mutations.
   a. Dizygosity for the X chromosome
   b. Skewed X-inactivation
      i. Cells expressing the mutant X chromosome are eliminated selectively around the time of birth so that females with IP exhibit extremely skewed X-inactivation, based on the Lyon hypothesis (random inactivation of one X chromosome in each cell of the female at an early developmental stage, resulting in an X-chromosomal mosaic for each female with one X functioning in some of the cells and the other X functioning in the rest of the cells).
      ii. Female heterozygous for an X-linked incontinentia pigmenti gene: The pigmented areas on the skin represent cell populations in which the abnormal gene is active and the areas of normal skin tissue in which the normal gene is active.
      iii. Highly variable phenotype explainable by the chance variability in the number and position of the cells carrying the active incontinentia pigmenti gene.
3. The gene for IP: linked genetically to the *factor VIII* gene in Xq28.
4. Molecular pathophysiology (Fryssira et al. 2010).
   a. Attributed to mutations in the gene of nuclear factor kappa B (*NF-κB*) essential modulator (*NEMO*) currently known as *IKBKG* (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma) (Smahi et al. 2000; Jentarra et al. 2006; Fusco et al. 2008).
   b. The *IKBKG* gene is located on chromosome X, band q28. It spans 23 kb and consists of 10 exons.
   c. An intrachromosomal rearrangement that deletes exons 4–10 of the gene accounts for approximately 80% of new mutations.
   d. The *IKBKG* gene encodes a protein which is essential for the activation of NF-jB transcription factor, which protects cells against tumor necrosis factor–induced apoptosis.

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e. The *IKBKG* gene also regulates the expression of various cytokines, chemokines, and adhesion molecules (Smahi et al. 2000; Berlin et al. 2002).

5. Mechanisms for occasional survival of affected males (Berlin et al. 2002).
   a. Presence of an extra X chromosome (47,XXY Klinefelter syndrome)
   b. Skewed X inactivation
   c. Hypomorphic alleles
   d. Mosaics for common mutations (somatic mosaicism)
   e. A parent with gonadal mosaicism
6. Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID):
   a. A disorder allelic to incontinentia pigmenti but with different phenotype due to various natures of genetic mutations underlying the two disorders
   b. A rare X-linked recessive disorder affecting only males
   c. Caused by mutations in the *NEMO* gene
   d. Possible family history of IP in boys with EDA-ID
   e. Presentation with severe recurrent infections caused by common encapsulated bacterial pathogens, suggesting functional defects in the immune response
   f. Rare opportunistic diseases
      i. Mycobacterial infections
      ii. Cytomegaloviral infections
      iii. *Pneumocystis carinii* pneumonitis
   g. Immunologic studies
      i. Normal or increased levels of B cells
      ii. Normal T-cell counts
      iii. Normal to low levels of IgG
      iv. Elevated levels of either IgM or IgA
7. Eosinophil recruitment through eotaxin release by activated keratinocytes.
8. Incontinentia nomenclature: The localization of the gene for IP to Xq28, coupled with reports of children with "incontinentia pigmenti" and X-autosome translocations with breakpoints at Xp11, resulting in a nomenclature differentiation of IP1 (sporadic) and IP2 (familial). However, IP1 and IP2 designation should be abandoned.
   a. IP1
      i. Disorder applied to cases associated with X-autosome translocations with Xp11 breakpoints and r(X) (Shastry 2000)
      ii. Skin changes different from patients to patients
      iii. Serves no useful purpose either causally or clinically
      iv. More appropriately using descriptive phrase "X-autosome translocation associated with pigmentary abnormalities"
   b. IP2: applied to cases of familial IP mapped to Xq28

Clinical Features

1. Highly variable clinical presentations among affected female family members (Berlin et al. 2002)
   a. Attributed to lyonization in females, resulting in functional mosaicism
   b. Clonal expansion of the progenitor cell along lines of embryonic development in that each cell determines which X chromosome to express during the first weeks of gestation
      i. Manifesting along the curvilinear lines of Blaschko in skin
      ii. Percentage of progenitor cells that express the mutated X chromosome reflecting the extent of expression
      iii. Mutation in a high percentage of ectodermal cells in severe cases
2. Clinical expression among small number of live-born male patients
   a. Generally not severer than that in affected females
   b. Many male patients with disease expression limited to cutaneous involvement of one or two limbs
3. Cutaneous manifestations: most often the first observed sign of IP and are present in nearly all patients. They are classically subdivided into the following four classic cutaneous stages:
   a. Vesicular, vesiculobullous, or inflammatory stage
      i. Frequency: about 90% of cases
      ii. Age of onset: within first 2 weeks of life (92%), by 6 weeks of age (4%), starting after the first year of life (several cases)
      iii. Age at resolution: blisters generally clearing by 4 months, recurrence usually short-

lived and less severe than the original eruption
   iv. Clinical features: erythema, superficial vesicles in linear distribution on torso and extremities (64%) and extremities alone (33%)
b. Verrucous (wart-like) stage
   i. Frequency: about 70% of cases
   ii. Age of onset: peak of onset between 2 and 6 weeks of age
   iii. Age at resolution: clearance by 6 months (80%)
   iv. Clinical features: verrucous hyperkeratotic papules and plaques almost exclusively involving extremities
c. Hyperpigmented stage
   i. Frequency: nearly all patients with IP (98%)
   ii. Age of onset: 12–26 weeks of age
   iii. Age at resolution: puberty
   iv. Clinical features: whorls and streaks of brown pigmentation following lines of Blaschko (multiple lines on the human body corresponding to the distribution of linear nevi and dermatoses) on torso and extremities (65%) and torso alone (27%)
d. Atrophic (dermal scarring) stage
   i. Frequency: 42%
   ii. Age of onset: early teens to adulthood
   iii. Age at resolution: permanent lesion
   iv. Clinical features: pale, hairless, atrophic patches, and/or hypopigmentation

4. Hair abnormalities (50%)
   a. Vertex alopecia
      i. The most common hair manifestation
      ii. Most commonly mild and unnoticed
      iii. Follows inflammation and vesiculation
      iv. May be associated with scarring
   b. Agenesis of eyebrows and eyelashes: infrequent
5. Nail abnormalities (7–40%)
   a. Ridging, pitting, or nail disruption
      i. Starting early childhood and involving all or most of the fingernails and toenails
      ii. Tend to regress and disappear with age
   b. Subungual and periungual keratotic tumors
      i. Appear at a later stage.
      ii. Affect fingers more than toes.
      iii. Continued growth results in pain, nail dystrophy, and destruction of the underlying bone of the terminal phalanx.
      iv. Bone lytic lesions caused by pressure from the overlying tumor.
6. Dental anomalies (>80%)
   a. Partial adontia or adontia (43%)
   b. Pegged and conical teeth (30%)
   c. Late eruption of teeth (18%)
   d. Enamel hypoplasia
7. Ophthalmologic anomalies (35%)
   a. Blindness (7.5%)
   b. Nonretinal manifestations
      i. Strabismus (18–33%)
      ii. Optic atrophy (4%)
      iii. Cataracts (4%)
      iv. Pseudoglioma (3.5%)
      v. Microphthalmia (3%)
      vi. Rare conjunctival pigmentation, iris hypoplasia, nystagmus, and uveitis
   c. Retinal manifestations
      i. Foveal hypoplasia
      ii. Mottled or hypopigmented retinal pigment epithelium
      iii. Avascular retina
      iv. Neovascularization
      v. Vitreous hemorrhages
      vi. Fibrovascular proliferation
      vii. Retinal detachment (3%)
8. Neurologic deficits (30%)
   a. Infantile spasms and seizure disorder (13%)
   b. Mental retardation (12%)
   c. Spastic paralysis (11%)
   d. Motor retardation (7.5%)
   e. Microcephalus (5%)
   f. Infrequent manifestations
      i. Cerebellar ataxia
      ii. Congenital hearing loss
      iii. Muscle paresis
      iv. Aseptic encephalomyelitis
9. Other associated anomalies
   a. Nipple anomalies
      i. Supernumerary nipple
      ii. Nipple hypoplasia
      iii. Breast hypoplasia/aplasia
   b. Oral anomalies
      i. High arched palate
      ii. Cleft lip/palate
   c. Skeletal anomalies
      i. Dwarfism
      ii. Chondrodysplasias
      iii. Short stature

iv. Spina bifida
v. Skull defects
vi. Club foot

d. Increased risk of serious and unusual infection in some patients
e. Occasional hypohidrosis with increased rates of bacterial skin infections: may be evidence of the continuum between IP and the allelic anhidrotic ectodermal dysplasia-immune deficiency
f. Cardiac abnormalities
i. Tricuspid insufficiency
ii. Pulmonary vein-to-superior vena cava shunt

10. Diagnostic criteria for incontinentia pigmenti (Landy and Donnai 1993)
a. Negative family history (no evidence of IP in a first-degree female relative): At least one major criterion is necessary to make a firm diagnosis of sporadic incontinentia pigmenti. The minor criteria, if present, will support the diagnosis. Because of their high incidence, complete absence of minor criteria should induce a degree of uncertainty.
i. Major criteria
a) Typical neonatal rash (erythema, vesicles, eosinophilia)
b) Typical hyperpigmentation (mainly trunk, Blaschko's lines, fading in adolescence)
c) Linear, strophic, hairless lesions
ii. Minor criteria
a) Dental involvement
b) Alopecia
c) Woolly hair/abnormal nails
d) Retinal disease
b. Positive family history (evidence of IP in a first-degree female relative of an affected female) plus demonstration of any of the following features, alone or in combination.
i. Suggestive history or evidence of typical rash
ii. Skin manifestation of IP
a) Hyperpigmentation
b) Scarring
c) Hairless streaks
d) Alopecia at vertex
iii. Anomalous dentition
iv. Woolly hair
v. Retinal disease
vi. Multiple male miscarriages

Diagnostic Investigations

1. Major histopathologic features from skin biopsy samples (Berlin et al. 2002)
a. Vesicular, vesiculobullous, or inflammatory stage
i. Spongiotic dermatitis
ii. Dermal and epidermal eosinophilia
iii. Eosinophil-filled vesicles
b. Verrucous stage
i. Papillomas
ii. Epidermal hyperplasia
iii. Hyperkeratosis
iv. Dyskeratotic cells
c. Hyperpigmented stage
i. Dermal melanophages
ii. Vascular changes in basal layer of epidermis
d. Atrophic stage
i. Loss of rete ridges
ii. Loss of dermal sweat coils
iii. Skin biopsy helpful for the diagnosis of IP at late stage (IV) (Fraitag et al. 2009)
a) Slight atrophy and some scattered apoptotic cells in the epidermis, epidermal hypopigmentation, and reduced melanocyte number.
b) The dermis appeared thickened and homogeneous and revealed a complete absence of hair follicles (23/26) and sweat glands (22/26).
c) There was no melanin incontinence or inflammatory cells, and the elastic network was normal.
2. CBC: marked peripheral blood leukocytosis and eosinophilia
3. Abnormal immune system: not a consistent finding
4. CT/MRI imagings of the brain
a. Optic atrophy
b. Retinal vasculopathy
c. Hypoplasia of the corpus callosum
d. Ventriculomegaly
e. Periventricular white matter lesions
f. Ischemic strokes
g. Hemorrhagic necrosis
h. Porencephalic cyst
5. Magnetic resonance angiography/spectroscopy for cerebral ischemia and a vaso-occlusive phenomenon

6. Fluorescein angiography for retinal vascular abnormalities
7. EEG for seizures
8. Chromosome analysis in male patients with IP
9. Molecular genetic testing: mutation detection for the majority of families, facilitated by the high frequency of specific deletion, using Southern blotting, PCR amplification, or DNA sequencing
   a. X-inactivation assay and Xq28 marker studies: X-inactivation analysis is indicated wherever a recombination event between Xq28 markers and the disease locus is suspected. Absence of recombination between the disease locus and Xq28 loci suggests that mosaicism is responsible for the discrepancy where Xq28 marker studies are at odds with the clinical assessment.
   b. Identification of the *IKBKG* (also known as *NEMO*) gene mutation as a biological marker for a molecular diagnosis of IP.
      i. Deletion/duplication analysis
      ii. Sequence analysis
      iii. Carrier testing for the mother who has an affected daughter with a known mutation
      iv. Determine whether the miscarried or stillborn male fetus has IP
      v. Prenatal testing of a fetus at risk

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Recurrence risk: $<1\%$, provided that the mother is not a carrier of the gene: a small increased risk due to either a new mutation in a second child or germ line mosaicism in a parent
      ii. Recurrence risk of 50% for sisters to be affected when the mother is a carrier of the gene
      iii. Recurrence risk of 50% for brothers to be affected (prenatally aborted fetuses or stillborns) when the mother is a carrier of the gene
   b. Offspring of an affected female
      i. Daughters: 50% affected; 50% normal
      ii. Sons: 50% affected (prenatally aborted fetuses or stillborns); 50% normal (all the live-born sons will be normal)
   c. Offspring of an affected male
      i. All daughters affected
      ii. All sons normal
2. Prenatal diagnosis possible if the disease-causing mutation has been detected in the families at risk
   a. Determination of the fetal sex by amniocentesis or CVS.
   b. An increased risk of miscarriage or stillborn for an affected male fetus (fetal karyotype 46,XY).
   c. If the fetal karyotype is 47,XXY: more severe IP phenotype in males and of Klinefelter syndrome.
   d. Molecular genetic testing of a female fetus: If the fetal karyotype is 46,XX, there is 50% of fetuses that are likely to be affected with IP.
   e. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified previously.
3. Management
   a. Reduce the risk of secondary infection of blisters
   b. Keep lesions dry
   c. Avoid trauma to blisters
   d. Dental care
   e. Early photocoagulation or cryotherapy in cases of retinal involvement
   f. Intervention programs for learning disabilities and developmental delay
   g. Antiseizure medications for seizures

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Fig. 1 (**a**, **b**) Two girls with incontinentia pigmenti showing classical hyperpigmentation on the trunk following Blaschko's lines

Fig. 2 (**a**, **b**) A girl with incontinentia pigmenti showing streaks and whorls of brown pigmentation on the leg and trunk

Infantile Myofibromatosis

Infantile myofibromatosis, previously known as congenital generalized fibromatosis, is the most prevalent fibrous tumor of infancy. It is characterized by the formation of tumors, either in a solitary or in a multicentric fashion, in the skin, muscle, viscera, bone, and subcutaneous tissue.

Synonyms and Related Disorders

Congenital generalized fibromatosis; Juvenile myofibromatosi

Genetics/Basic Defects

1. Etiology: unknown but appears to originate in utero. Fetal estrogenic hormone stimulation or hamartomas of myofibroblasts have been considered.
   a. Sporadic in most cases
   b. Several reports of familial cases (Zand et al. 2004)
      i. Autosomal dominant
      ii. Autosomal recessive
2. Types
   a. Solitary myofibroma
      i. More common in males (69%)
      ii. Affects chiefly the soft tissues of the head-neck region and the trunk
   b. Multicentric myofibromatosis (more common in females, 63%)
      i. Without visceral involvement (bones)
      ii. With visceral involvement (bones and viscera)
3. Spontaneous regression of tumors: possibly due to apoptotic cell death

Clinical Features

1. Affects almost exclusively infants and young children
   a. Sixty percent noted at birth or shortly thereafter
   b. Eighty percent occurred before the age of 2 years
2. Characteristics of tumors
   a. Superficial
      i. Palpable, rubbery, firm, and freely moveable nodules
      ii. Fibrotic, plaquelike, indurated, and crusted lesions
   b. Deeper lesions: generally immovable
   c. Nontender and painless
3. Overlying skin
   a. Erythema or a purple discoloration resembling a hemangioma
   b. Ulceration and atrophic scar
4. Affected bones
   a. Radiolucent lytic lesions (cystic defects)
   b. Most commonly involved locations
      i. Cranium
      ii. Femurs
      iii. Tibias
      iv. Spine
      v. Ribs
   c. Circumscribed lytic tumors not present at birth but develop quickly over the first few days or weeks of life
5. Solitary form (myofibroma)
   a. About 80% of the cases
   b. Boys more commonly affected

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c. Mostly involves the skin and bones, and rarely the CNS and viscera
d. A good outcome provided there is no visceral involvement
e. Natural history of myofibromas of the CNS without visceral involvement: frequently characterized by a period of initial rapid growth, subsequent stabilization, and spontaneous regression in many cases

6. Multicentric form (myofibromatosis)
   a. Without visceral involvement
      i. Girls more commonly affected
      ii. Typically undergoing spontaneous regression within the first 1 or 2 years of life when limited to the skin or bone
      iii. A good outcome
   b. With visceral involvement
      i. One fourth of cases of multicentric cases
      ii. Multiple nodules distributed throughout the body
         a) Soft tissues
         b) Bone
         c) Skeletal muscle
         d) Viscera (kidney, pancreas, retroperitoneum, lungs, gastrointestinal tract, peritoneum, diaphragm, heart, tongue, lymph nodes, peripheral nerves, liver)
      iii. Fatal outcome with visceral involvement usually within 4 months of life
         a) Localized mass effect on the lung, gastrointestinal tract, or within the conduction system of the heart
         b) Mortality rate approaches 75%.
      iv. Possible survival: spontaneous resolution of visceral lesions within the first year of life
      v. Disseminated pathologic process including proliferation of multiple nodules of collagen-forming fusiform cells
      vi. Likely origin of proliferating cells: myofibroblast (displaying both smooth muscle and fibroblast features)
7. Differential diagnosis
   a. Neurofibromatosis
   b. Leiomyomas
   c. Hyaline fibromatoses
   d. Hemangiomas
   e. Soft tissue sarcomas
   f. Metastatic neuroblastomas
8. Prognosis depending on the extent of involvement and location of the lesions (Orozco-Covarrubias et al. 2002)
   a. Solitary forms usually cause little morbidity and virtually no mortality. However, a solitary nodule involving the central nervous system (CNS) may be fatal.
   b. Lesions confined to soft tissue and bone: usually self-limited with good prognosis
   c. Good prognosis with frequent spontaneous regression when viscera are not involved
   d. Poor prognosis with infantile myofibromatosis with multiple visceral involvement
      i. May cause significant morbidity
      ii. Progression to death: usual outcome
      iii. Fatal in neonates (up to 75% of cases (Wiswell et al. 1998)
      iv. Death resulting from complications due to cardiopulmonary or gastrointestinal involvement

Diagnostic Investigations

1. Radiography, U/S, CT, and MRI
   a. Soft tissue lesions: round and well defined on U/S and MRI
   b. Invaluable in assessing the extent and progression or regression of the disease
      i. Soft tissue lesions (multiple subcutaneous and intramuscular tumors)
      ii. Bone lesions
      iii. Visceral lesions
   c. Radiography: lesions appearing as multiple areas of osteolysis with a sclerotic margin
   d. Ultrasonography: hyperechoic nodules with peripheral hyperperfusion on color Doppler
   e. CT scan
      i. Masses: isoattenuating with muscle or as low attenuating with slight enhancement in the periphery (Koujok et al. 2005)
      ii. Brain (Tamburrini et al. 2003)
         a) Partially calcific masses or isodense cystic lesions with intense peripheral contrast enhancement and smoothly marginated bone erosion

b) Typical absence of sclerosis of the margins

f. MRI: intramuscular, subcutaneous, and visceral (liver, lungs) lesions (Tamburrini et al. 2003; Koujok et al. 2005)
   i. Low signal on T1-weighted images
   ii. High or low signal of the center on T2-weighted images
   iii. All masses showed peripheral enhancement after gadolinium administration.

2. Histology (biopsy of tumors) (Chung and Enzinger 1981)
   a. Gross appearance of tumors: well demarcated
   b. Lesion consisting of bundles of elongated cells with features of both fibroblasts and smooth muscle cells
   c. Staining characteristics: intermediate between fibroblasts and smooth muscle
   d. Central part of the tumors often necrotic
3. Electron microscopy
   a. Characteristic intracytoplasmic myofilaments
   b. Dense bodies
   c. Focal basal lamina and macula adherens

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Sporadic form: not increased
      ii. Autosomal recessive form: 25% risk
      iii. Autosomal dominant form: not increased unless a parent is affected
   b. Patient's offspring
      i. Sporadic form: not increased
      ii. Autosomal recessive form: not increased unless the spouse is a carrier
      iii. Autosomal dominant form: 50% risk
2. Prenatal diagnosis by ultrasonography for detecting solitary or multicentric tumors in soft tissue, bones, or viscera
3. Management
   a. Observation
      i. Spontaneous regression
      ii. Possible sequelae (tissue loss or damage) resulting from spontaneous regression
   b. Surgical excision (Stanford and Rogers 2000)
      i. To prevent complications and improve prognosis
      ii. Reserved for symptomatic lesions or if vital organs are compromised, in view of the tendency to spontaneous regression
      iii. Radical resection reserved for those lesions posing an immediate threat due to their locations or massive size and those showing obvious progression
      iv. Seven to ten percent of lesions recurred after excision (Tamburrini et al. 2003).
   c. Chemotherapy with or without radiotherapy
      i. Necessary for recurrent or unresectable lesions
      ii. A combination of vincristine, adriamycin-D, and cyclophosphamide
      iii. Interferon
      iv. Successful use of combination of vinblastine and low-dose methotrexate in an infant with generalized infantile myofibromatosis (Azzam et al. 2009)

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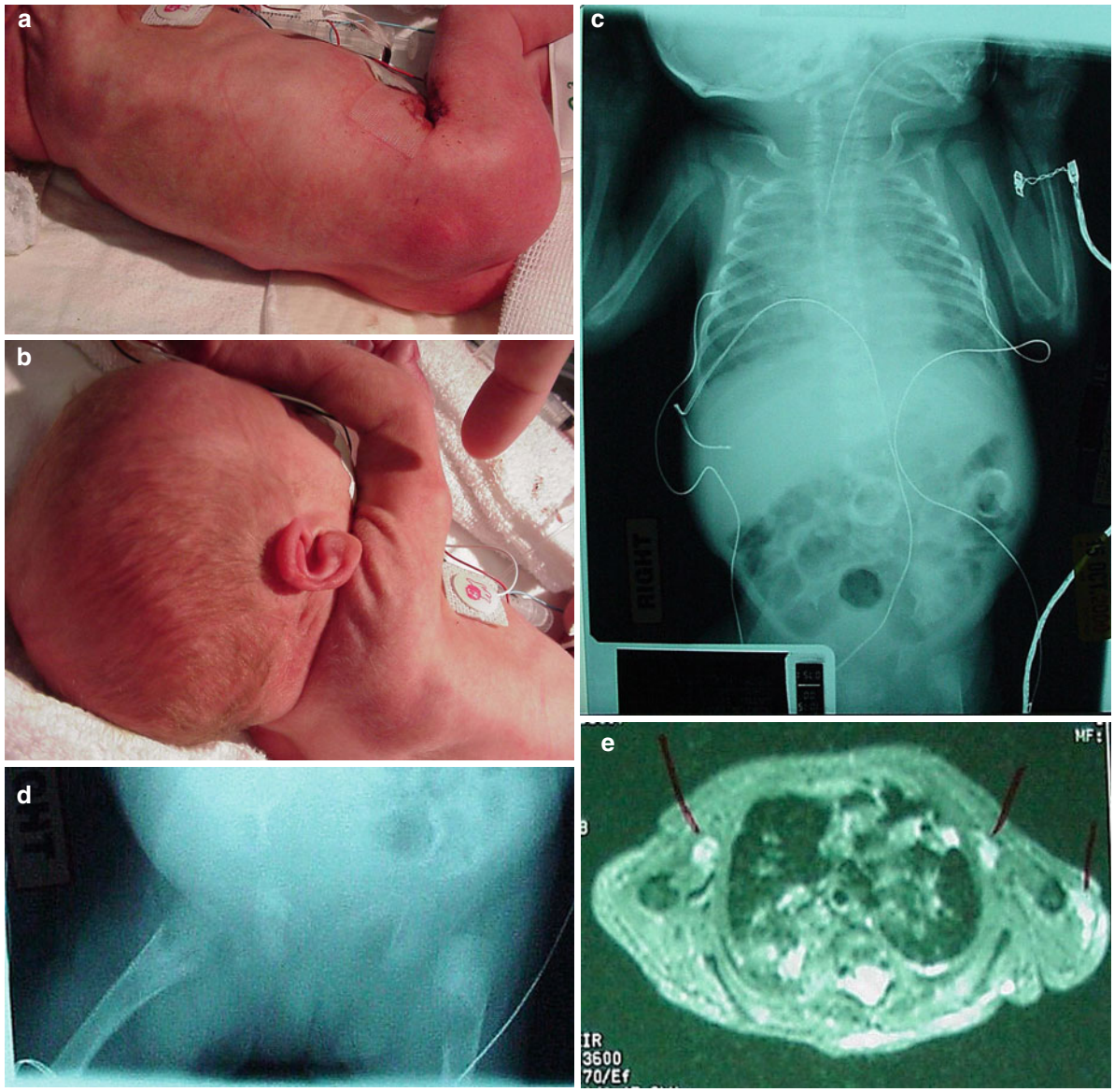

Fig. 1 (**a**–**e**) An infant with multicentric myofibromatosis showing subcutaneous nodules in the back, arm (pointed by a finger), cystic lytic lesions in the humeri and femora (radiographs), and multicentric nodules (identified by dark lines) in the chest wall by MRI

Ivemark Syndrome

Ivemark syndrome consists of visceroatrial heterotaxia associated with asplenia. It is also known as asplenia syndrome, heterotaxy syndrome, cardiosplenic syndrome, right atrial isomerism (two morphologically right atrial appendages), or bilateral right-sidedness. The incidence of the syndrome is estimated to be 1/10,000–1/40,000 live births (Rose et al. 1975; Noack et al. 2002). Ivemark syndrome accounts for 1–3% of all congenital heart defects (Cesko et al. 1997).

Synonyms and Related Disorders

Cardiosplenic syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive suggested by
   a. Reports of multiple affected siblings, both males and females, born to normal parents
   b. Reports of several instances of parental consanguinity
   c. Report of mutations in the gene encoding connexin 43 (Cx43)
2. Other possible cause: maternal diabetes
3. Heterotaxy syndrome: Heterotaxy results from failure of the embryo to establish normal left-right asymmetry (Bartram et al. 2005).
   a. A rare congenital disorder occurring in approximately 0.8% of patients with congenital heart disease
   b. Often associated with complex cyanotic heart disease and an abnormal cardiac conduction system
   c. Consisting of the following two groups of disease:
      i. Right isomerism (asplenia syndrome)
         a) Commonly has a combination of complete atrioventricular canal defect, total anomalous pulmonary venous return, double-outlet right ventricle, and pulmonary stenosis
         b) Often has paired atrioventricular nodes that may serve as the substrate for a special reentrant tachycardia ("nodal-to-atrioventricular nodal tachycardia")
      ii. Left isomerism (polysplenia syndrome)
         a) Tends to have few complex cardiac anomalies and therefore a better prognosis
         b) Likely to have defective sinus and atrioventricular nodes that may result in sinus node dysfunction, junctional escape rhythm, and atrioventricular block

Clinical Features

1. Congenital absence of the spleen (asplenia)
2. Congenital heart malformations
   a. Cardiac malpositions (44%)
      i. Dextrocardia
      ii. Right-sided aortic arch
   b. Venous system
      i. Systemic veins: bilateral superior vena cava (53%)
      ii. Pulmonary veins
         a) Total anomalous pulmonary venous drainage (72%)

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   b) Partial anomalous pulmonary venous drainage (6%)
  c. Great vessels
    i. Transposition of the great arteries (72%)
    ii. Pulmonary stenosis or atresia (78%)
  d. Coronary arteries: single coronary artery (19%)
  e. Intracardiac defects
    i. Single ventricle (44%)
    ii. Single AV valve (87%)
    iii. Absent coronary sinus (85%)
    iv. Endocardial cushion defect
    v. Double-inlet ventricle
    vi. Discordant ventriculoarterial connection
3. Maldevelopment of the abdominal organs (Mishalany et al. 1982)
  a. Abnormalities of the mesenteric attachment (intestinal malrotation), a major predisposing cause of midgut volvulus
  b. Situs inversus (heterotaxia)
  c. A midline (central) liver
  d. Tubular stomach
  e. Imperforate anus
  f. Annular pancreas and obstructing duodenal bands
  g. Esophageal varices
  h. Duplication of stomach
  i. Agenesis of gallbladder
  j. Rudimentary pancreas
  k. Meckel diverticulum
  l. Esophageal atresia and TE fistula
  m. Hiatus hernia
  n. Gastric hypoplasia
  o. Acute gastric volvulus: a rare complication
  p. Cleft palate
  q. Duplication of the hindgut
  r. Aganglionosis
4. Bronchopulmonary isomerism
  a. Abnormal lobation of the lungs
    i. Bilaterally trilobed
    ii. Bilaterally bilobed
  b. Bilateral eparterial bronchi
  c. Pulmonary hypoplasia
5. CNS malformations: uncommon
  a. Agenesis of the corpus callosum
  b. Porencephalic cyst
  c. Cerebellar cysts
  d. Focal cerebellar dysplasia
  e. Hydrocephalus
  f. Septum pellucidum abnormality
6. Genitourinary anomalies
  a. Horseshoe kidney
  b. Cystic kidney
  c. Bilobed urinary bladder
  d. Hydroureter
  e. Posterior urethral valves
  f. Ureteral valve with hydronephrosis
  g. Double collecting system
  h. Rectourethral fistula
  i. Bicornuate uterus
  j. Ovarian cysts
7. Endocrine abnormalities
  a. Fused or horseshoe adrenal
  b. Absent adrenal
8. Musculoskeletal abnormalities
  a. Equinovarus deformity
  b. Overlapping toes
  c. Clubbing of hands
  d. Absent radii
9. Miscellaneous
  a. Microphthalmia
  b. Single umbilical artery
10. Prognosis (Tkebuchava et al. 1997)
  a. Prognosis related to cardiac malformations
    i. Severe and incompatible with life (as a rule)
    ii. Anoxia
    iii. Cyanotic neonates die from cardiac insufficiency.
    iv. Most die from cardiac disease during the first year of life (usually the first month).
    v. Complications of surgery
    vi. Hemorrhage
  b. Prognosis related to asplenia
    i. Greater risk from infection for those who survive the first 12 months
    ii. Sudden death in infancy from sepsis and impaired resistance to infection

Diagnostic Investigations

1. Echocardiography for delineating congenital heart defects (Biggar et al. 1981)
2. Diagnosis of asplenia
  a. No splenic uptake on technetium sulfur colloid scan
  b. Presence of Howell-Jolly bodies in a peripheral blood smear after the first week of life

3. Immunologic assessment in congenital asplenia
   a. Quantitation of serum immunoglobulins
   b. Most common pathogens
      i. In children less than 6 months of age
         a) *Escherichia coli*
         b) *Klebsiella*
      ii. In children surviving past 6 months of age
         a) *Haemophilus influenzae*
         b) *Pneumococci*

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis by fetal echocardiography (Noack et al. 2002)
   a. No identifiable spleen (the fetal spleen can usually be detected at 20 weeks of gestation in the left gastrorenal angle) (Chitayat et al. 1988)
   b. Levocardia
   c. Complete atrioventricular septal defect
   d. Double-outlet right ventricle
   e. Dextro-malposition of the great arteries
   f. Pulmonary atresia/stenosis
   g. Other cardiac anomalies
3. Management
   a. Prophylactic antibiotics to prevent life-threatening sepsis
   b. Palliative cardiac surgery for congenital heart defects
   c. Surgical intervention for gastrointestinal malformations and other anomalies

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Fig. 1 A 3-month-old with Ivemark syndrome who has asplenia with complex cardiovascular malformations (AV canal, single ventricle, transposition of the great vessels, pulmonary atresia, and total anomalous pulmonary venous return). She also has malrotation of intestine

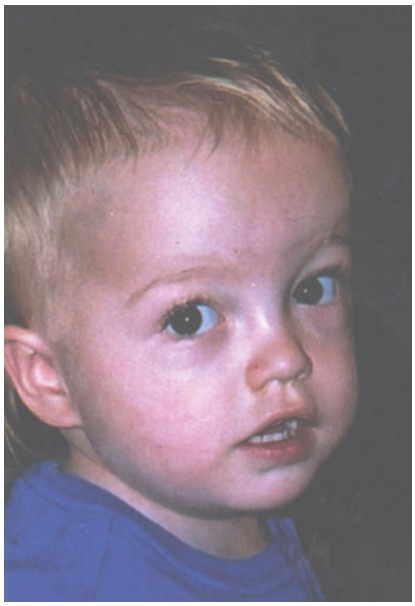

Fig. 2 A 19-month-old boy with Ivemark syndrome. He had heterotaxy syndrome with asplenia, situs inversus, and complex congenital heart defects consisting of a single ventricle, atrioventricular septal defect with small ostium primum ASD, pulmonary stenosis, interrupted IVC with azygous continuation to a left SVC, right aortic arch, and congenital complete heart block

Fig. 3 A 25-month-old girl with Ivemark syndrome. She had dextrocardia, situs inversus, complete AV canal, interrupted inferior vena cava, trachea compression by aorta, and status post pulmonary artery banding. Her complete AV canal was surgically repaired. Chromosome analysis was normal with normal FISH for DiGeorge syndrome

Jarcho–Levin Syndrome

In 1938, Jarcho and Levin first described a syndrome of malformations with abnormal fusion of thoracic vertebrae and ribs associated with a short trunk and respiratory insufficiency. At present, Jarcho–Levin syndrome is an eponym used to describe a variety of clinical phenotypes, consisting of short-trunk dwarfism associated with rib and vertebral anomalies. Two phenotypic subtypes of spondylothoracic dysostosis and spondylocostal dysostosis have recently been proposed.

Synonyms and Related Disorders

Costovertebral dysplasia; Costovertebral segmentation anomalies; Spondylocostal dysostosis/dysplasia; Spondylothoracic dysostosis/dysplasia

Genetics/Basic Defects

1. Inheritance and molecular defects (Cornier et al. 2003)
   a. Presence of considerable genetic heterogeneity with varied clinical presentations and associated abnormalities
   b. Spondylothoracic dysostosis
      i. Autosomal recessive inheritance
      ii. Linked to chromosome 2q32.1
      iii. No mutations found in the *DLL3* gene
   c. Spondylocostal dysostosis (Whittock et al. 2004; Turnpenny et al. 2009)
      i. Inheritance: either autosomal recessive or autosomal dominant
      ii. Mutations in the delta-like three gene (*DLL3*) on chromosome 19q13.1-q13 (Bulman et al. 2000; Turnpenny et al. 2003; Bonafe et al. 2003)
         a) As the major cause of autosomal recessive spondylocostal dysostosis
         b) *DLL3* encodes a ligand in the Notch gene signal pathway. When mutated, defective somitogenesis occurs resulting in a consistent and distinctive pattern of abnormal vertebral segmentation affecting the entire spine.
      iii. Mutated mesoderm posterior two homolog gene (*MESP2*) that codes for a basic helix-loop-helix transcription factor was found to cause spondylocostal dysostosis in one consanguineous family with two affected children (linkage to 15q21.3-15q26.1) (Whittock et al. 2004; Cornier et al. 2008).
      iv. Mutation in the *LFNG* O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase (on 7p22) (Sparrow et al. 2006)
      v. Mutations in the *HES7* (hairy and enhancer of split 7) gene (on 17p13.2)
2. Pathogenesis
   a. Vertebral anomalies: probably attributed to defective segmentation of the somite at about the fourth or fifth week of intrauterine life
   b. Costal anomalies: probably secondary to the vertebral anomalies
   c. *Pax1* and *Pax9* might be required for the phenotypic expression of Jarcho–Levin syndrome.

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Clinical Features

1. Spondylothoracic dysostosis (Cornier et al. 2003)
   a. Vertebral segmentation and formation defects throughout cervical, thoracic, and lumbar spine
      i. Hemivertebrae
      ii. Block vertebrae
      iii. Unsegmented bars
   b. Fusion of all the ribs at the costovertebral joints bilaterally
   c. Absence of intrinsic rib anomalies
   d. Other clinical features
      i. Short-trunk dwarfism
      ii. Craniofacial features
         a) Brachycephaly
         b) Low posterior hairline
         c) Prominent nasal bridge
         d) High-arched palate
      iii. Short and rigid neck
      iv. Short thorax
      v. Protuberant abdomen
      vi. Inguinal and umbilical hernias
      vii. Urinary tract abnormalities
      viii. Talipes equinovarus
   e. Prognosis: poor but not an invariably lethal condition with 56% of survival among the prospectively evaluated patients
      i. Normal intelligence
      ii. Respiratory complications such as pneumonia
      iii. Congestive heart failure
      iv. Pulmonary hypertension
2. Spondylocostal dysostosis
   a. Constitutes a heterogeneous group of radiologic phenotypes with axial skeletal malformations
   b. Generally milder phenotype
   c. Multiple vertebral segmentation and formation defects
   d. Typical findings
      i. Intrinsic asymmetric rib anomalies
         a) Broadening
         b) Bifurcation
         c) Fusion
      ii. No symmetric fusion of the ribs
      iii. Do not display a fanlike configuration of the thorax
      iv. No cervical spine anomalies in some patients
      v. Short-trunk dwarfism
   e. Associate anomalies
      i. Congenital heart disease
      ii. Urogenital and anal anomalies
      iii. Limb abnormalities
      iv. Torticollis
      v. Diaphragmatic, umbilical, and inguinal hernias
   f. Prognosis
      i. A good prognosis, due in part to the asymmetry of the thoracic anomalies resulting in a less restrictive thorax
      ii. Normal intelligence

Diagnostic Investigations

1. Radiography (Cornier et al. 2003)
   a. Spondylothoracic dysostosis
      i. Bilateral fanning of the ribs with posterior fusion, giving the appearance of a common origin of ribs at the posterior thoracic spine
      ii. A decreased number of cervical, thoracic, and lumbar vertebrae
      iii. Multiple vertebral segmentation and formation defects
         a) Block and wedge vertebrae
         b) Unsegmented bars
         c) Hemivertebrae
         d) Anterior-posterior-lateral failure of closure
   b. Spondylocostal dysostosis
      i. Multiple vertebral formations and segmentation defects along the entire spine
         a) A decreased number of cervical, thoracic, and lumbar vertebrae
         b) Block and wedge vertebrae
         c) Agenesis of the coccygeal region
         d) Progressive scoliosis of the thoracic spine due to tethering effect secondary to the rib anomalies
      ii. Asymmetric intrinsic rib malformations
         a) Broading
         b) Bifurcation
         c) Fusion
         d) Do not display a fanlike configuration of the thorax as in spondylothoracic dysostosis

2. Reconstructed tridimensional CT scan of the chest
   a. Spondylothoracic dysostosis
      i. Bilateral rib fusion at the costovertebral junction
      ii. Segmentation and formation defects in all cervical, thoracic, and lumbar vertebrae. Sacrococcygeal regions are spared from any abnormality.
      iii. Increase in the coronal diameter of the thoracic and lumbar vertebrae which acquire a sicklelike appearance
   b. Spondylocostal dysostosis
      i. Varying extent of the thoracic fusion
      ii. Thoracic fusion always asymmetric with respect to each side of the thorax
      iii. Increase in the coronal diameter of the thoracic and lumbar vertebrae which acquire a sicklelike appearance
3. Pulmonary function tests for restrictive lung disease
4. Molecular genetic analysis (Turnpenny et al. 2009)
   a. *DLL3* mutations in spondylocostal dysostosis (homozygous or compound heterozygous mutations)
   b. Other subtypes are defined by identification of two mutant alleles in other three genes known to be associated with autosomal recessive spondylocostal dysostosis: *MESP2*, *LFNG*, and *HES7*.

Genetic Counseling

1. Recurrence risk
   a. Autosomal recessive inheritance (spondylothoracic dysostosis and spondylocostal dysostosis)
      i. Patient's sib: 25%
      ii. Patient's offspring: not increased unless the spouse is also a carrier, in which case, there is a 50% risk of having an affected offspring
   b. Autosomal dominant inheritance (spondylocostal dysostosis)
      i. Patient's sib: not increased unless a parent is affected, in which case, there is a 50% risk of having an affected sibling
      ii. Patient's offspring: 50%
2. Prenatal diagnosis by ultrasonography
   a. Ultrasonography
      i. Grossly distorted thoracic and lumbar spine
      ii. Marked kyphoscoliosis
      iii. Multiple vertebral segmentation anomalies
      iv. Fanned ribs
      v. A small chest with foreshortened spine
      vi. Increased fetal nuchal translucency thickness
      vii. Inguinoscrotal hernia in a fetus with vertebral anomalies: a clue for Jarcho–Levin syndrome and other pathologies that increase abdominal pressure (Basaran et al. 2010)
   b. Prenatal diagnosis by molecular genetic analysis of *DLL3*, *MESP2*, *LFNG*, or *HES7* gene mutations by sequencing entire coding region of fetal DNA obtained from amniocentesis or CVS, provided the disease-causing allele has been previously identified
   c. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have identified previously.
3. Management (Cornier et al. 2003)
   a. Minimize positive end-expiratory pressure to avoid bronchopulmonary dysplasia.
   b. Continuous feeding instead of in boluses to avoid stomach distension that will lead to increase diaphragmatic pressure
   c. Aggressive treatment of infections
   d. Treat the spinal deformities.

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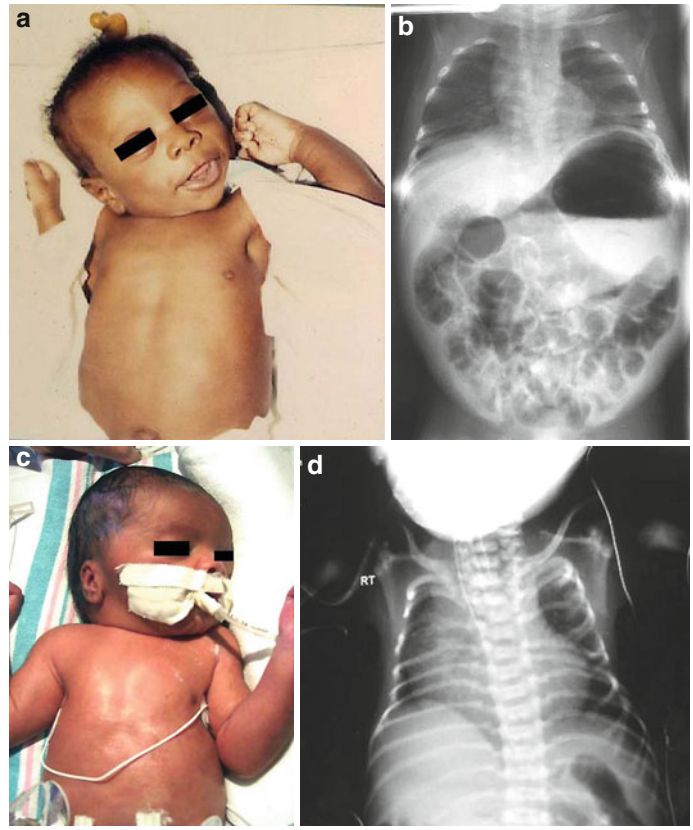

Fig. 1 (**a**–**d**) Two infants with spondylocostal dysostosis with typical crablike deformities of the chest with fused ribs (radiographs)

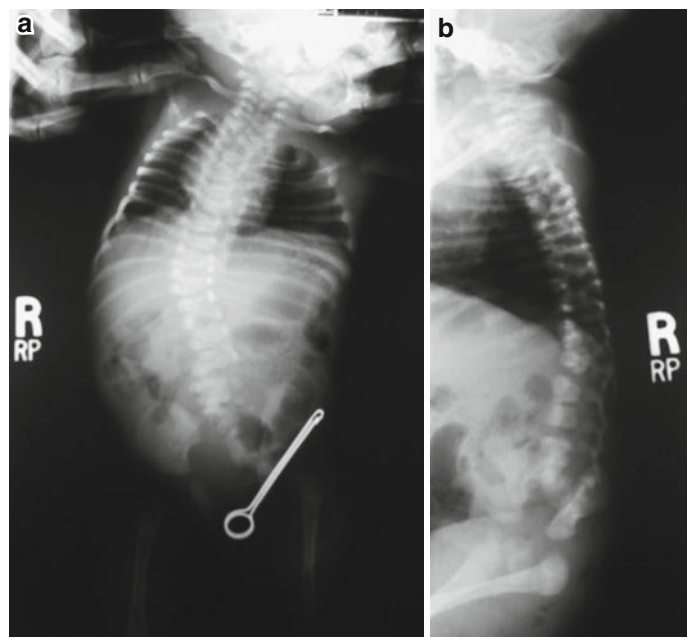

Fig. 2 (**a**, **b**) Radiographs of another infant with spondylocostal dysostosis showing fused ribs and fused vertebrae

Fig. 3 Radiographs of another infant with spondylothoracic dysostosis showing severe chest deformity

Fig. 4 (**a**–**d**) An Arabic female newborn was evaluated for multiple vertebral and rib anomalies. Her prenatal ultrasound showed vertebral anomalies, hydramnios, and possible TE fistula. Postnatally, she was noted to have short neck, short chest, and protuberant abdomen. The postnatal radiographs showed vertebral segmentation and formation defects throughout cervical, thoracic, and lumbar spine. Fusion of the ribs was present. Clinical diagnosis of Jarcho–Levin syndrome was made. The parents are first cousins. Molecular genetic diagnosis showed positive *DLL3* mutation. This patient is apparently homozygous in the *DLL3* gene for a frameshift mutation defined as c.329delT which is predicted to result in premature protein termination (p.Val110GlyfsStope22). This particular mutation has not been reported previously. However, it is the type expected to be pathogenic (e.g., Turnpenny et al. 2003). The homozygous c.329delT mutation is very likely the cause of recessive spondylocostal dysostosis

Fig. 5 (**a**–**c**) The previous infant at 3 months of age with follow-up X-rays

Joubert Syndrome

In 1969, Joubert et al. first documented three brothers and one sister who had episodic hyperpnea, abnormal eye movements, ataxia, mental retardation, and cerebellar vermian hypoplasia and aplasia. Later in 1977, Boltshauser and Isler reported three more cases with variable degrees of clinical symptoms and suggested the syndrome be called Joubert syndrome.

The prevalence in the United States has been estimated as approximately 1:100,000 (Parisi et al. 2006). This is likely to be an underestimate due to lack of recognition of the clinical signs or MRI findings and failure to diagnose the condition in more mildly affected individuals (Parisi et al. 2007).

Synonyms and Related Disorders

Cerebellooculorenal syndrome; Cerebelloparenchymal disorder; Jubert-Boltshauser syndrome

Genetics/Basic Defects

1. A rare autosomal recessive brain malformation disorder
2. Causative gene defects (genetic complexity) in Joubert syndrome and related disorders (JSRD) individuals (Parisi et al. 2006; Harris 2007)
   a. *NPHP1* (nephronophthisis 1, 2q13) gene homozygous deletion associated with juvenile nephronophthisis present in a subset of individuals with Joubert syndrome (Parisi et al. 2004) (1–2%)
   b. *AHI1* (Abelson helper integration site, 6q23.11) gene mutations (Parisi et al. 2006) (10–15%)
   c. *CEP290* (encoding centrosomal protein, 12q21.3) gene mutations causing pleiotropic forms of Joubert syndrome (Valenti et al. 2006) (approximately 10%)
   d. *NPHP6* (encoding centrosomal protein nephrocystin-6, 12q21.3) gene mutations in Joubert syndrome (Sayer et al. 2006)
   e. *ARL13B* cilia gene mutation leading to classical form of Joubert syndrome (Cantagre et al. 2008)
   f. Mutations in three genes (MKS3, CC2D2A, and RPGRIP1L) in COACH syndrome (Joubert syndrome with congenital hepatic fibrosis) (Doherty et al. 2010)

Clinical Features

1. Clinical features often cited as necessary for the diagnosis of classic Joubert syndrome (Joubert et al. 1969; Saraiva and Baraitser 1992; Steinlin et al. 1997; Maria et al. 1999a, b; Parisi et al. 2006; 2007)
   a. Cranial MRI findings of molar tooth sign (100%)
      i. Midline cerebellar vermis hypoplasia
      ii. Deepened interpeduncular fossa
      iii. Thick, elongated superior cerebellar peduncles
   b. Hypotonia in infancy (100%)
   c. Developmental delay/mental retardation, of variable severity (100%)
   d. One or both of the following (not absolutely required but supportive of the diagnosis):
      i. Irregular breathing pattern in infancy (episodic tachypnea and/or apnea)
      ii. Abnormal eye movements (including nystagmus, jerky eye movements, and oculomotor

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apraxia or difficulty with smooth visual pursuits)

2. Typical facial features during childhood (Maria et al. 1999a)
   a. High rounded eyebrows
   b. Broad nasal bridge
   c. Mild epicanthus
   d. Anteverted nostrils
   e. Triangular-shaped open mouth with tongue frequently resting on the lower lip
   f. Low-set and coarse ears
3. Joubert syndrome may be considered an oculo-cerebello-renal syndrome because of the coincident involvement of all three organ systems (Valente et al. 2003).
4. JSRD: disorders sharing the MRI molar tooth sign (Gleeson et al. 2004). Clinical features in JSRD with the molar tooth sign (MTS) (Parisi et al. 2007) are:
   a. Other central nervous system anomalies
      i. Hypotonia
      ii. Mental retardation
      iii. Oculomotor apraxia
      iv. Breathing abnormalities
      v. Encephalocele
      vi. Polymicrogyria
   b. Ocular abnormalities
      i. Ocular coloboma
      ii. Retinal dystrophy
      iii. Leber congenital amaurosis
   c. Renal diseases
      i. Cystic dysplastic kidneys
      ii. Nephronophthisis
   d. Hepatic fibrosis
   e. Polydactyly
   f. Tongue hamartomas/oral frenulae
5. Proposed classification system for Joubert syndrome and related disorders (Zaki et al. 2008)
   a. Primary criteria include:
      i. Neurological signs
         a) Hypotonia/ataxia
         b) Developmental delay
         c) Oculomotor apraxia
      ii. Radiological hallmark of molar tooth sign
      iii. Occasional features (seen in all forms)
         a) Mental retardation
         b) Breathing abnormalities
         c) Postaxial polydactyly
         d) Mild retinopathy
         e) Polymicrogyria
         f) Corpus callosum abnormality
   b. Secondary criteria
      i. Joubert syndrome: may include
         a) Mild ocular sign (retinopathy)
         b) Mild renal sign
         c) Postaxial polydactyly
      ii. Cerebellar vermis hypo-/aplasia-oligophrenia-ataxia-ocular coloboma-hepatic fibrosis (COACH syndrome): at least one (typically both)
         a) Hepatic fibrosis
         b) Coloboma (choroidal or retinal)
      iii. Cerebello-oculo-renal syndrome (CORS): at least one ocular sign and at least one renal sign
         a) Ocular signs: retinopathy (typically congenital blindness), coloboma
         b) Renal signs: cysts, nephronophthisis, renal failure
      iv. Oro-facio-digital syndrome type VI (OFD-VI) syndrome: at least one orofacial sign and at least one digital sign
         a) Orofacial signs: cleft lip/palate, tongue tumors, notched upper lip
         b) Digital signs: mesaxial polydactyly (most specifically), preaxial polydactyly, bifid digits
   c. The presence of the primary criteria and the secondary criteria are used to support the diagnosis of a specific type of JSRD.

Diagnostic Investigations

1. Molar tooth sign, demonstrated by a high-quality MRI scan of the brain (Zaki et al. 2008) (Parisi et al. 2007)
   a. Result from images of cerebellar vermis hypoplasia, thick and maloriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa (Maria et al. 1999b)
   b. Extraordinarily useful in differentiating JSRD conditions from other hindbrain malformations
      i. Dandy-Walker malformation
      ii. Isolated cerebellar vermis hypoplasia
      iii. Pontocerebellar hypoplasia
      iv. Rhombencephalosynapsis

2. Medical genetics evaluation
   a. Family history
   b. Demonstration of congenital anomalies
      i. Micro-/macrocephaly
      ii. Facial dysmorphism
      iii. Clefts
      iv. Lingual nodules
      v. Polydactyly
      vi. Genital anomalies
      vii. Others
3. Developmental assessment
4. Neurologic evaluation for cerebellar function
5. EEG for seizures
6. Polysomnogram for abnormal sleep history (apnea/hyperpnea)
7. Ophthalmological evaluation
   a. Eye malformations such as coloboma
   b. Retinopathy or blindness
   c. Abnormal eye movement such as nystagmus or oculomotor apraxia
8. Abdominal ultrasonography
   a. Renal cystic disease
   b. Liver fibrosis
9. Clinical laboratory tests
   a. BUN
   b. Creatinine
   c. CBC for anemia
   d. First-morning void urinalysis with specific gravity
10. Liver function tests
    a. Transaminases
    b. Albumin
    c. Bilirubin
    d. Prothrombin time
11. Chromosome analysis: no consistent chromosomal aberrations identified
12. Molecular genetic testing
    a. FISH or microsatellite marker analysis for homozygous deletion of the *NPHP1* gene associated with juvenile nephronophthisis (Hildebrandt et al. 2001; Parisi et al. 2004) identified in only 1–2% of subjects with JS (Parisi et al. 2006)
    b. Molecular testing for mutations in the *AHI1* gene and the *CEP290* gene: clinically available. Each of these genes is estimated to account for about 10% of cases of JSRD. Mutations in both *AHI1* and *CEP290* are more likely to be associated with retinal disease, with *CEP290* implicated in some cases with congenital blindness or Leber amaurosis (den Hollander et al. 2006; Sayer et al. 2006).
    c. In rare families with a large number of affected children and/or known consanguinity, linkage analysis may be feasible on a research basis.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: a 25% risk
   b. Patient's offspring: low recurrence risk unless the partner is a carrier or affected
2. Prenatal diagnosis
   a. Possible for pregnancy at risk, provided the disease-causing mutations have been identified in the affected individual
   b. Prenatal imaging for all other at-risk pregnancies
      i. Prenatal diagnosis of Joubert syndrome has been accomplished as early as the first trimester on the basis of extracranial anomalies, such as polydactyly or renal cysts, and major structural CNS malformations such as encephalocele (Wang et al. 1999).
      ii. Early diagnosis: more challenging when extracranial abnormalities are not present, because cerebellar vermis hypoplasia cannot be reliably diagnosed until 18–20 weeks gestation (Bromley et al. 1994) and the MTS has not been observed before 27 weeks gestation (Fluss et al. 2006)
   c. Prenatal diagnosis: suspected at 32 weeks gestation in the absence of a family history by observation of vermian agenesis, bilateral ventriculomegaly, postaxial polydactyly, and episodes of tachypnea (Aslan et al. 2002)
   d. Sensitivity and specificity of prenatal imaging findings for JSRD: not known (Doherty et al. 2005)
3. Management
   a. No specific treatments for Joubert syndrome exist.
   b. Supportive treatments with interventions for individuals with developmental disabilities
      i. Special education programs
      ii. Physical, occupational, and speech therapy

iii. Adaptive equipments as needed
iv. Seizure control

c. Dialysis and renal transplantation for nephronophthisis
d. Specific surgical interventions for esophageal varices or portal hypertension in liver fibrosis
e. Liver transplantation for COACH syndrome

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Fig. 1 Patient 1 with Joubert syndrome. This 6-week-old boy presented with respiratory distress, tachypnea with episodes of apnea, and abnormal eye movement. Ultrasound revealed multiple bilateral renal cysts

Fig. 2 Lateral view of the patient

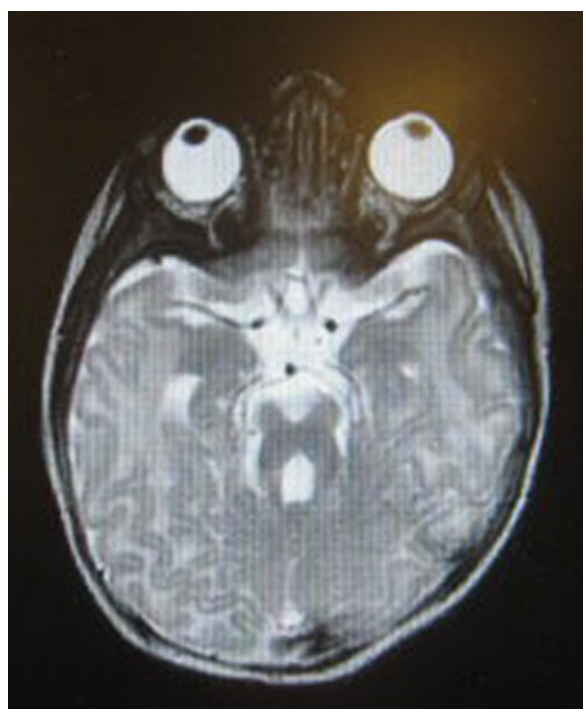

Fig. 3 MRI of the brain showed hypoplasia of cerebellum with "molar tooth sign" leading to diagnosis of Joubert syndrome

Fig. 4 This 22-month-old boy was evaluated for Joubert syndrome. He was delivered at 41 weeks of gestation via cesarean section with cord wrapping around the neck twice. Birth weight was 4,035 g and birth length 55 cm. Fetal ultrasound examination showed possible cerebellar hypoplasia. Follow-up MRI of the brain showed "molar tooth sign" consistent with Joubert syndrome. He had neonatal breathing dysregulation, delayed psychomotor development, hypotonia, and macrocephaly with prominent forehead, high-round eyebrows, low set and "tilted" ears, abnormal jerky eye movement with right chorioretinal coloboma, epicanthal folds, and ptosis. FISH using a probe to the NPHP1 locus showed no deletion of the *NPHP1* region. The result does not exclude the clinical diagnosis of Joubert syndrome and does not exclude a mutation in the *NPHP1* gene or other genes not detectable with this assay

Fig. 5 Note psychomotor retardation

Fig. 6 Note the genital hypoplasia

Kabuki Syndrome

In 1981, Niikawa and Kuroki independently described a previously unrecognized mental retardation-malformation syndrome, characterized by a unique combination of craniofacial anomalies, congenital heart defects, skeletal anomalies, persistent fetal fingertip pads, dermatoglyphic abnormalities, mental retardation, and short stature. Because the peculiar facial appearance resembles the makeup of Kabuki actors in a traditional Japanese theater, the Niikawa-Kuroki syndrome is also known as Kabuki or Kabuki makeup syndrome. The prevalence of the syndrome is estimated to be 1 in 32,000 live births in Japan (Niikawa et al. 1988). The syndrome is increasingly recognized in other parts of the world.

Synonyms and Related Disorders

Kabuki makeup syndrome; Niikawa–Kuroki syndrome

Genetics/Basic Defects

1. Sporadic in most cases
2. Autosomal dominant inheritance suggested in a few families
3. Other hypotheses
   a. Postzygotic mutation, suggested by discordance between the twins, although multifactorial causes cannot be ruled out
   b. Several instances of chromosomal abnormalities have been reported in the literature but without identical breakpoints in those autosomal abnormalities.
   c. Microdeletion involving several contiguous genes, suggested by sporadic cases in the majority of patients and a wide spectrum of clinical manifestations. So far, no chromosomal deletion was detected at the sites of the DiGeorge/velocardiofacial chromosomal region within 22q11.2 or flanking the van der Woude syndrome region at 1q32–q41.
   d. 8p23.1–p33 duplication, detected by CGH and FISH in six unrelated patients with Kabuki syndrome, was postulated to be a common etiology for the syndrome (Milunsky and Huang 2003). However, studies by Miyake et al. (2004) detected no aberrations of the 8p region by either CGH or FISH on other patients and suggested that the patients studied by Milunsky and Huang had either atypical Kabuki syndrome or possibly an "8p23.1–p33 duplication syndrome."
   e. It is possible that Kabuki syndrome is a heterogeneous disorder and abnormalities not only on chromosome 8 but also on other chromosomes, such as the X chromosome, could lead to similar Kabuki syndrome features (Adam and Hudgins 2004).
   f. Molecular karyotyping in 17 patients and mutation screening in 41 patients with Kabuki syndrome revealed no causative gene, but the locus of 9q21.11–q21.12, including *TRPM3*, *KLF9*, *SMC5*, and *MAMDC2*, may contribute to the cleft palate of Kabuki syndrome (Kuniba et al. 2009).

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Clinical Features

1. Craniofacial abnormalities (Matsumoto and Nikawa 2003)
   a. Peculiar facial appearance (100%): The most striking feature of the syndrome
      i. Peculiar face that consists of eversion of the low lateral eyelid that is reminiscent of a Kabuki actor's makeup and arched eyebrows with sparseness of their lateral one third
      ii. Long palpebral fissures
      iii. Depressed nasal tip
      iv. Prominent, large ears
   b. Microcephaly (26%)
   c. Eye abnormalities
      i. Long palpebral fissure (99%)
      ii. Lower palpebral eversion (92%)
      iii. Arched eyebrow (85%)
      iv. Ptosis (50%)
      v. Epicanthus (46%)
      vi. Strabismus (36%)
      vii. Blue sclerae (31%)
   d. Nasal abnormalities
      i. Short nasal septum (92%)
      ii. Depressed nasal tip (83%)
   e. Ear abnormalities
      i. Prominent ears (84%)
      ii. Malformed ears (87%)
      iii. Preauricular dimple/fistula (22%)
   f. Oral abnormalities
      i. High-arched palate (72%)
      ii. Abnormal dentition (68%)
      iii. Microganthia (40%)
      iv. Cleft palate/lip (35%)
      v. Lower lip pit (27%)
   g. Low posterior hairline (57%)
2. Skeletal abnormalities (88%)
   a. Pilonidal sinus (83%)
   b. Short fifth phalanxes (80%)
   c. Short fifth fingers (79%)
   d. Joint laxity (74%)
   e. Clinodactyly of fifth fingers (50%)
   f. Sagittal cleft of vertebral body (36%)
   g. Scoliosis (35%)
   h. Short metacarpals (35%)
   i. Deformed vertebra/rib (32%)
   j. Foot deformity (24%)
   k. Spina bifida occulta (19%)
   l. Hip dislocation (18%)
   m. Rib anomaly (18%)
   n. Coarse carpal bone (17%)
   o. Cone-shaped epiphyses (13%)
   p. Patellar dislocation
   q. Craniosynostosis: rare (6%) (Armstrong et al. 2005)
3. Dermatoglyphic abnormalities
   a. Abnormal dermatoglyphics (96%)
      i. Frequent fingertip ulnar loop patterns
      ii. Absence of digital triradius "c" or "d"
      iii. An interdigital triradius "bc" or "cd"
      iv. Fourth interdigital area patterns
         a) Hypothenar loop patterns
         b) Ulnar loop patterns
   b. Presence of fingertip pads (89%): possible remnants of fetal pads
4. Neurologic abnormalities
   a. Mild to moderate mental retardation (IQ <80) (84%)
   b. Hypotonia (68%)
   c. Neonatal hypotonicity (28%)
   d. Seizures (17%)
   e. Brain atrophy (4%)
   f. Retinal pigmentation (3%)
5. Short stature (55%)
6. Visceral abnormalities
   a. Cutaneous abnormalities
      i. Hyperpigmented nevus (22%)
      ii. Generalized hirsutism (11%)
   b. Cardiovascular anomalies (42%)
      i. Ventricular septal defect
      ii. Atrial septal defect
      iii. Coarctation of the aorta
      iv. Transposition of great vessels
   c. Gastrointestinal abnormalities
      i. Umbilical hernia (9%)
      ii. Inguinal hernia (7%)
      iii. Malrotation of the colon (6%)
      iv. Anal atresia/rectovaginal fistula (5%)
   d. Genitourinary abnormalities
      i. Kidney/urinary tract malformations (28%)
      ii. Undescended testes (24%)
      iii. Small penis (10%)
7. Other features
   a. Susceptibility to infections
      i. Recurrent otitis media (63%)
      ii. Repeat upper respiratory tract infections and pneumonias

iii. Single case reports
a) Severe immunodeficiency
b) Autoimmune hemolytic anemia and polycythemia
c) Chronic idiopathic thrombocytopenia
d) Acquired hypogammaglobulinemia with anti-IgA antibody
b. Early breast development (28%)
c. Hearing loss (27%)
d. Neonatal hyperbilirubinemia (20%)
e. Obesity (19%)
f. Anemia (9%)
g. Polycythemia (4%)
h. Cystic fibrosis (2%)
i. Primary ovarian dysfunction (2%)

Diagnostic Investigations

1. Blood sugar during infancy for neonatal hypoglycemia (7%)
2. Thyroid profile for rare TBG deficiency (2%)
3. Growth hormone determination for rare growth hormone deficiency
4. Workup for autoimmune hemolytic anemia, if present
5. Audiologic screening for hearing loss
6. Radiography for skeletal abnormalities (Niikawa et al. 1981)
   a. Frequent features
      i. Abnormalities of the spinal column
         a) Thoracic or lumbar scoliosis
         b) Sagittal cleft vertebra
         c) Narrow disc space
         d) Cervical ribs
         e) Schmorl node
      ii. Dislocation of the hip joints
      iii. Abnormalities of the hands
         a) Brachymesophalangy of the fifth fingers
         b) Short fifth metacarpals
         c) Cone-shaped epiphysis of proximal phalanges II–V
   b. Less frequent features
      i. Defective dentition
      ii. Underpneumatized mastoids
      iii. Sacral spina bifida occulta
      iv. Osteoporotic changes of the carpal bone and metacarpals
      v. Underdeveloped ulnar styloids
      vi. Dysplastic acetabulum
      vii. Horseshoe kidney
      viii. Bifid renal pelvis
7. Renal ultrasonography for renal abnormalities
8. Echocardiography for congenital heart defects
9. EEG for seizures: characteristic features are focal seizures more frequently origin in fronto-central area (Lodi et al. 2010)
10. MRI/CT scan for rare CNS anomalies
11. Dermatoglyphic analysis

Genetic Counseling

1. Recurrence risk (Kawame et al. 1999)
   a. Patient's sib: low recurrence risk, unless a parent has an autosomal dominant form of the syndrome
   b. Patient's offspring: low recurrence risk, unless the patient has an autosomal dominant form of the syndrome
2. Prenatal diagnosis: none described to date
3. Management
   a. Multidisciplinary approach to developmental delay and mental retardation
   b. Hearing aids for hearing loss
   c. Treat infections
   d. Growth hormone replacement therapy for growth hormone deficiency
   e. Orthopedic intervention for scoliosis, dislocations, and foot deformities
   f. Cardiac surgery for severe congenital heart defects
   g. Surgical repair of cleft lip/palate, gastrointestinal, anorectal, and craniosynostosis anomalies

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Fig. 1 (**a**–**c**) A 12-year-old girl with Kabuki syndrome showing arched eyebrows, long palpebral fissures, everted lateral half of the lower eyelid, short nasal septum, post–cleft lip repair, prominent ears, and prominent finger pads

Fig. 2 A 1-year-old girl with Kabuki syndrome showing arched eyebrows, long palpebral fissures, short nasal septum, and hypertrophic breasts. The infant also has cleft palate, large ears, and congenital hip dislocations

Fig. 3 A 1-year-old boy with Kabuki syndrome showing arched eyebrows, long palpebral fissures, everted lateral half of the lower eyelids, blue sclera, strabismus, short nasal septum, small chin, and large and prominent ears

Fig. 4 (**a**–**c**) A 12-year-old boy with Kabuki syndrome showing characteristic facial features consisting of long palpebral fissures, arched eyebrows, bilateral lower lateral palpebral eversion, short nasal septum, high-arched palate, low hairline, and prominent finger pads. Other anomalies include mild mental retardation, neonatal hypotonia, recurrent otitis media and upper respiratory infections, joint laxity, ventricular septal defect, hip dysplasia, and short and clinodactyly of the fifth fingers

Kasabach–Merritt Syndrome

Kasabach–Merritt syndrome (or phenomenon) is the association of a vascular tumor and thrombocytopenic coagulopathy (Enjolras et al. 2000). It is a life-threatening, localized consumptive coagulopathy, characterized by profound thrombocytopenia and microangiopathic anemia.

In 1940, Kasabach and Merritt described the first case of Kasabach–Merritt syndrome with a case report of consumptive coagulopathy associated with a hemangioma. However, it is now recognized that Kasabach–Merritt syndrome is usually associated with Kaposiform hemangioendothelioma and tufted angioma, rather than the classic involuting hemangioma of infancy (Enjolras et al. 1997).

Synonyms and Related Disorders

Hemangioma-thrombocytopenia syndrome

Genetics/Basic Defects

1. Genetics
   a. Sporadic in majority of cases
   b. Autosomal dominant inheritance in rare reports
   c. Can be a part of recognized syndromes
2. Pathophysiology (Hall 2001)
   a. Platelet trapping by abnormally proliferating endothelium within the hemangioma, resulting in the activation of platelets with a secondary consumption of clotting factors
   b. Continued consumption of both platelets and clotting factors along with the initiation of fibrinolysis eventually resulting in intralesional bleeding which manifests as rapid enlargement of the hemangioma

Clinical Features

1. Diverse clinical presentation (Enjolras et al. 2000; Hall 2001)
   a. Type of hemangiomas
      i. Kaposiform hemangioendothelioma: often found in noncutaneous sites such as the retroperitoneum, mediastinum, and pelvis, as well as the skin
      ii. Tufted angioma
      iii. Mixture of Kaposiform hemangioendothelioma and tufted angioma
      iv. Not "true" common hemangioma of infancy
   b. Reddish brown skin lesion progressing to a violaceous bulging mass
      i. Often painful
      ii. Aggressive infiltration with ulceration
      iii. Bruising in other areas
      iv. Possible infection
   c. Bleeding from thrombocytopenia and intravascular coagulopathy
   d. Increase in size and becoming tense, woody, and purplish of preexisting hemangiomas during pregnancy
2. Cutaneous involvement of Kaposiform hemangioendothelioma
   a. Smooth, shiny, dark purple, indurated, tender, and poorly delineated
   b. Nearly always single

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3. Visceral involvement of hemangiomata
   a. Single
   b. Multiple
   c. Isolated within one organ as single or diffuse lesions
   d. Retroperitoneal hemangiomata
      i. Often giant in size
      ii. Easily missed clinically: diagnosis suspected in patients presenting with an unexplained thrombocytopenia and coagulopathy
      iii. Generally associated with high mortality
4. Diffuse and multiple nature
   a. Diffuse infantile (neonatal) hemangiomatosis
      i. Presence of multiple cutaneous and visceral hemangiomata
      ii. High morbidity and mortality
   b. Intraosseous and soft tissue hemangiomata
5. Lifelong hemangioma in adults
   a. Hormone alterations and increase in blood volume in pregnancy may affect preexisting lesions, triggering episodes of acute disseminated intravascular coagulation
   b. Development of acute consumptive coagulopathy after surgery of other unrelated tumor
6. Thrombocytopenic coagulopathy in patients with hemangiomata as a part of a recognized syndrome
   a. Klippel–Trenaunay syndrome
      i. A rare congenital generalized mesodermal abnormality
      ii. Macular vascular nevus, skeletal/soft tissue hypertrophy
      iii. Venous and lymphatic anomalies including viscera and facial hemangiomata
   b. Blue rubber bleb nevus syndrome
      i. Multiple cutaneous cavernous hemangiomata
      ii. Cutaneous and occasional visceral hemangiomata
   c. Gorham–Stout disease ("vanishing bone disease")
      i. Massive osteolysis (Gorham sign)
      ii. Followed by replacement of the bony matrix by proliferating thin-walled vascular and lymphatic channels
      iii. Extension of these angiomatous masses into soft tissues
7. Prognosis
   a. Incomplete regression of the lesion after months or years
   b. Visceral involvement
      i. Mediastinum
      ii. Neck
      iii. Retroperitoneum
      iv. Pelvis
   c. Hemorrhage by aggressive invasion
   d. Petechiae, ecchymoses, or purpura
   e. Profound thrombocytopenia
   f. Anemia
   g. Congestive heart failure
   h. Severe infections
   i. Residual lesions after "cure" of Kasabach–Merritt phenomenon (Enjolras et al. 2000)
      i. Common after the resolution of thrombocytopenia and coagulopathy
      ii. Clinical patterns
         a) Cutaneous red stain with or without associated red papules
         b) Telangiectatic streaks and swelling
         c) A minor, firm, irregular subcutaneous mass assessed by palpation or deep infiltration evidenced by CT scan or MRI
         d) Sequelae in muscles and/or joints
   j. Overall mortality (estimated to be 20–30%) (El-Dessouky et al. 1988) due to complications such as (Enjoiras et al. 1990):
      i. Disseminated intravascular coagulation
      ii. Respiratory failure due to a pressured airway
      iii. High-output heart failure due to presence of a huge tumor

Diagnostic Investigations

1. Laboratory studies (Hall 2001)
   a. Generally severe thrombocytopenia: occurs in 1–2 per 300–700 cases of hemangioma
   b. Consumptive coagulopathy
      i. Prominent fibrinogenopenia
      ii. Usually elevated fibrin split (degradation) products
      iii. Usually elevated D-dimers (a measure of fibrin split products)
      iv. Depressed clotting factors V and VII
2. Ultrasound, MRI, or CT
   a. To assess extent of the lesions
   b. To identify the occult lesions

3. Histology to determine subtypes of hemangioma
   a. Kaposiform hemangioendothelioma of infancy and childhood
      i. The most frequently reported histological type
      ii. A locally aggressive, low-grade malignant tumor
      iii. Lobules or sheets of tightly packed spindle cells or more rounded endothelial cells and pericytes
      iv. Infiltrative pattern of the cellular areas in the dermis and subcutaneous fat and muscles, generally containing few obvious vascular lumina
      v. Aggregates of rounded dilated capillaries, lined by attenuated endothelial cells with small dark nuclei and filled with red blood cells
      vi. Containing lymphatic-like vessels
   b. Tufted angioma
      i. A benign lesion
      ii. Small tufts or lobules of rounded capillaries with small lumina
      iii. Tufts: discrete and evenly distributed in a cannon ball pattern, characterized by peripheral crescentic slit-like vessels and fibrosis
      iv. Aggregates of rounded dilated capillaries, lined by attenuated endothelial cells with small dark nuclei and filled with red blood cells

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased unless a parent is affected
   b. Patient's offspring: 50% in case of autosomal dominant inheritance
2. Prenatal diagnosis: Prenatal diagnosis of fetal facial hemangioma in a case of Kasabach–Merritt syndrome
3. Management (Ryan et al. 2010)
   a. General premise regarding treatment: Resolution of the lesion will lead to a correction of the consumptive coagulopathy, which is heralded by a recovery in the platelet count.
   b. Principle of management of thrombocytopenia in Kasabach–Merritt syndrome should be to "treat the patient and not the numbers."
   c. Prompt and vigorous management
      i. Help to optimize the outcome
      ii. No one treatment modality established as consistently efficacious
   d. Blood product support in the presence of sudden decompensation or enlargement of the lesion
      i. Fresh frozen plasma
      ii. Cryoprecipitate if fibrinogen still less than 1.0 g/L
      iii. Platelets transfusion should be reserved for thrombocytopenic patient who is actively bleeding or in preparation for a surgical procedure.
      iv. Tranexamic acid for profound fibrinolysis
   e. Simple or single lesion
      i. Vascular ligation
      ii. Embolization
      iii. Surgical excision
         a) Surgical removal of a giant hemangioma: usually hazardous in the presence of an uncontrolled consumptive coagulopathy
         b) Supporting and stabilizing hemostasis while trying to remove or ablate the lesion
         c) Partial resection of tumor, reduction of tumor blood, and vincristine chemotherapy (Shen et al. 2010): Since the huge tumor is the major cause of rapid platelet destruction, the partial removal of the tumor and U-shaped suture to reduce tumor blood supply would reduce the platelet destruction and, therefore, improve the clinical condition, followed by skin graft or flaps of the wound, and vincristine chemotherapy necessary to prevent the enlargement of the remaining tumor.
   f. Diffuse or extensive lesions
      i. Prednisone
      ii. Alpha interferon
   g. Adjuvant therapies
      i. Vincristine
      ii. Localized radiotherapy
      iii. Combination chemotherapy (vincristine, cyclophosphamide)
      iv. Antifibrinolytic or antiplatelet agents (tranexamic acid, ε-amino caproic acid, pentoxifylline, ticlopidine)

h. Potential future therapies
   i. Laser therapy
   ii. Antiangiogenic agents
   iii. Pegylated recombinant human megakaryocyte growth and development factor (peg-rHuMGDF)

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Fig. 1 (**a**–**b**) An infant with Kasabach–Merritt syndrome showing a giant cavernous hemangioma over most of the chest

Fig. 2 (**a**–**c**) A patient with blue rubber bleb nevus syndrome

KID Syndrome

KID syndrome is an acronym for the syndrome characterized by *k*eratitis, *i*chthyosis, and *d*eafness, a term proposed by Skinner et al. in 1981 (Skinner et al. 1981).

Synonyms and Related Disorders

Keratitis-ichthyosis-deafness syndrome

Genetics/Basic Defects

1. Genetic heterogeneity
   a. Sporadic in most cases
   b. Existence of familial cases suggesting a genetic etiology
      i. A vertical transmission suggesting an autosomal dominant disease
      ii. The occurrence in two sisters born to consanguineous, unaffected parents suggesting an autosomal recessive inheritance
2. Caused by heterozygous missense mutations in the connexin-26 gene, *GJB2*, which is implied in the normal corneal function, hair growth, and carcinogenesis
   a. Mutations in *GJB2* were identified de novo in 13 unrelated patients with KID and in a case of transmission of the disease from father to son (Richard et al. 2002a; Van Steensel et al. 2002; Alvarez et al. 2003; Yotsumoto et al. 2003).
   b. Mutations in several other genes [*GJB3* (connexin-31), *GJB6* (connexin-30)], which encode members of the connexin family of gap junction proteins, are shown to be responsible for hearing impairment and skin disorders.
3. Occurrence of parental germ line mosaicism in the lethal form of KID syndrome: suggested by three affected children (carry the same G45E mutation) born to healthy parents (mutation not detected) (Sbidian et al. 2010)
4. Fatal form of KID syndrome (Janecke et al. 2005)
   a. A fatal course of KID in the first year of life, due to severe infections of the skin lesions and septicemia, has been reported in at least nine patients (Gilliam and Williams 2002; Janecke et al. 2005).
   b. Caused by G45E mutation of *GJB2* gene.
   c. The phenotype bears similarities to cutaneous disorders associated with sensorineural hearing loss (HL) known to be caused by mutations in genes encoding gap junction proteins (connexins).
      i. Vohwinkel syndrome (Maestrini et al. 1999)
      ii. Dominant HL associated with palmoplantar keratoderma (Heathcote et al. 2000)
      iii. Keratoderma without HL
         a) Clouston syndrome (Lamartine et al. 2000)
         b) Erythrokeratodermia variabilis (Richard et al. 1998b)
5. Pathogenesis: failure in development and differentiation of multiple stratifying epithelia

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Clinical Features

1. Cutaneous features (McGrae 1990)
   a. Abnormal skin at birth: red, dry, thickened, and leathery
   b. Subsequent development of keratodermatous, nonscaly plaques
      i. Generally develop during the first year of life
      ii. Described as verrucous, ichthyotic, doughy, rugal, or elephant-skin-like
      iii. Develop primarily on the face and extremities
      iv. Plaques sharply demarcated and map-like in contour
      v. Plaques symmetrically located on the face
         a) Especially the cheeks
         b) With variable involvement of the forehead, ears, chin, and nose
         c) Furrows in the thickened skin of the chin and around the mouth
      vi. Transverse ripples marking the surface of plaques over the knees
      vii. Follicular keratoses, occasionally with spine like projections, on the extremities, eyebrows, scalp, earlobes, neck, and nose
   c. Distinct keratoderma of the palms and soles
      i. Pebbly excrescences and an intervening coarsely stippled pattern analogous to heavily grained leather
      ii. Patulous stippling rendering a moth-eaten appearance
   d. Abnormal hair
      i. Sparse, fine, and sometimes absent scalp, eyebrow, and eyelash hair
      ii. Pattern of patch scalp alopecia resembling pseudopelade
      iii. Body hair may be absent
      iv. Nails
         a) Thickened
         b) Hypoplastic
         c) Absent
         d) White
         e) Infrequently normal
2. Ophthalmologic features (Ghadially and Chong 1992)
   a. Invariably involving epibulbar structures with inflammation of the cornea
      i. Vascularized keratitis in majority of cases
      ii. Secondary pannus formation
   b. Photophobia
   c. Varying degree of visual impairment
   d. Onset: usually before adolescence
3. Auditory features
   a. Sensorineural deafness
   b. Repeat otitis media and externa
4. Other ectodermal abnormalities
   a. Dental abnormalities
      i. Carious
      ii. Brittle
      iii. Malformed
      iv. Delayed adult dentition
   b. Hypohidrosis
5. Neuroectodermal abnormalities
   a. Short heel cord
   b. Cerebellar hypoplasia
6. Other associated features
   a. Normal intelligence
   b. Growth delay
   c. Increased risk of developing squamous cell carcinoma
   d. Increased susceptibility to viral, bacterial, and mycotic infections
      i. Most commonly reported pathogens.
         a) Staphylococcus aureus
         b) E. coli
         c) Pseudomonas aeruginosa
         d) Trichophyton rubrum
         e) Candida albicans
      ii. Invasive and overwhelming infection may be present in infancy and early childhood. Death secondary to overwhelming sepsis has been reported in infancy.
      iii. Infections typically persistent and recurrent but usually limited to the skin in older children and adults.
      iv. No consistent pattern of immunologic dysfunction demonstrated in patients with KID syndrome.
7. Fatal form of KID syndrome
   a. A fatal course of KID has been reported in the first year of life due to severe infections of the skin lesions and septicemia.
   b. Characteristic severe neonatal phenotype (Sbidian et al. 2010).
      i. Facial dysmorphism
      ii. Severe cornification with massive focal hyperkeratosis of the skin with erythroderma
      iii. Dystrophic nails

iv. Complete atrichia (absence of hair)
v. Absence of foreskin

Diagnostic Investigations

1. Dental examinations for teeth abnormalities
2. Ophthalmological examination for corneal pathology and visual acuity
3. Audiologic examination to demonstrate sensorineural hearing loss
4. Histopathology of the skin (McGrae 1990)
   a. Findings not specific.
   b. Stratum corneum.
      i. Always hyperkeratotic, usually with a basket weave pattern
      ii. Orthokeratotic and occasionally parakeratotic
   c. Stratum granulosum: generally intact.
   d. Eccrine sweat glands appearing normal, although a diminished number and aberrant morphology have been noted.
   e. Absent or atrophic hair follicles indicating the customary state of alopecia.
   f. Follicular plugging is the rule.
5. Molecular genetic study to detect connexin-26 gene (*GJB2*) mutation: clinically available

Genetic Counseling

1. Recurrence risk.
   a. Patient's sib
      i. Autosomal dominant inheritance: not increased unless a parent is affected or parental germ line mosaicism exists
      ii. Autosomal recessive inheritance: 25%
   b. Patient's offspring
      i. Autosomal dominant inheritance: 50%
      ii. Autosomal recessive inheritance: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis: Prenatal molecular genetic diagnosis of the lethal form of KID syndrome relating to a G45E mutation has been reported (Sbidian et al. 2010).
3. Management.
   a. No specific treatment for the skin lesions.
   b. Isotretinoin with inconsistent results.
      i. May cause exacerbation of eye lesion
         a) Marked increase in pannus formation
         b) Marked increase in vascularization
      ii. Side effects of higher doses of isotretinoin
         a) Corneal opacities
         b) Punctate erosions
         c) Blepharoconjunctivitis
   c. Ophthalmologic evaluations and follow-up. Corneal grafts revascularize rapidly with subsequent loss of vision.
   d. Treat infections vigorously.
   e. Surveillance for skin and mucosal malignancy.
   f. Hearing aids.
   g. Appropriate school placement.

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Fig. 1 (**a**–**b**) A 26-year-old woman with keratitis, ichthyosis, and deafness. Cutaneous manifestations show sharply demarcated red–brown hyperkeratotic plaques on the central face, around both eyes, and upper and lower extremities

Fig. 2 Marked hyperkeratosis is visible around the eye and the outer rim of the ear

Fig. 3 Chronic *Candida albicans* onychia and paronychia with hypertrophy of the distal digits and hyperkeratosis of the skin are apparent on both hands

Klinefelter Syndrome

In 1942, Klinefelter et al. published a report on nine men who had enlarged breasts, sparse facial and body hair, small testes, and an inability to produce sperm. In 1959, these men with Klinefelter syndrome were discovered to have an extra sex chromosome (genotype XXY) instead of the usual male sex complement (genotype XY).

Klinefelter syndrome is the most common sex chromosomal disorder associated with male hypogonadism and infertility. Approximately 1 in 500–1,000 males is born with an extra X chromosome. Over 3,000 affected males are born yearly in the USA.

Synonyms and Related Disorders

47,XXY syndrome; Klinefelter syndrome mosaicism (46,XY/47,XXY, 46,XY/48,XXXY, 47,XXY/48,XXXY); Klinefelter syndrome variants (48,XXYY, 48,XXXY, 49,XXXYY, 49,XXXXY); Klinefelter syndrome with structurally abnormal X chromosome [47,X,i(Xq)Y, 47,X,del(X)Y]

Genetics/Basic Defects

1. Caused by at least an additional X chromosome in a male
2. The XXY form of Klinefelter syndrome
   a. Due to meiotic nondisjunction of the sex chromosomes during gametogenesis in either parent
   b. Responsible meiotic nondisjunction
      i. About 40% occur in the father
      ii. About 60% occur in the mother
         a) Meiosis I errors (75%) when origin is maternal
         b) Presence of maternal age effect in the maternally derived cases
3. The mosaic forms of Klinefelter syndrome
   a. Due to mitotic nondisjunction after fertilization of the zygote
   b. Can arise from a 46,XY zygote or a 47,XXY zygote
4. The variant forms
   a. 48,XXXY: nondisjunction occurring either at the first or second meiotic divisions of oogenesis, resulting an XXX ovum which is then fertilized by a Y bearing sperm
   b. 49,XXXXY: please refer to 49,XXXXY chapter
   c. 48,XXYY and 49,XXXYY: occurrence of nondisjunction in paternal meiosis to have two Y chromosomes
      i. An X ovum fertilized by an XYY sperm arising from successive nondisjunction in the first and second meiotic divisions, or
      ii. An XX ovum from 47,XXX mother fertilized by a YY sperm
5. Pathophysiology (Chen 2011)
   a. The X chromosome carries genes that play roles in many body systems, including testis function, brain development, and growth (Giedd et al. 2007).
   b. The addition of more than one extra X or Y chromosome to a male karyotype results in variable physical and cognitive abnormalities.
   c. In general, the extent of phenotypic abnormalities, including mental retardation, is directly related to the number of supernumerary X chromosomes.
   d. As the number of X chromosomes increases, somatic and cognitive development are more likely to be affected.

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Clinical Features

1. Growth
   a. Infants and children: normal heights, weights, and head circumferences
   b. Adolescents and adults
      i. Eunuchoid body habitus
      ii. Usually taller than average
      iii. Disproportionately long arms and legs
2. Mild developmental, learning, and behavioral difficulties (70% of patients)
   a. Delayed speech and language acquisition
   b. Academic and reading difficulties
   c. Attention deficit disorder
   d. Poor self-esteem
   e. Insecurity
   f. Shyness
   g. Poor judgment
   h. Inappropriate assertive activity
   i. Decreased ability to deal with stress
   j. Fatigue
   k. Weakness
3. CNS
   a. Normal intelligence in most cases
   b. Subnormal intelligence or mental retardation associated with a higher number of X chromosomes
   c. Diminished short-term memory
   d. Prone to epilepsy and essential tremor
   e. Psychiatric disorders involving anxiety, depression, neurosis, and psychosis: more common than general population
4. Taurodontism (enlargement of the molar teeth by an extension of the pulp): present in about 40% of patients (versus 1% in normal XY individuals)
5. Cardiac and circulatory problems
   a. Mitral valve prolapse (55% of patients)
   b. Varicose veins (20–40% of patients)
      i. Venous ulcers
      ii. Deep vein thrombosis
      iii. Pulmonary embolism
6. A slightly increased risk of autoimmune disorder
   a. Rheumatic diseases (Rovensky et al. 2010)
      i. Inflammatory rheumatic diseases
      ii. Rheumatoid arthritis
      iii. Juvenile idiopathic arthritis
      iv. Psoriatic arthritis
      v. Polymyositis/dermatomyositis
      vi. Systemic lupus erythematosus
      vii. Systemic sclerosis
      viii. Mixed connective tissue disease
      ix. Antiphospholipid syndrome
      x. Ankylosing spondylitis
   b. Thyroid disease
   c. Sjogren syndrome
   d. Diabetes mellitus
7. Sexual characteristics
   a. Gynecomastia secondary to elevated estradiol levels and increased estradiol/testosterone ratio
      i. Develop by late puberty in 30–50% of boys with Klinefelter syndrome
      ii. Risk of developing breast cancer: at least 20 times higher than normal
   b. Lack of secondary sexual characteristics secondary to decrease in androgen production
      i. Sparse facial, body, and sexual hair
      ii. High-pitched voice
      iii. Female type of fat distribution
   c. Male psychosexual orientation in most patients
   d. Subnormal libido
   e. Erectile dysfunction
   f. Oligospermia or azoospermia
   g. Testicular dysgenesis in postpubertal patients
      i. Small, firm testes
      ii. Testis size <10 mL
   h. Infertility and azoospermia resulting from atrophy of the seminiferous tubules
      i. Seen practically in all patients with a 47, XXY karyotype
      ii. Klinefelter syndrome mosaics (46,XY/47, XXY): can be fertile
8. Other characteristics
   a. An increased prevalence of extragonadal germ cell tumors in the mediastinum (Völki et al. 2006) and brain.
   b. More common varicose veins, venous stasis ulcers, and thromboembolic disease.
   c. The syndrome may go undiagnosed in the majority of affected men.
9. Klinefelter mosaics and variants
   a. Klinefelter mosaic (46,XY/47,XXY)
      i. Less severe manifestations
      ii. May have normal-sized testes
      iii. Less severe endocrine abnormalities
      iv. Less common gynecomastia and azoospermia
      v. Occasional fertile men

b. Klinefelter variants (Visootsak and Graham 2006)
   i. 48,XXYY variant (Tartaglia et al. 2008)
      a) Tall stature.
      b) Disproportionately long lower extremities.
      c) Clinodactyly.
      d) Pes planus.
      e) Hypertelorism.
      f) Dental problems.
      g) Gynecomastia.
      h) Intention tremor.
      i) Neurodevelopmental disorders, including developmental delays, ADHD, autism spectrum disorders, mood disorders, and tic disorders.
      j) Unusual dermatoglyphic patterns.
      k) Peripheral vascular disease, especially varicose veins and stasis dermatitis.
      l) Poorly developed secondary sexual characteristics.
      m) Hypogonadism.
      n) Testicular histology similar to that of 47, XXY patients.
      o) The sex chromatin pattern indistinguishable from that of the 47,XXY patients except two fluorescent Y bodies are present in a high proportion of somatic nuclei.
   ii. 48,XXXY variant
      a) Moderate to severe mental retardation
      b) Behavior: often immature and consistent with IQ level, typically described as passive, cooperative, and not particularly aggressive
      c) Normal to tall stature
      d) Dysmorphic facies
      e) Radioulnar synostosis
      f) Fifth finger clinodactyly
      g) Hypergonadotropic hypogonadism
      h) Small testes
      i) Signs of androgen deficiency
   iii. 49,XXXYY variant
      a) Mental retardation
      b) Somatic anomalies
      c) Small testes
   iv. 49,XXXXY variant: severity and frequency of somatic anomalies increase as the number of X chromosomes increases
      a) Mental retardation
      b) Microcephaly
      c) Short stature
      d) Hypotonia with lax joints
      e) Facial dysmorphic features: ocular hypertelorism, flat nasal bridge, epicanthal folds, bifid uvula, or cleft palate
      f) Short neck
      g) Congenital heart defects
      h) Radioulnar synostosis
      i) Genu valgum
      j) Pes cavus
      k) Fifth finger clinodactyly
      l) Hypergonadotropic hypogonadism with small genitalia
      m) Behavioral disorders: shy, friendly, occasional irritability, temper tantrums, low frustration tolerance, and difficulty changing routines

Diagnostic Investigations

1. Cytogenetic studies
   a. 47,XXY (80–90%)
   b. Mosaicism (10%)
      i. 46,XY/47,XXY
      ii. 46,XY/48,XXXY
      iii. 47,XXY/48,XXXY
   c. Variants
      i. 48,XXYY
      ii. 48,XXXY
      iii. 49,XXXYY
      iv. 49,XXXXY
   d. Structural abnormal X in addition to a normal X and Y
      i. 47,X,i(Xq)Y
      ii. 47,X,del(X)Y
2. Endocrinologic studies
   a. A variable degree of feminization and insufficient androgenization
      i. Elevated plasma FSH, luteinizing hormone, and estradiol levels
      ii. Low plasma testosterone levels in patients age 12–14 years
   b. Subnormal increased testosterone in response to human chorionic gonadotropin administration
3. Imaging studies
   a. Echocardiography to demonstrate mitral valve prolapse

   b. Radiography
      i. Lower bone mineral density
      ii. Radioulnar synostosis
      iii. Taurodontism
4. Histology
   a. Small, firm testes
   b. Seminiferous tubular hyalinization, sclerosis, and atrophy with focal hyperplasia of mostly degenerated Leydig cells
   c. Deficient or absent germ cells
   d. Rare spermatogenesis (azoospermia)
   e. Progressive degeneration and hyalinization of seminiferous tubules after puberty in mosaic patients

Genetic Counseling

1. Recurrence risk
   a. Patient's sibs: recurrence risk not increased for nonmosaic patients
   b. Patient's offspring
      i. Recurrence risk not increased since all 47, XXY individuals are infertile
      ii. Report of paternity in nonmosaic 47,XXY males (no other tissues were examined for possible mosaicism with a 46,XY cell line)
   c. A risk of having a 47,XXY offspring in a few 46, XY/47,XXY mosaic patients who fathered a child
2. Prenatal diagnosis
   a. Cytogenetic analysis of fetal cells obtained from amniocentesis and CVS.
   b. Dilemma for parents since prognosis for the fetus with XXY is good but the possibility of phenotypic abnormalities does exist.
   c. Explanation to each couple the genetic risks resulting from intracytoplasmic sperm injection (ICSI) (increased risk of sex chromosome and autosome abnormalities).
   d. Preimplantation genetic diagnosis by embryo biopsy offers an efficient tool for embryo selection (Friedler et al. 2001).
3. Management
   a. Speech therapy.
   b. Physical therapy.
   c. Occupational therapy.
   d. Educational services.
   e. Reassurance of patients that most of the clinical features can be explained by the diminished ability of the testes to produce testosterone.
   f. Testosterone replacement: Optimal time to initiate therapy is at age 11–12 years of age to allow for the maximum effect and permit boys to experience pubertal changes with their peers.
      i. Corrects hormone imbalance (symptoms of androgen deficiency)
      ii. Improves self-image
      iii. Positive effect on mood and behavior
      iv. Increase in masculinity
      v. Increase in strength
      vi. Increase in libido
      vii. Increase in facial and pubic hair
      viii. Diminish fatigue and irritability
      ix. No positive effect on infertility
   g. Management of gynecomastia
      i. Androgen replacement therapy effective in achieving regression of less severe gynecomastia in some patients
      ii. Reduction mammoplasty or liposuction for severe or psychologically disturbing gynecomastia
   h. Management of infertility (Lanfranco et al. 2004)
      i. Nowadays patients with Klinefelter syndrome, including the nonmosaic type, need no longer be considered irrevocably infertile because intracytoplasmic sperm injection offers an opportunity for procreation even when there are no spermatozoa in the ejaculate.
      ii. In a substantial number of azoospermic patients, spermatozoa can be extracted from testicular biopsy samples, and pregnancies and live births have been achieved.
      iii. The frequency of sex chromosomal hyperploidy and autosomal aneuploidies is higher in spermatozoa from patients with Klinefelter syndrome than in those from normal men. Thus, chromosomal errors might in some cases be transmitted to the offspring of men with this syndrome.
      iv. The genetic implications of the fertilization procedures, including pretransfer or prenatal genetic assessment, must be explained to patients and their partners.

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Fig. 1 A child with Klinefelter syndrome (47,XXY) showing normal phenotype

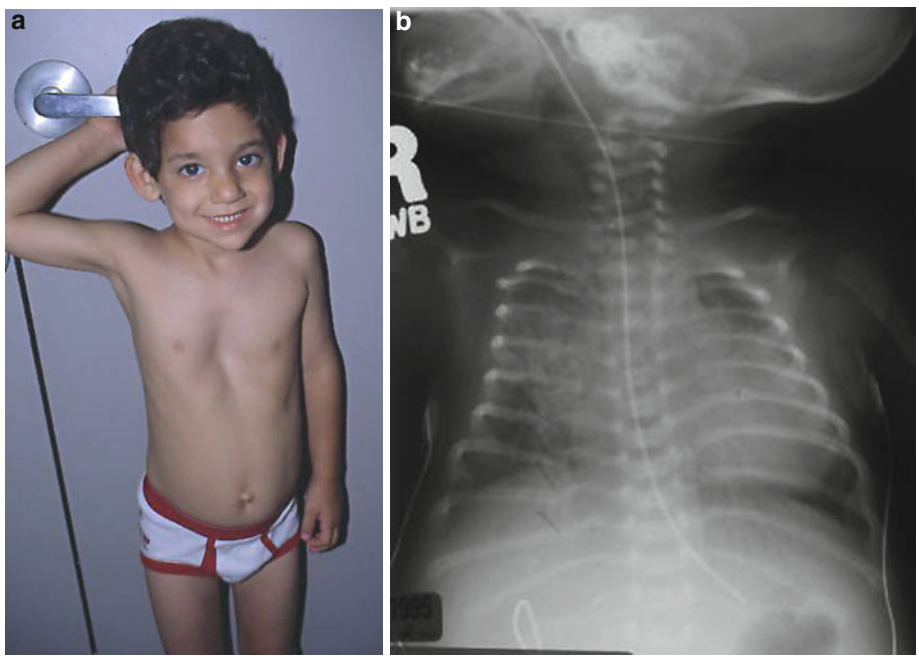

Fig. 2 (**a**, **b**) A child with Klinefelter syndrome (47,XXY) showing pectus excavatum and multiple fractures of ribs in the neonatal period during hospital stay

Fig. 3 The previous child at 14 years of age

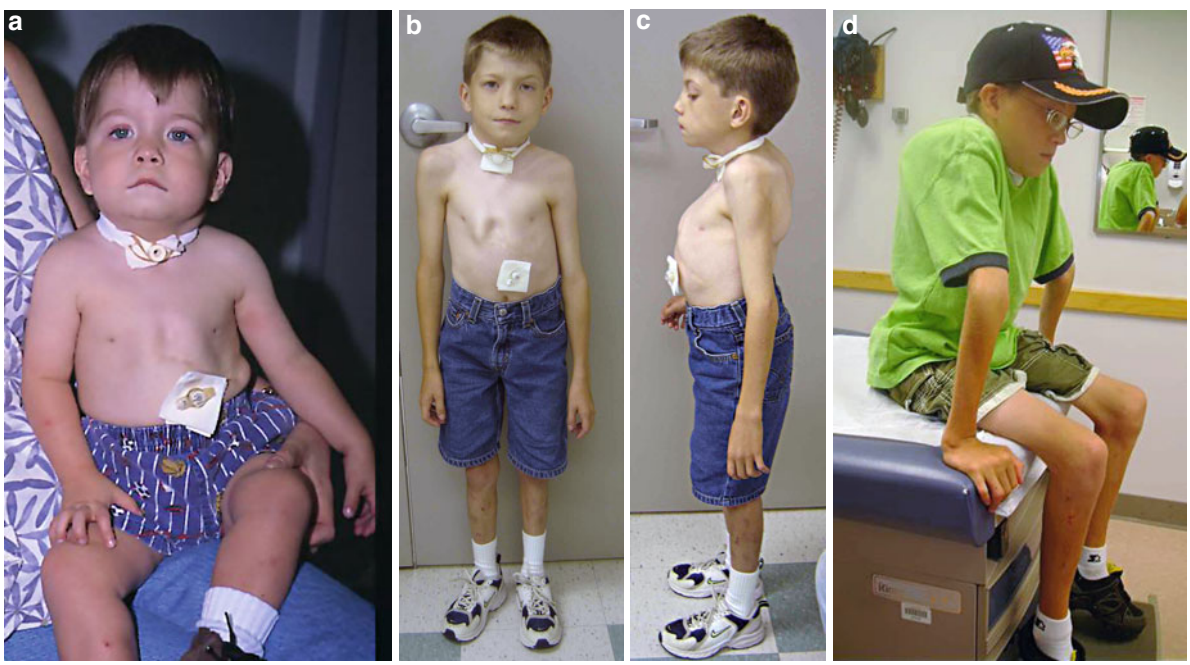

Fig. 4 (**a**–**d**) A child with Klinefelter syndrome (47,XXY) associated with paralyzed diaphragm requiring intubation. The photos were taken at early childhood, 9 and 12 years of age showing pectus excavatum, long extremities with hyperextended elbow, and kyphoscoliosis.

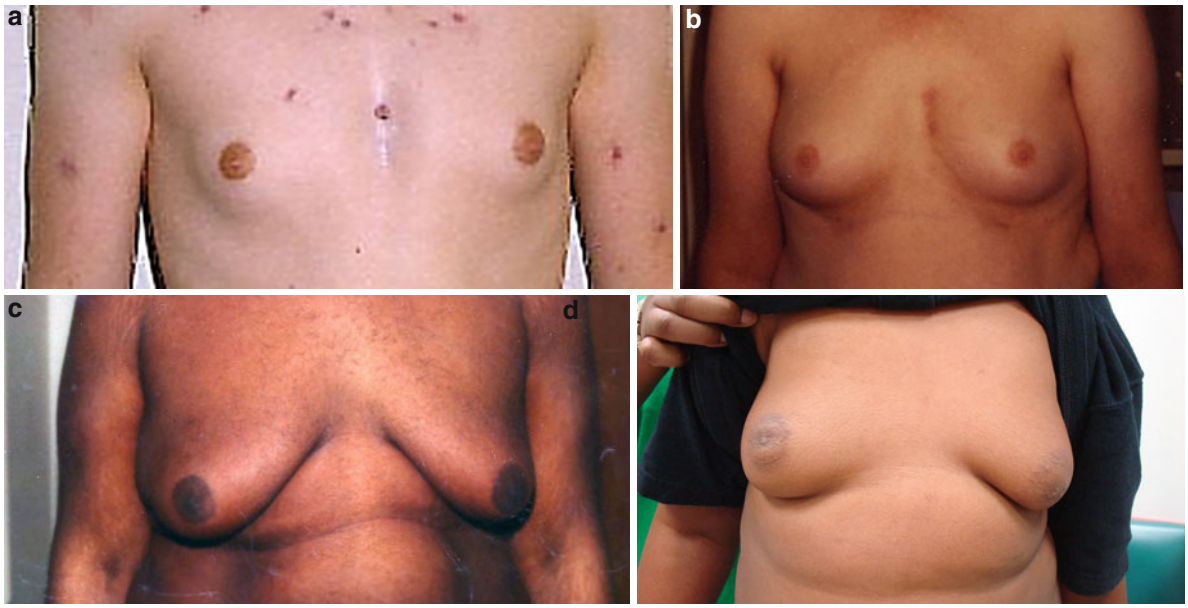

Fig. 5 (**a**–**d**) Two adolescent boys and two adults with Klinefelter syndrome (47,XXY) showing gynecomastia

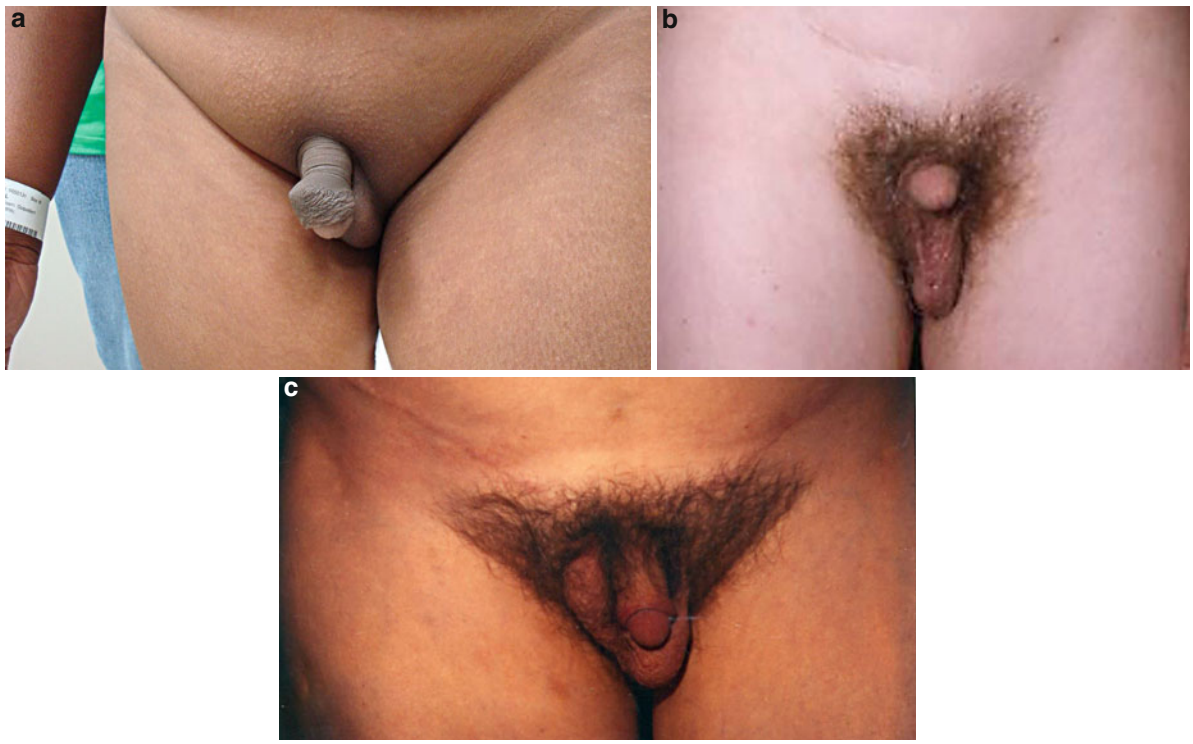

Fig. 6 (**a**–**c**) A 13-year-old boy, an adolescent boy and an adult male with Klinefelter syndrome (47,XXY) showing female distribution of pubic hair (last two patients) and small scrotum containing atrophic testicles

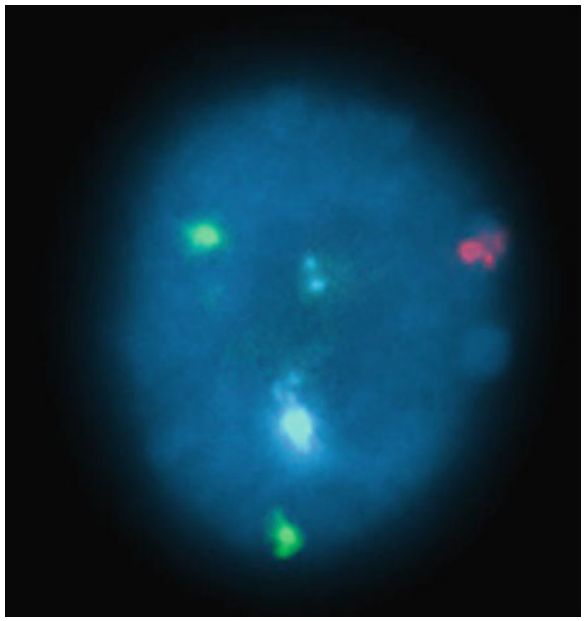

Fig. 7 Interphase FISH showing two copies of CEPX (*green*), one copy of CEPY (*orange*), and two copies of CEP18 (*aqua*), which was confirmed by chromosome karyotype of 47,XXY

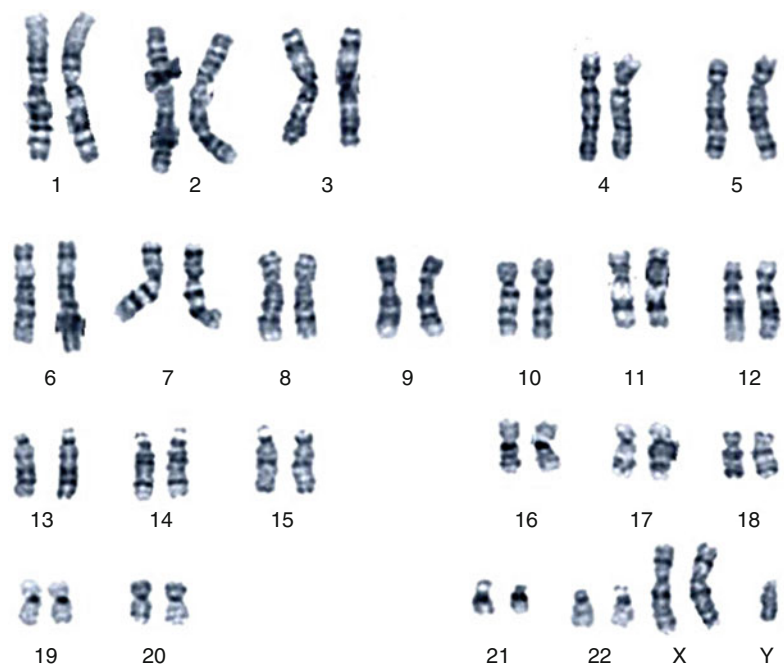

Fig. 8 A G-banded Karyotype showing 47,XXY chromosome constitution

Klippel–Feil Syndrome

In 1912, Klippel and Feil described a patient with a short neck, a low posterior hairline, and a severe restriction of motion of the neck due to complete fusion of the cervical vertebrae. These features now constitute a clinical triad of the Klippel–Feil syndrome (KFS) (Hensinger et al. 1974).

Synonyms and Related Disorders

Cervical vertebral fusion

Genetics/Basic Defects

1. Genetic etiology unknown.
   a. Sporadic in majority of cases
   b. Rare autosomal dominant transmission: identification of a familial KFS gene locus on 8q [inv(8)(q22.2q23.3)] segregated with congenital vertebral fusion
2. Mechanism: failure in the process of segmentation of the vertebra.
3. Possible causes of phenotypic variation (Pourguie and Kusumi 2001).
   a. Variable expression of single genes
   b. Associated phenotypes due to deletions or large-scale rearrangements that disrupt several genes
   c. Secondary phenotypes resulting from disruption of normal cervical vertebral patterning
4. Familial Klippel–Feil syndrome.
   a. Characterized by congenital fusion of spinal vertebrae in addition to other congenital anomalies
      i. Otolaryngological abnormalities
      ii. Craniofacial abnormalities
   b. The first KFS gene (*SGM1*) locus identified on chromosome 8q [inv(8)(q22.2q23.3)] segregating with vertebral fusions and associated vocal impairment within the family
5. Suggestion of a possible role of *PAX1* haploinsufficiency in Klippel–Feil syndrome (McGaughran et al. 2003).
   a. Observation that the mouse *PAX1* mutant phenotype *undulated* is characterized by vertebral segmentation defects reminiscent of the human disorder Klippel–Feil syndrome.
   b. Observation of differences in the *PAX1* sequence (missense, silent, or intronic changes not represented in the control panel tested) in 6 out of 63 patients.
6. Mutations in growth/differentiation factor 6 (*GDF6*, on chromosome 8q22.1) are associated with vertebral segmentation defects in Klippel–Feil syndrome (Tassabehji et al. 2008).
   a. Mutations at the *GDF6* gene locus in familial and sporadic cases of KFS including the recurrent missense mutation of an extremely conserved residue c.866T>C (p.Leu289Pro) in association with mirror movements and an inversion breakpoint downstream of the gene in association with carpal, tarsal, and vertebral fusions.
   b. *GDF6* is expressed at the boundaries of the developing carpals, tarsals, and vertebrae and within the adult vertebral disc.
   c. *GDF6* knockout mice are best distinguished by fusion of carpals and tarsals, and *GDF6* knockdown in *Xenopus* results in a high incidence of anterior axial defects consistent with a role for *GDF6* in the etiology.

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Clinical Features

1. Triad seen in <50% of patients indicating almost complete cervical involvement and may be clinically evident at birth (Herman and Pizzutillo 1999)
   a. Short, webbed neck
   b. Low posterior hairline
   c. Limitations of cervical motion (lateral bend and rotation) with associated congenital cervical fusions
2. Facial asymmetry
3. Torticollis
4. Associated anomalies
   a. Congenital scoliosis (60%)
   b. Sprengel deformity (30%)
      i. Congenital elevation of the scapula resulting from interruption of the normal caudal migration of the scapula
      ii. Hypoplastic scapula
      iii. Scapula fixation
      iv. Associated anomalies including absent or fused ribs, chest wall asymmetry, Klippel–Feil syndrome, cervical ribs, congenital scoliosis, cervical spina bifida, and presence of omovertebral bone
   c. Hearing impairment (audiologic testing) (30%)
   d. Synkinesia (mirror movements) (20%)
   e. Renal anomalies (35%) (renal ultrasound)
      i. Unilateral renal agenesis (most common renal anomaly)
      ii. Renal malrotation
      iii. Horseshoe kidney
      iv. Ectopic kidney
      v. Renal pelvic and ureteral duplication
      vi. Renal dysgenesis
   f. Congenital heart disease (14%): most common being ventricular septal defect
   g. Hemifacial microsomia
   h. Neural tube defects
   i. Ptosis
   j. Cervico-oculo-acoustic (Wildervanck) syndrome
      i. Mixed hearing loss
      ii. Fused cervical vertebra
      iii. Bilateral abducens palsy with retracted bulb (Duane syndrome)
   k. Lateral rectus palsy
   l. Facial nerve palsy
   m. Upper extremity anomalies
5. Complaints
   a. Issues of appearance
   b. Torticollis (head tilt)
   c. Neck pain
   d. Changes in exercise tolerance
   e. Excessive instability of the upper cervical spine
   f. Problems related to associated anomalies
   g. Neurological problems from direct irritation of or impingement on a nerve root or from compression of the spinal cord
      i. Cranial nerve abnormalities
      ii. Cervical radiculopathy from involvement of the nerve root
      iii. Symptoms from spinal cord compression
         a) Spasticity
         b) Hyperreflexia
         c) Muscle weakness
         d) Complete paralysis
      iv. At risk of sustaining a neurologic deficit including quadriplegia after minor trauma
6. Three clinical subtypes (Gunderson et al. 1967)
   a. Type I characterized by massive cervical and thoracic vertebral fusions into bony blocks
   b. Type II with fusion at one or two vertebral junctures, occipitoatlantal fusion, lower thoracic abnormalities, and more severe cervicothoracic fusions
   c. Type III with both cervical and lower thoracic or lumbar fusions
7. Risk factors
   a. Type I and III fusions
      i. Various neurologic, cutaneous, cardiac, skeletal, and oral anomalies
      ii. Difficulty in the birth process
      iii. Marked abnormal facial appearance with Sprengel deformity, accessory ear lobes, and pterygium colli
      iv. Serious neurologic anomalies with early death or long-term neurologic deficits
   b. Type II fusion
      i. Normal appearance
      ii. Normal lives
      iii. Incidental symptoms from osteoarthritis, basilar impression, or occiptio-atlas fusion
   c. Hypermobility of the upper cervical spine at increased risk of neurologic injury

with presentation of neurologic sequelae in the teens or 20s
   d. Lower cervical involvement at risk of developing cervical spondylosis at more advanced ages

Diagnostic Investigations

1. Audiologic evaluation for hearing loss
2. Renal ultrasonography
3. Radiography (Hensinger et al. 1974)
   a. Cervical spine fusion on flexion and extension views: roentgenographic hallmark of the Klippel–Feil syndrome
      i. Type I cervical fusion (C2–C3 fusion with occipitalization of the atlas)
      ii. Type II cervical fusion (long cervical fusion with an abnormal occipitocervical junction)
      iii. Type III cervical fusion (two blocked vertebral segments with a single open interspace)
   b. Other associated skeletal anomalies
      i. Flattening and widening of involved vertebral bodies
      ii. Absent disc spaces
4. CT scan helpful in diagnosing nerve root and spinal cord impingement by osteophyte
5. MRI to evaluate instability and the risk of neurological compromise
   a. Spinal stenosis
   b. Cord compression
   c. Syringomyelia
6. Molecular genetic diagnosis: clinically available
   a. Analysis of the entire coding region
   b. Sequence analysis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased unless a parent has an autosomal dominant disorder
   b. Patient's offspring: not increased unless the patient has an autosomal dominant type of the disorder
2. Prenatal diagnosis
   a. Ultrasonography: difficult to diagnose cervical vertebral anomalies and torticollis by ultrasonography
   b. Molecular genetic analysis on fetal DNA obtained from amniocentesis or CVS for *GDF6* mutation, provided the disease-causing allele of an affected family member has been identified prior to prenatal diagnosis
3. Management
   a. Treat renal, cardiovascular, and auditory anomalies accordingly
   b. Mechanical symptoms caused by degenerative joint disease
      i. Traction
      ii. Wearing a cervical collar
      iii. Analgesics
   c. Neurological symptoms
      i. Surgical stabilization with or without decompression
      ii. Surgical correction of Sprengel deformity to improve appearance

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Fig. 1 (**a**–**c**) A child with Klippel–Feil syndrome and Sprengel deformity showing torticollis, short/webbed neck, and inability to raise left arm due to congenital elevation of left scapula

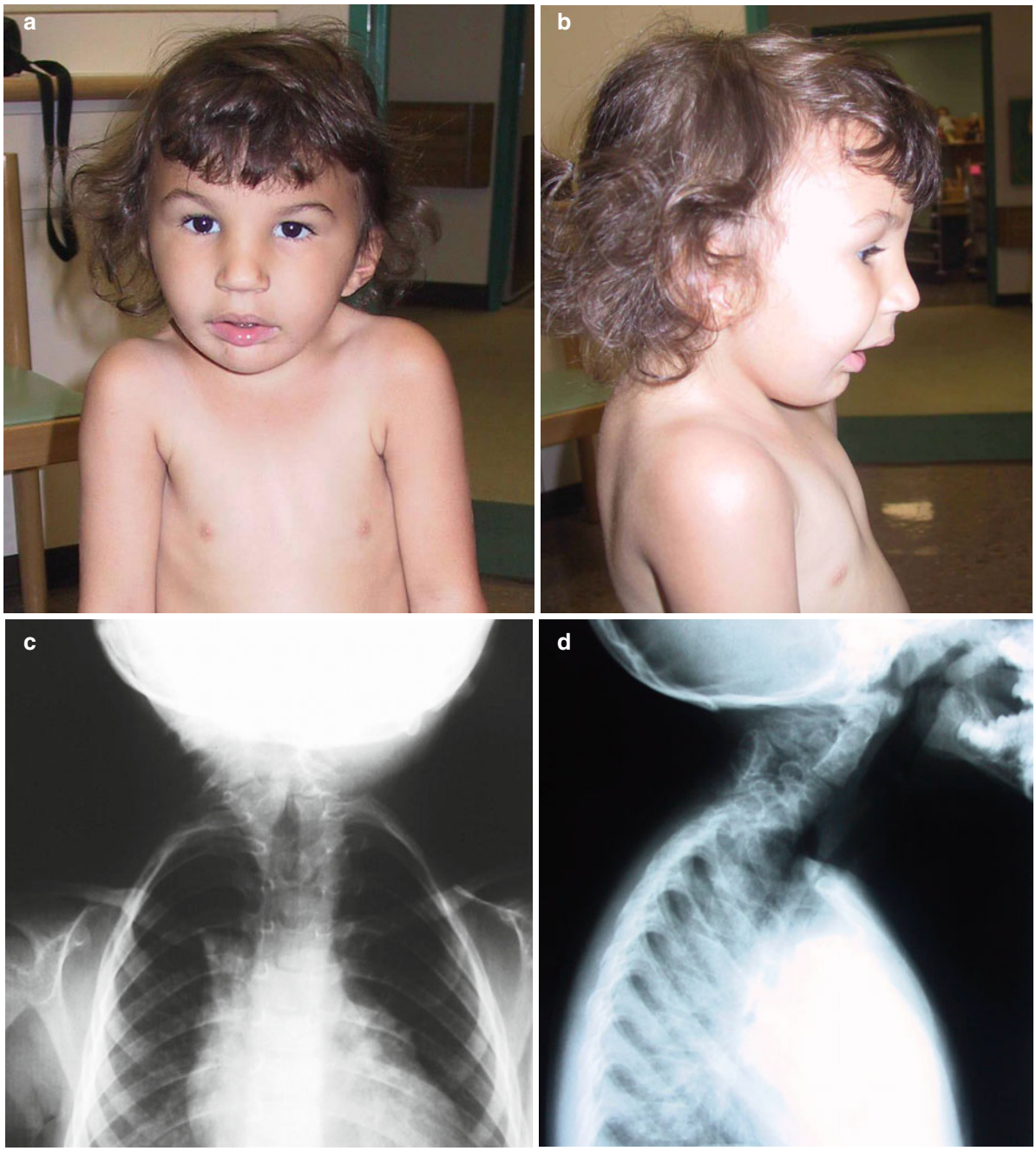

Fig. 2 (**a**–**d**) A girl with Klippel–Feil syndrome showing torticollis; short, webbed, and stiff neck; and cervical fusion (failure of segmentation) demonstrated by radiographs

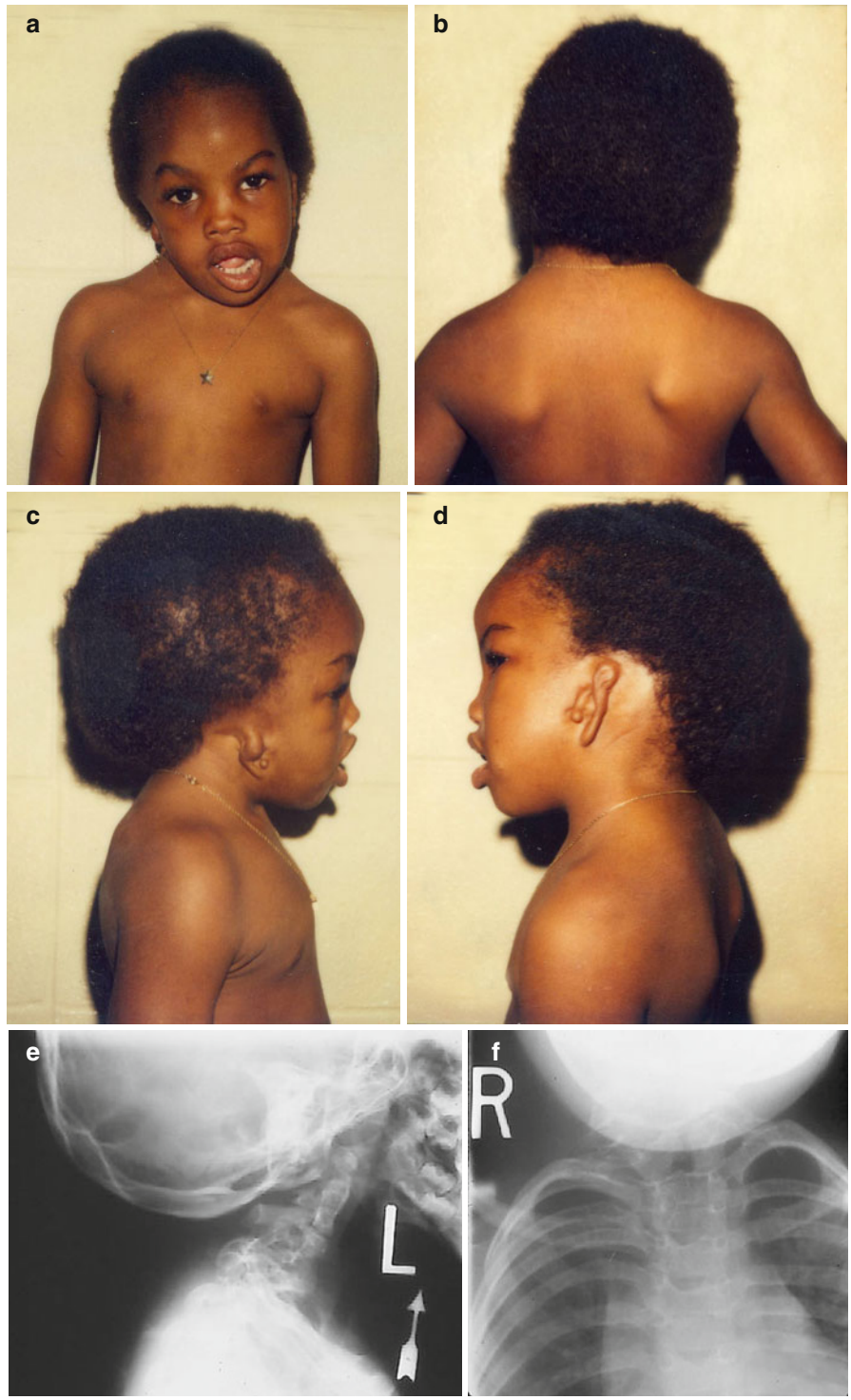

Fig. 3 (**a**–**f**) A child with Klippel–Feil syndrome showing torticollis; short, webbed, and stiff neck; hemifacial microsomia; microtia; and cervical fusion demonstrated by radiograph

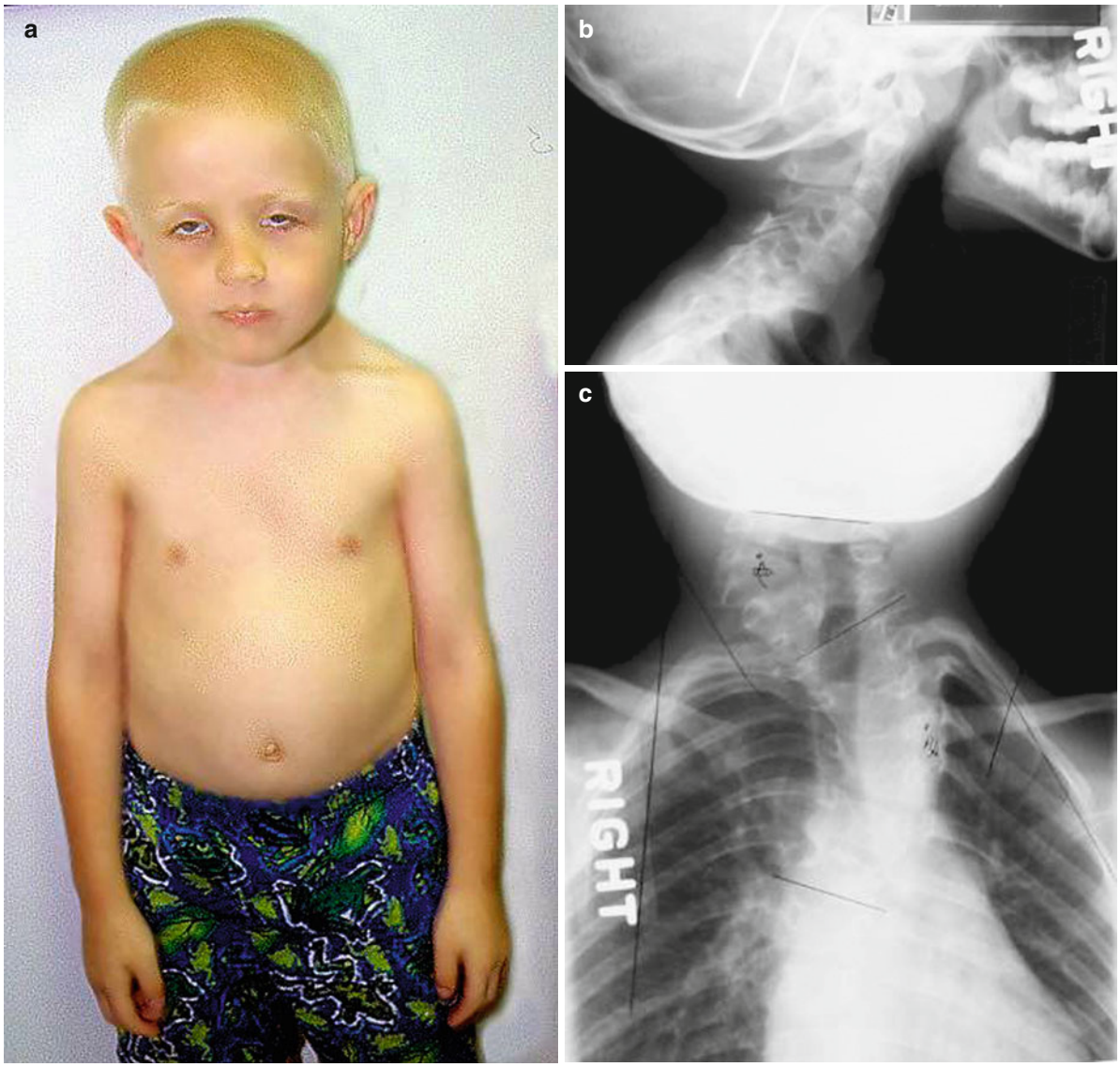

Fig. 4 (**a**–**c**) A 10-year-old with Klippel–Feil syndrome showing torticollis; short, webbed, and stiff neck; low posterior hairline; elevated left scapul; failure of segmentation (fusion) of the cervical vertebrae; and cervicothoracic scoliosis demonstrated by radiograph. He has no neurologic defects or cervical discomfort

Fig. 5 A 15-year-old with Klippel–Feil syndrome, Sprengel deformity, and deafness

Klippel–Trenaunay Syndrome

Klippel–Trenaunay syndrome (KTS) is primarily a rare congenital capillary-venous vascular malformation associated with altered limb bulk and/or length. In 1900, Klippel and Trenaunay first reviewed systematically a condition consisting of capillary nevus, early onset of varicosities, and hypertrophy of tissues and bones of the affected limb. These three features constitute the primary diagnostic criteria of the syndrome today. The additional name Weber is sometimes added to describe those individuals who also have clinically significant arteriovenous malformations as a component of the syndrome, an association noted by Weber in 1918. More than 1,000 cases of Klippel–Trenaunay syndrome have now been reported in the literature (Berry et al. 1998).

Synonyms and Related Disorders

Klippel–Trenaunay–Weber syndrome

Genetics/Basic Defects

1. Etiology
   a. Sporadic occurrence
   b. Somatic mutation of an as-yet-unknown gene
   c. Multifactorial inheritance
   d. Autosomal dominant inheritance with variable expression
2. Genetics of KTS (Wang 2005): three chromosomal abnormalities reported in three different KTS patients
   a. Two balanced translocations t(5;11)(q13.3;p15.1) (Tian et al. 2004).
      i. Chromosomal breakpoints involved in translocation t(5;11)(q13.3;p15.1) have been fully characterized, which has led to the identification of a susceptibility gene, *AGGF1* (previously known as *VG5Q*), for KTS.
      ii. *AGGF1* is located on chromosome 5q13.3 and encodes an angiogenic factor.
      iii. *AGGF1* as the first susceptibility gene that confers a risk to the development of KTS, and suggests that that the molecular mechanism for the pathogenesis of KTS is the "increased" angiogenesis. These results are consistent with histological studies that showed an increase in both the number and diameter of the venules in the dermis and subdermal fat of KTS tissues (Baskerville et al. 1985).
   b. Translocation t(8;14)(q22.3;q13) (Wang et al. 2001) and an extra supernumerary ring chromosome 18 (Timur et al. 2004) were reported in patients with KTS.
      i. Shown to arise de novo, which strongly suggests that genetic factors contribute to the pathogenesis of KTS.
      ii. The specific vascular gene disrupted by either 8q22.3 or 14q13 breakpoints remains to be identified.
      iii. The ring chromosome 18, r(18), was mostly derived from the short arm of chromosome 18, and further analyses of the genes on the r (18) may lead to the identification of a vascular gene.
   c. Sporadic occurrence of KTS and a mosaic pattern of KTS features may be explained by the two-hit hypothesis and the concept of

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paradominant inheritance proposed by Happle (Happle 1986, 1987, 1993).
   i. Germline mutations in a KTS gene (e.g., *AGGF1*) are important for development of KTS, but not sufficient
   ii. A "second hit," somatic mutation in the same KTS gene or in a different gene is required for the development of KTS features
3. Possible mechanisms/pathogenesis leading to overgrowth of the affected limb: poorly defined
   a. Two phases of manifestations
      i. Increased bulk or girth
      ii. Increased length accompanied by bone enlargement
   b. Increased girth and size of bone due to venous hypertension, based on observations following hind leg deep vein ligation in dogs
   c. Atresia of the venous system leading to stasis, edema, varicosities, and ultimately to limb elongation and hypertrophy
   d. Limb enlargement seen in children following thrombosis or ligation of a deep vein postnatally
   e. Overgrowth in fetal life promoted by increased blood flow through the abnormal capillary network and cutaneous venous channels
   f. A mesodermal defect acting on angiogenesis leading to the formation of hemangiomas and varicose veins (Martin et al. 2001)
   g. A defect in the process of vessel remodeling during embryogenesis

Clinical Features

1. Triad (Berry et al. 1998; Cohen 2000)
   a. Combined vascular malformations of the capillary, venous, and lymphatic types
   b. Varicosities of unusual distribution, in particular the lateral venous anomaly observed during infancy or childhood
   c. Limb enlargement
2. Cutaneous manifestations
   a. Primarily a diffuse capillary malformation
   b. Typically present on an affected limb
   c. May be present on any body part
   d. Often presenting as an irregular but relatively linear border
   e. Rarely crossing the midline when present on the trunk, sometimes exhibiting a sharp demarcation
3. Vascular malformations
   a. Typically combined with cutaneous capillary malformation
   b. Persistence of abnormal superficial veins associated with deep venous hypoplasia/duplications and abnormal venous valve formation
   c. Presence of mixed vascular malformations including capillary, venous, arterial, and lymphatic systems
   d. Classification of vascular malformations by Mulliken and Glowacki (1982)
      i. Capillary-venous malformation (CVM): typical finding
      ii. CVLM (CVM+lymphatic malformation): common finding
      iii. CLAVM (including arterial malformation): uncommon
   e. Congenital in nature
   f. Not responding to agents used in the treatment of hemangiomas such as prednisone or interferon-α
4. Limb hypertrophy
   a. Due to an increase in bulk of the subcutaneous tissues
   b. Bony hypertrophy
5. Sites of involvement (Mueller-Lessmann et al. 2001)
   a. Lower limb most common (about 95%)
   b. Upper limb (about 5%)
   c. Trunk only: uncommon
   d. Orofacial involvement
      i. Jaw enlargement
      ii. Facial asymmetry
      iii. Malocclusions
      iv. Premature tooth eruption
      v. Hemangioma of the lips, tongue, and oral mucosa
6. Sex ratio: males and females affected equally
7. Complications
   a. Abnormal vasculature
      i. Thrombosis
      ii. Coagulopathy
      iii. Pulmonary embolism
      iv. Heart failure (in the presence of significant AVM)
      v. Bleeding from abnormal vessels in gut, kidney, or genitalia

b. Gastrointestinal varicoses
   i. Bleeding
   ii. Pain
   iii. Diarrhea
c. Protein-losing enteropathy secondary to intestinal lymphangiectasia
d. Infection is a particular risk for patients with abnormal lymphatic drainage. Antibiotics indicated in:
   i. Cellulitis
   ii. Surgery
   iii. Injury in an affected limb
e. Pain due to venous insufficiency or lymphedema in some older children and adults
f. Venous thromboembolism
   i. Chronic thromboembolic pulmonary hypertension
   ii. Subsequent right ventricular failure
g. Occurrence of ulceration on affected leg
h. Rare occurrence of skin tumors on the affected limb
   i. Squamous cell carcinoma possibly secondary to a long-standing venous ulcer
   ii. Basal cell carcinoma
i. Pregnancy and KTS: known perinatal risks to both the mother and fetus (Fait et al. 1996; Stein et al. 2006)
   i. Hemorrhage secondary to increased hemangiomas and varices
   ii. Deep and superficial thrombosis
   iii. Acute and chronic disseminated intravascular coagulation
   iv. Kasabach–Merritt syndrome (Neubert et al. 1995)
   v. Placental abnormalities

8. Four levels of severity of Klippel–Trenaunay syndrome (You et al. 1983)
   a. Venous dysplasias: phlebectasic dysplasias (Klippel–Trenaunay syndrome)
   b. Arterial dysplasias
   c. Arterial and associated venous dysplasias:
      i. Phlebarterectasia (no arteriovenous shunt)
      ii. Angiodysplasias with shunt (Klippel–Trenaunay–Weber syndrome)
   d. Mixed angiodysplasias: a typical Klippel–Trenaunay syndrome
9. Diagnostic criteria: Presence of two of the three following cardinal features is sufficient to make a diagnosis (Jacob et al. 1998)
   a. Capillary malformations (98%)
   b. Venous malformations or varicose veins (72%)
   c. Hypertrophy of the affected tissues (67%)
10. Diagnostic criteria and proposed definition: two major features at least one from congenital vascular malformations, which should always include either capillary malformations or venous malformations and at least one from disturbed growth (bi or bii) (Oduber et al. 2008)
   a. Congenital vascular malformations
      i. Capillary malformations (CMs). This includes port-wine stains
      ii. Venous malformations (VMs): This includes hypoplasia or aplasia of veins, persistence of fetal veins, varicosities, hypertrophy, tortuosity, and valvular malformations
      iii. Arteriovenous malformations (AVMs): This includes only very small AVMs or arteriovenous fistulas (AVF)
      iv. Lymphatic malformations (LM): This includes any LM
      v. Localization
         a) CM can be located anywhere on the body, although location in the face is exceedingly rare
         b) AVM, VM, and LM are mainly located on the extremities and adjacent parts of the trunk (pelvis, shoulder) but in expressed forms of KTS also elsewhere (bladder, rectum, lower GI tract, penis, uterine, vulva, vagina, liver, kidneys, lung, spine)
         c) AVM, VM, and LM are not located in the face or brain
   b. Disturbed growth
      i. Disturbed growth of bone in the length or girth
      ii. Disturbed growth of soft tissue in the length or girth
      iii. The disturbed growth includes:
         a) Hypertrophy (frequent) of a small body part (isolated finger, macrodactyly) or larger body part (total limb, half of the total body)

b) Hypotrophy (infrequent) of a small or larger body part
iv. Can be present both on the same site as the vascular malformation(s) (frequent) and at another site (infrequent)

11. Four commonly held conceptions about Klippel–Trenaunay syndrome challenged
    a. Renaming Klippel–Trenaunay–Weber syndrome by addition of arteriovenous fistulas
        i. Significant arteriovenous communications not observed in Klippel–Trenaunay syndrome in large surgical series
        ii. Parkes Weber syndrome characterized by enlarged arteries and veins, capillary or venous malformations and enlargement of a limb
        iii. Lymphatic malformations found in Klippel–Trenaunay syndrome not observed in Parkes Weber syndrome
    b. Overlap with Sturge–Weber syndrome
        i. Characteristics of Sturge–Weber syndrome: craniofacial angiomatosis, port-wine nevus, and cerebral calcification.
        ii. Overgrowth in Sturge–Weber syndrome tends to be minor and is always secondary to the vascular anomaly. In contrast, overgrowth in Klippel–Trenaunay syndrome is striking.
    c. Presence of a bleeding diathesis of the Kasabach–Merritt type
        i. Kasabach–Merritt syndrome erroneously applied to patients with extensive venous or lymphaticovenous malformations who develop a localized intravascular coagulopathy in which the platelet count is minimally depressed (varying from 50,000 to 150,000/mm^3)
        ii. Profound thrombocytopenia in true Kasabach–Merritt phenomenon (varying from 3,000 to 60,000/mm^3)
    d. Familial aggregation with various genetic interpretations
        i. Inadequate documentation of cases
        ii. Over interpretation of minor manifestations in relatives, including "nevus flammeus," hemangiomas, and varicosities (common manifestations in general populations)
        iii. Klippel–Trenaunay syndrome defined as a capillary malformation with or without "hemihypertrophy" without mentioning of lymphatic malformations, lateral venous anomaly, lymphatic vesicles, or venous flares within the capillary malformation, or macrodactyly
    e. Klippel–Trenaunay syndrome, Parkes Weber syndrome, and Sturge–Weber syndrome
        i. Each occurring sporadically
        ii. Each considered separate entity because clinical manifestations and types of complications are different

Diagnostic Investigations

1. Color duplex ultrasonography (Berry et al. 1998)
    a. AV malformation
    b. Deep venous hypoplasia (a decrease in caliber of at least 50% of a vein along its length)
    c. Venous duplication
    d. Variable varicosities
2. Radiography
    a. Enlargement of the limb bones
    b. Yearly to monitor evidence of leg length discrepancy
3. Noninvasive imaging and endoscopy for severe gastrointestinal bleeding
4. Lymphoscintigraphy using radionuclide tracers
    a. Indication: edema or a girth discrepancy more than 4 cm
    b. No uptake of tracer along major lymphatics of the affected limb during repeated scans over at least a 1-h period
5. MRI
    a. Pelvis: to look for vascular malformations involving the kidneys, bladder, or intestines
    b. MRI with gadolinium to distinguish lymphatic from venous malformations
    c. Magnetic resonance venogram or phlebography/venography to document the lateral venous anomaly and any abnormalities that may be present in the deep veins of the leg
    d. Able to demonstrate arteriovenous fistulas in Parkes Weber syndrome

Genetic Counseling

1. Recurrence risk
    a. Patient's sib: not increased
    b. Patient's offspring: not increased (doubtful that autosomal dominant inheritance exists)

2. Prenatal diagnosis
   a. Ultrasonography
      i. Asymmetric limb hypertrophy associated with cutaneous or subcutaneous cystic or multicystic lesions
      ii. Limb edema
      iii. Cardiac failure ranging from isolated cardiomegaly to severe hydrops
   b. MRI
      i. Limb hypertrophy
      ii. Multiple subcutaneous and internal hemangiomas
      iii. Good definition of soft tissue lesions
      iv. Identify vascular malformations and their extent
      v. Presence of low signal indicating flow voids, hemosiderin deposits or calcification indicative of vascular malformations
3. Management (James et al. 1999; Gloviczki and Driscoll 2007)
   a. Elastic garment or compression bandage: beneficial in managing both lymphedema and chronic venous insufficiency
   b. Physical therapy using massage treatment and intermittent pneumatic compression therapy
   c. Local wound care, compression dressings, special orthopedic footwear, and lifestyle modification
   d. Psychological support: participate in the activities of a support group
   e. Stripping of superficial varicose veins
   f. Pulsed dye laser treatment for superficial hemangioma component (Jih 2003)
   g. Sclerotherapy and embolotherapy
   h. Reduction of significant arteriovenous malformations
   i. Rare reconstructive surgery at sites of deep venous obstruction
   j. Orthopedic procedures for overgrowth
      i. Significant leg length discrepancy (epiphysiodesis)
      ii. Excision of soft tissue hypertrophy

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Fig. 1 A newborn with Klippel–Trenaunay syndrome showing overgrowth of left leg with vascular malformation

Fig. 2 A neonate with Klippel–Trenaunay syndrome showing left leg overgrowth with vascular malformation

Fig. 3 (**a**, **b**) A boy with Klippel–Trenaunay syndrome showing overgrowth of the right arm and leg with vascular malformation

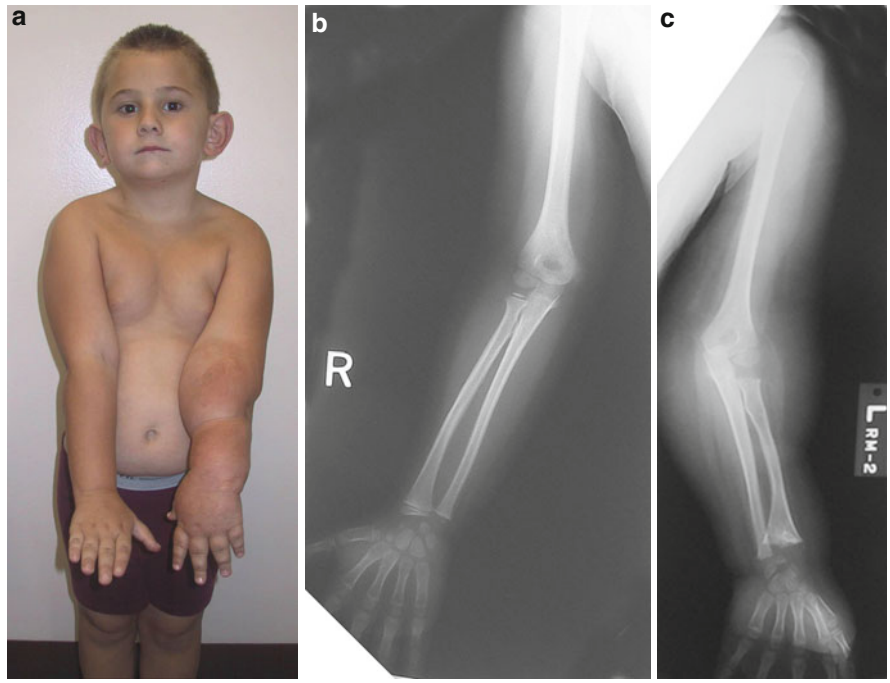

Fig. 4 (**a**–**c**) A 6-year-old boy with Klippel–Trenaunay syndrome showing overgrowth of left arm (illustrated by radiographs) associated with vascular malformation

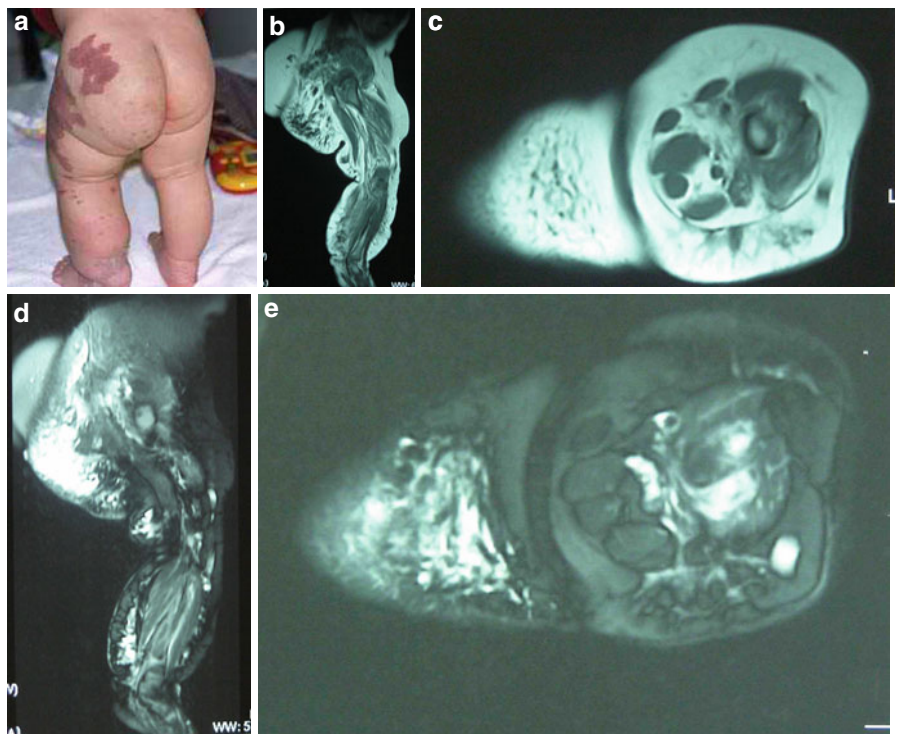

Fig. 5 A 1-year-old infant with Klippel–Trenaunay syndrome showing asymmetric lower extremities with hypertrophic left lower extremity associated with vascular malformation (**a**). T1-enhanced MRI (**b**, **c**) and T2-enhanced MRI (**d**, **e**) images at thigh level show cystic and vascular lesions, indicated by high signals suggesting lymphangiomas and hemangiomas

Kniest Dysplasia

Kniest dysplasia is a type II collagenopathy with characteristic clinical, radiographic, and histological findings. Kniest dysplasia is distinguished by platyspondyly and delay in ossification of the proximal epiphyses. After ossification, the epiphyses are enlarged resulting in dumbbell-shaped long bones.

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant (Wilkin et al. 1999)
   b. New dominant mutations in most cases
2. Molecular basis
   a. Caused by mutations in the gene (*COL2A1*) that encodes type II collagen, the predominant protein of cartilage
   b. A specific type of mutation and/or position of mutation within the collagen chain may explain the unique features of Kniest dysplasia among the type II collagenopathies
3. Kniest dysplasia in the middle of the following phenotypic spectrum of disease
   a. Achondrogenesis type II/hypochondrogenesis at the severe end
   b. Spondyloepiphyseal dysplasias/spondyloepimetaphyseal dysplasias in the middle
   c. Genetically heterogeneous Stickler syndrome and familial osteoarthritis at the milder end

Clinical Features

1. Sk eletal anomalies (Wilkin et al. 1999)
   a. Disproportionate dwarfism
   b. A short trunk
   c. Short, slightly bowed limbs
   d. More severe rhizomelic shortness in the lower limbs
   e. Prominent joints
   f. Delayed motor milestones secondary to joint deformities
   g. Progressive and painful joint enlargement accompanied by joint contractures
   h. Muscle atrophy resulting from disuse
   i. Short and broad thorax with sternal protrusion
   j. Kyphoscoliosis
      i. Dorsal kyphosis
      ii. Accentuated lumbar lordosis
      iii. Thoracic scoliosis
   k. Odontoid hypoplasia resulting in atlantoaxial instability
   l. Clubfoot
   m. Small pelvis
   n. Premature osteoarthritis that restrict movement
   o. Waddling gait
2. Craniofacial characteristics
   a. Relatively large head
   b. Flat face
   c. Shallow supraorbital ridges

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   d. Prominent eyes
   e. Flat nasal bridge
   f. Short nose
   g. Micrognathia
   h. Cleft palate
3. Ocular manifestations
   a. Abnormal long axial length causing high early-onset myopia
   b. Vitreoretinal degeneration
   c. Retinal detachment
   d. Cortical and posterior subcapsular opacity of the lens
   e. Veil-like vitreous opacity in the periphery
   f. Congenital glaucoma
   g. Blindness
4. Hearing loss
5. Prognosis: phenotype varying significantly
   a. Frequently potentially life-threatening complications
      i. Early postnatal tracheomalacia resulting in respiratory insufficiency and feeding difficulties
      ii. Secondary failure to thrive
   b. Can lead a relatively normal life with mild disproportionate short stature, kyphoscoliosis, and/or craniofacial manifestations

Diagnostic Investigations

1. Radiography (Gilbert-Barnes et al. 1996; Wilkin et al. 1999)
   a. Distinguishing radiographic features from other type II collagenopathies identifiable at birth
      i. Coronal clefts of the vertebrae
      ii. Dumbbell-shaped femora
   b. Other radiographic features
      i. Narrowed joint spaces
      ii. Platyspondyly
      iii. Kyphoscoliosis
      iv. Short tubular bones
      v. Dysplastic epiphyses and metaphyses
         a) Broad metaphyses
         b) Enlarged and deformed epiphyses
2. MR imaging of both unossified and ossified epiphyses reveals a similar pattern of lakes of bright T2 signal against a relatively normal background, representing an interesting analogue to the histologic and radiographic features (Dwek 2005)
3. Histopathology (Gilbert-Barnes et al. 1996)
   a. Pathologic changes of cartilage
      i. "Swiss cheese" appearance of the cartilage matrix (a bizarre pattern of chondrocytes lying amid a highly vacuolated matrix) (Dwek 2005)
      ii. Ossified epiphyses: unusual in showing clouds of dense punctuate calcifications randomly distributed throughout
      iii. Soft crumbly cartilage
   b. Microscopic changes
      i. Disorganization of the growth plate.
      ii. Deficiency of collagen matrix.
      iii. Poorly staining cartilage with myxoid degeneration.
      iv. PAS positive cytoplasmic inclusions in many chondrocytes. Ultrastructurally, the inclusions correspond to pools of proteinaceous material within dilated rough endoplasmic reticulum.
4. Hearing test
5. Visual evaluation
6. Molecular genetic analysis of *COL2A1* gene mutation
   a. Targeted mutation analysis
   b. Mutation scanning
   c. Sequencing of entire coding region

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: low recurrence risk unless a parent is affected or has gonadal mosaicism
   b. Patient's offspring: 50%
2. Prenatal diagnosis
   a. Difficult to diagnose Kniest dysplasia by early sonography since the biometry does not become notably abnormal until the third trimester (Bromley et al. 1991).
   b. Fetal MRI findings: By delineating the cartilaginous abnormalities, fetal MRI can contribute to the prenatal diagnosis of chondrodysplasias (Yazici et al. 2010).
      i. Enlarged hyaline cartilaginous structures with abnormally high T2 signal intensity
      ii. Delayed ossification of the pubic and ischial bones
      iii. Platyspondyly

c. Molecular genetic analysis of *COL2A1* mutation on fetal DNA obtained from amniocentesis or CVS for previously characterized disease-causing gene mutation in the proband.

3. Management
   a. Cleft palate repair
   b. Hearing aid for hearing loss
   c. Vitrectomy and silicon oil injection for reattaching the retina from retinal detachment
   d. Orthopedic care for clubfoot and kyphoscoliosis

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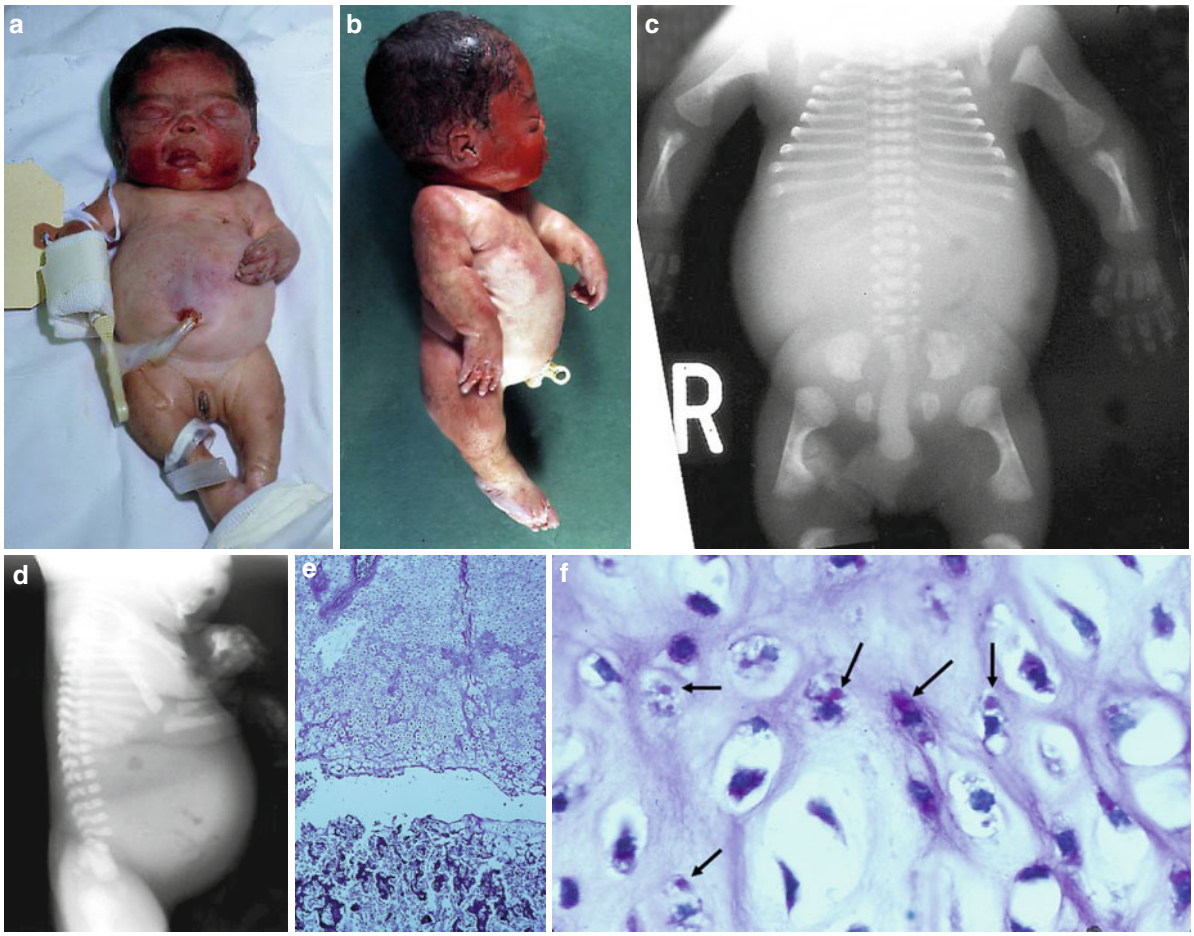

Fig. 1 (**a**–**f**) A neonate with Kniest dysplasia showing short trunk and large head, similar to SED congenita. However, the moderately shortened limbs show prominent joints. Radiographs show enlarged metaphyses of limb bones (dumbbell-shaped femora) and coronal clefts of the vertebrae. The remaining findings are similar to those of SED congenita. The physeal growth zone of femur is hypercellular and disorganized. The transverse cleft beneath the physis is an artifact. Many chondrocytes contain cytoplasmic inclusions (*arrows*); they are seen in the resting cartilage and the zone of proliferation, similar to those of SED congenita

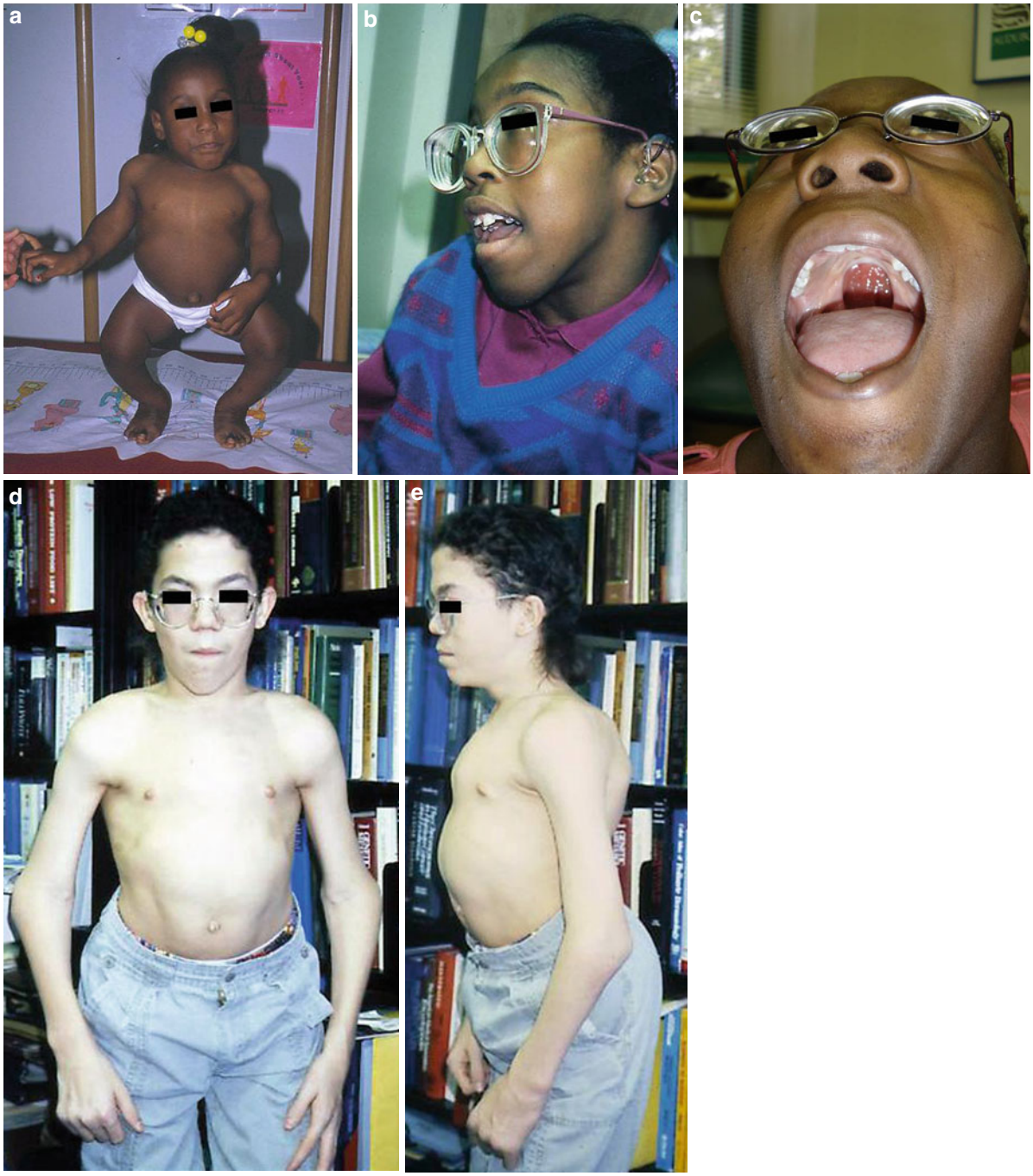

Fig. 2 (**a**–**e**) Three children with Kniest dysplasia showing varying features of the dysplasia: short trunk dwarfism, flat facies, myopia, cleft palate, deafness requiring hearing aids, dorsal kyphosis, accentuated lumbar lordosis, short and broad thorax with sternal protrusion, and prominent joints with restricted joint mobility

Larsen Syndrome

In 1950, Larsen et al. described a condition characterized by multiple large joint dislocations and flat face (Larsen et al. 1950). The condition occurs in approximately 1 in 100,000 births.

Synonyms and Related Disorders

Lethal Larsen-like syndrome; Multiple joint dislocations, short stature, craniofacial dysmorphism, and congenital heart defects

Genetics/Basic Defects

1. Subtypes
   a. Sporadic form
   b. Autosomal dominant form
   c. Autosomal recessive form: clinical phenotype more debilitating with higher mortality than the autosomal dominant form
   d. Possible lethal form
2. The first known gene mutated in Larsen syndrome, *LAR1*, for autosomal dominant form: mapped to 3p21.1-14.1 in the proximity of, but distinct from, the *COL7A1* locus.
3. Clinical similarities between Larsen syndrome and a group of lethal osteochondrodysplasias including atelosteogenesis types I (AOI) and III (AOIII) and boomerang dysplasia suggested that they represent an allelic series of conditions (Hunter and Carpenter 1991; Sillence et al. 1997).
   a. These more severe dysplasias are characterized by underossification of skeletal elements, hypoplastic or absent limb bones, joint dislocations, and craniofacial abnormalities.
   b. These observations, with the phenotypic similarities between Larsen syndrome and otopalatodigital syndrome type 1 (OPD1), an X-linked skeletal disorder caused by mutations in *FLNA* (Robertson et al. 2003), the gene encoding filamin A, led to the description of mutations in the paralogous gene filamin B gene (*FLNB*) underlying Larsen syndrome, AOI, AOIII, and boomerang dysplasia. (Bicknell et al. 2005; Krakow et al. 2004).
   c. Mutations leading to AOI and AOIII were clustered in calponin homology domain 2 (CH2) and repeats 13–17 (Farrington-Rock et al. 2006).
4. Molecular and clinical study of Larsen syndrome caused by mutations in *FLNB* (Bicknell et al. 2007)
   a. The clinical signs most frequently associated with an *FLNB* mutation are the presence of supernumerary carpal and tarsal bones and short, broad, spatulate distal phalanges, particularly of the thumb.
   b. All individuals with Larsen syndrome–associated *FLNB* mutations are heterozygous for either missense or small inframe deletions.
      i. Three mutations are recurrent, with one mutation, 5071GRA, observed in 6 of 20 subjects.
      ii. The distribution of mutations within the *FLNB* gene is nonrandom, with clusters of mutations leading to substitutions in the actin-binding domain and filamin repeats 13–17 being the most common cause of Larsen syndrome.

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   c. These findings collectively define autosomal dominant Larsen syndrome and demonstrate clustering of causative mutations in *FLNB*.
5. Molecular basis of recessive Larsen syndrome (Hermanns et al. 2008)
   a. Eight *CHST3* (carbohydrate sulfotransferase 3, also known as chondroitin 6-sulfotransferase) mutations, causing CHST3 deficiency, were identified in six unrelated individuals who presented at birth with congenital joint dislocations.
      i. These patients had been given a diagnosis of either Larsen syndrome (three individuals) or humero-spinal dysostosis (three individuals), and their clinical features included congenital dislocation of the knees, elbow joint dysplasia with subluxation and limited extension, hip dysplasia or dislocation, clubfoot, short stature, and kyphoscoliosis developing in late childhood.
      ii. Analysis of chondroitin sulfate proteoglycans in dermal fibroblasts showed markedly decreased 6-O-sulfation but enhanced 4-O-sulfation, confirming functional impairment of CHST3 and distinguishing them from diastrophic dysplasia sulfate transporter (DTDST)–deficient cells.
   b. These observations provide a molecular basis for recessive Larsen syndrome and indicate that recessive Larsen syndrome, humero-spinal dysostosis, and spondyloepiphyseal dysplasia Omani type form a phenotypic spectrum.
6. Unilateral manifestation of typical skeletal defects in some patients indicates that this condition might represent unilateral somatic cell-line mosaicism.

Clinical Features

1. Broad inter- and intrafamilial clinical variability
2. Characteristic flat facial appearance ("dish face")
   a. Prominent forehead (frontal bossing)
   b. Hypertelorism
   c. Hypoplastic midface
   d. Depressed nasal bridge
   e. Micrognathia
   f. Occasional cleft palate, lip, or uvula
3. Bilateral multiple joint dislocations
   a. Shoulders
   b. Elbows
   c. Wrists
   d. Hips
   e. Patella
   f. Ankles
   g. Knees
4. Variable handicap due to joint luxations
5. Hand abnormalities
   a. Long, cylindrical, and tapering fingers (pseudoclubbing)
   b. Spatulate/bifid thumbs
   c. Dislocation of distal radioulnar joint
   d. Delayed carpal ossification
   e. Supernumerary ossification centers
   f. Brachymetacarpia
   g. Brachytelephalangia
   h. Hyperextension of distal interphalangeal joints
6. Feet abnormalities
   a. Spatulate hallux
   b. Equinovarus or valgus deformities of the feet
7. Respiratory distress due to tracheolaryngomalacia
   a. Stridor
      i. Inspiratory reflecting laryngomalacia or extrathoracic cervical tracheomalacia
      ii. Expiratory reflecting intrathoracic tracheomalacia
   b. Cyanosis
   c. Obstructive apnea
   d. Possibly life-threatening
8. Bronchomalacia
   a. Lobar atelectasis
   b. Hyperinflation
   c. Pneumonias
9. Respiratory embarrassment in infancy due to soft tracheolaryngeal cartilage
10. Soft/collapsing thorax
11. Cardiovascular abnormalities
   a. Congenital defects
      i. Bicuspid aortic valve
      ii. Subaortic stenosis
      iii. Atrial septal defect
      iv. Ventricular septal defect
      v. Patent ductus arteriosus
      vi. Pulmonary stenosis
      vii. Endocardial fibroelastosis

b. Acquired lesions
   i. Dilated aortic root
   ii. Elongated aorta
   iii. Mitral valve prolapse
   iv. Aneurysm of ductus arteriosus
   v. Arterial tortuosity and dilatation
12. Associated spinal anomalies (Banks et al. 2003)
   a. Cervical spine involvement
      i. More often affected than thoracic or lumbar spine
      ii. Results in:
         a) Midcervical kyphosis, usually at the C4-5 region
         b) Cervicothoracic lordosis
         c) Spinal instability
      iii. Flattened, hypoplastic, and often bifid cervical vertebrae
   b. Atlantoaxial instability
      i. A rare finding
      ii. May be associated with other abnormalities of the upper cervical spine
         a) Occipitalization of the atlas
         b) Basilar impression
   c. Lumbosacral dysraphism: may lead to neurological impairment
   d. Thoracic scoliosis
   e. Hypoplasia of the vertebral bodies or posterior elements
   f. Quadriplegia secondary to segmentation abnormalities of the vertebrae
13. Mixed hearing loss due to ossicular abnormality
14. CNS anomalies
   a. Hydrocephalus (rare)
   b. Glial proliferation in the brain
15. Short stature
16. Normal intelligence
17. Possible lethal form
   a. Tracheomalacia
   b. Pulmonary hypoplasia
   c. Collagen fiber dysmaturity
18. Prognosis
   a. Generally good after aggressive orthopedic management, except some lethal cases due to tracheolaryngomalacia and/or lung hypoplasia
   b. Compatible with successful pregnancy if the maternal and fetal safety issues are properly considered

Diagnostic Investigations

1. Radiography
   a. Bilateral dislocations of shoulders, elbows, wrists, hips, patella, ankles, and knees (anterior dislocation of the tibia on the femur, most characteristic)
   b. Genu recurvatum
   c. Talipes deformities (clubfeet)
   d. Spatulate thumbs
   e. Shortened metacarpals
   f. Multiple supernumerary carpal ossification centers (short, small, and increased in number)
   g. Poor ossification of phalanges
   h. Delayed coalescence (duplication) of calcaneal ossification centers
   i. Occasional abnormal segmentation of vertebrae (+/− fusion defects of cervical spine)
   j. Cervical kyphosis
   k. Spina bifida occulta
   l. Scoliosis
   m. Craniofacial disproportion
2. Polysomnography for assessing the severity of airway obstruction
3. Echocardiography for cardiovascular lesions
4. MRI of the brain for cerebral malformations
5. Diagnosis: based on clinical and radiographic findings and confirmed by *FLNB* molecular genetic testing

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Sporadic form (consider germ-line mosaicism when neither parent appears to be affected)
      ii. Autosomal dominant inheritance: risk not increased unless a parent is affected
      iii. Autosomal recessive inheritance: 25% risk of having sibs affected
   b. Patient's offspring
      i. Sporadic form: risk not increased unless the patient has germ-line mosaicism
      ii. Autosomal dominant inheritance: 50% risk of having offspring affected

iii. Autosomal recessive inheritance: risk not increased unless the spouse is also a carrier

2. Prenatal diagnosis
   a. Ultrasonography: prenatal diagnosis accomplished in rare cases by ultrasonography in pregnancies at risk
      i. Multiple joint dislocations
         a) Elbow
         b) Knees
         c) Hips
      ii. Flat facial profile
         a) Prominent forehead
         b) Hypertelorism
         c) A depressed nasal bridge
         d) Micrognathia
         e) Cleft palate
      iii. Genu recurvatum
      iv. Clubfeet
   b. Molecular genetic testing: possible for at-risk pregnancies provided that prior identification of the disease-causing mutation(s) in the family is done
3. Management
   a. Supporting therapy for airway difficulty
      i. Antibiotics as needed
      ii. Supplemental oxygen
      iii. Chest physiotherapy to augment mucus clearance
      iv. Require intubation for severe respiratory distress with positive end-expiratory pressure (PEEP) to maintain a patent airway (Rock et al. 1988)
   b. Cleft palate repair
   c. Closed or open reduction and stabilization of dislocated joints (Lutter 1990)
      i. Securing stability of the knee joints for weight-bearing: primary importance
      ii. Correction of foot deformities through operative and nonoperative measures
   d. Stabilization of the cervical spine (Banks et al. 2003)
      i. Early bracing and stabilization
      ii. Stabilization of the neck may be required before surgical correction of joint abnormalities to prevent possible complications associated with the induction of anesthesia.
   e. Care for possible poor wound healing
   f. Obstetrical care of an affected mother and fetus (Rochelson et al. 1993)
      i. Regional anesthesia for possible difficulty in intubation and the cervical spine may be subluxated during extension of the neck for intubation
      ii. Cesarean section if the patient is unable to abduct the hips, making vaginal delivery potentially traumatic for both mother and infant
      iii. Risk of fetal injury includes cervical spine instability.

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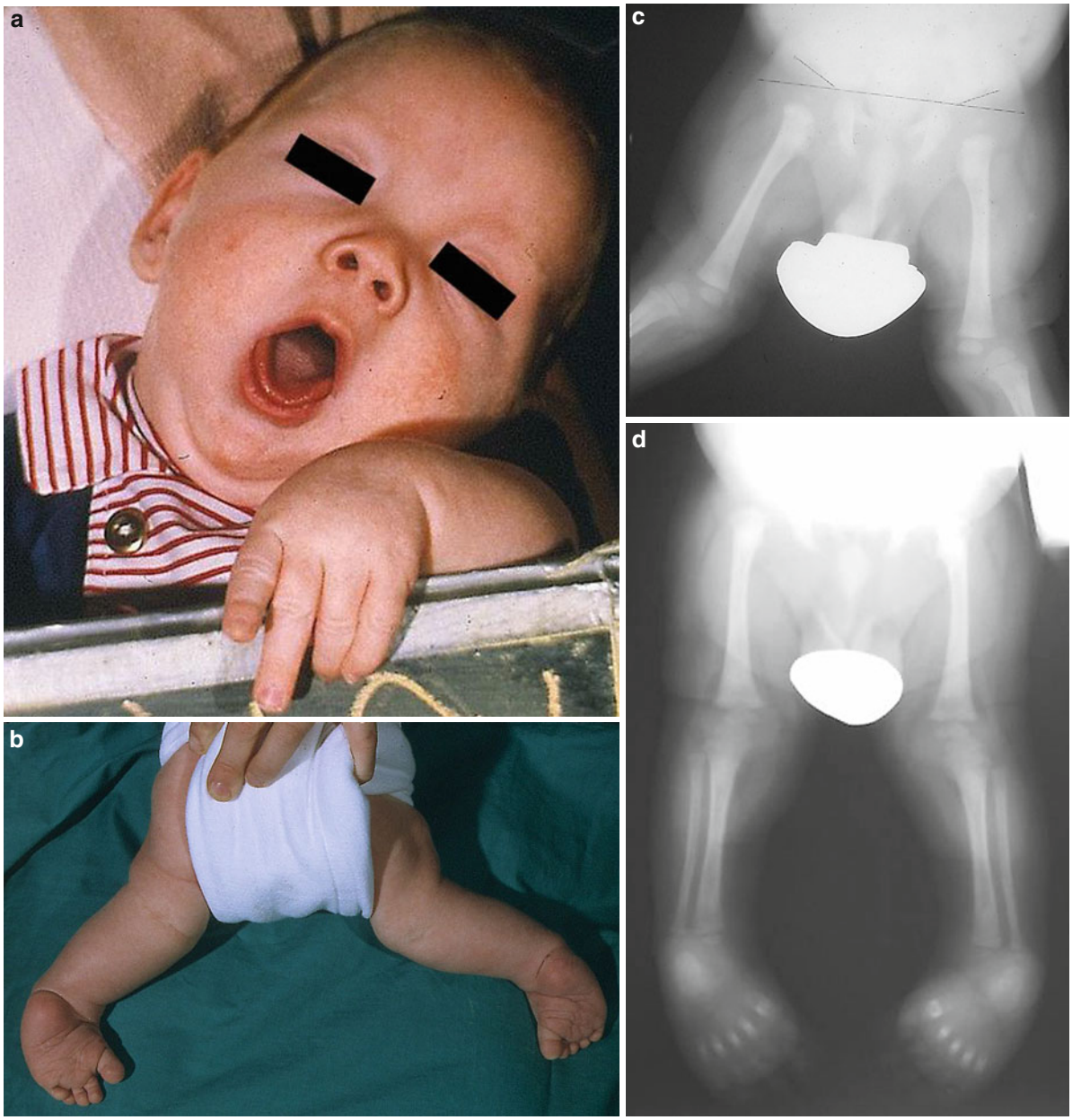

Fig. 1 (**a**–**d**) An infant with Larsen syndrome showing characteristic flat facies with hypertelorism, depressed nasal bridge, cleft palate, dislocations of hips, knees, and talipes equinovarus, demonstrated by radiographs

Fig. 2 (**a**, **b**) Another infant with Larsen syndrome showing flat facies with prominent forehead, hypertelorism, depressed nasal bridge, micrognathia, tracheostomy for tracheomalacia, scoliosis, dislocation of knees, and club feet

Fig. 3 (**a**–**e**) A girl with Larsen syndrome showing characteristic flat facies with prominent forehead, depressed nasal bridge, bilateral knee dislocations, and long, cylindrical fingers with spatulate thumbs and great toes. Radiograph shows lateral and anterior dislocation of both knees

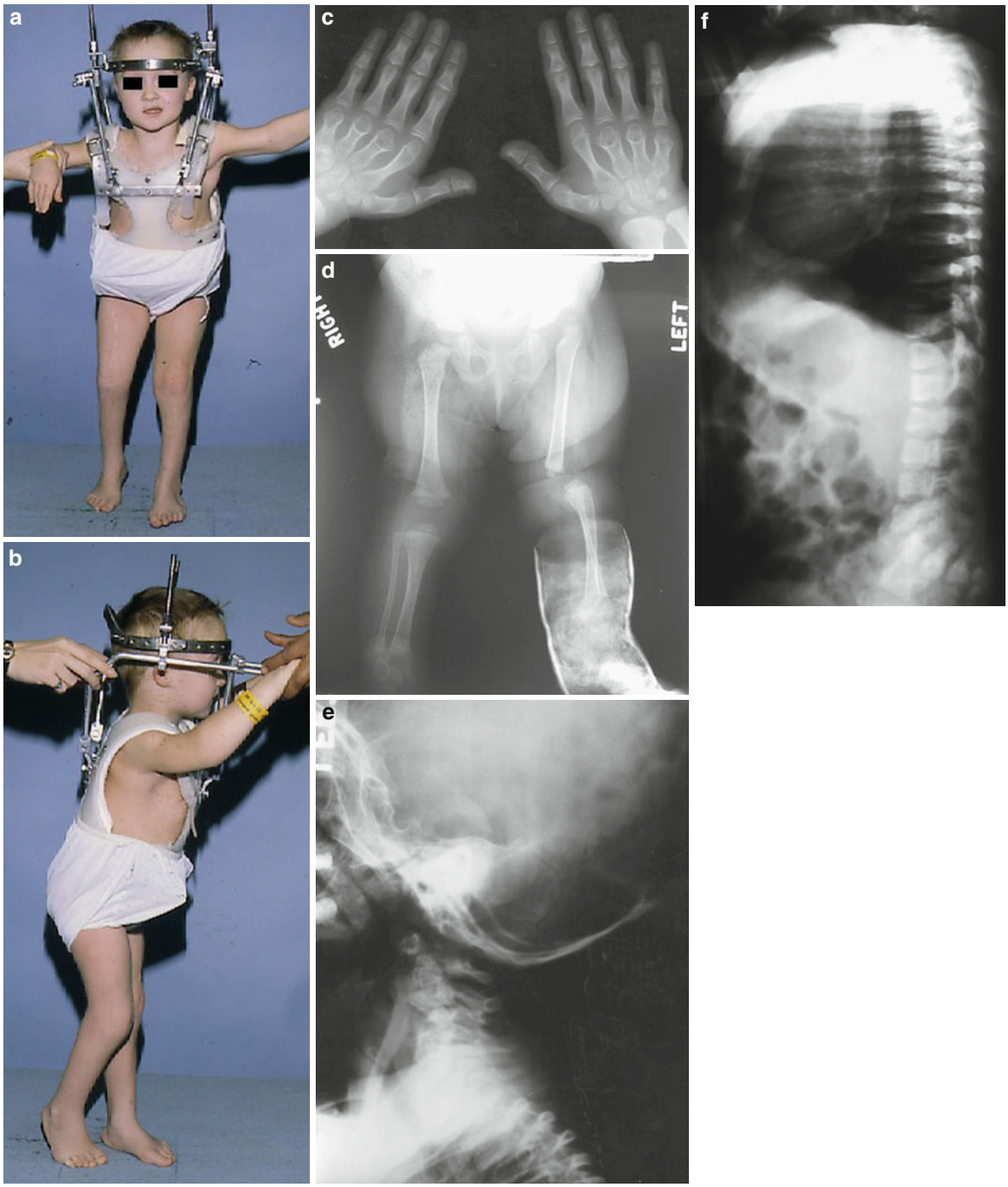

Fig. 4 (**a**–**f**) A girl with Larsen syndrome wearing orthosis, showing flat facies. Radiographs show increased number of carpal bones, anterior and lateral dislocation of tibiae, hyperextended cervical vertebrae, and coronal clefting of the lumbar vertebrae

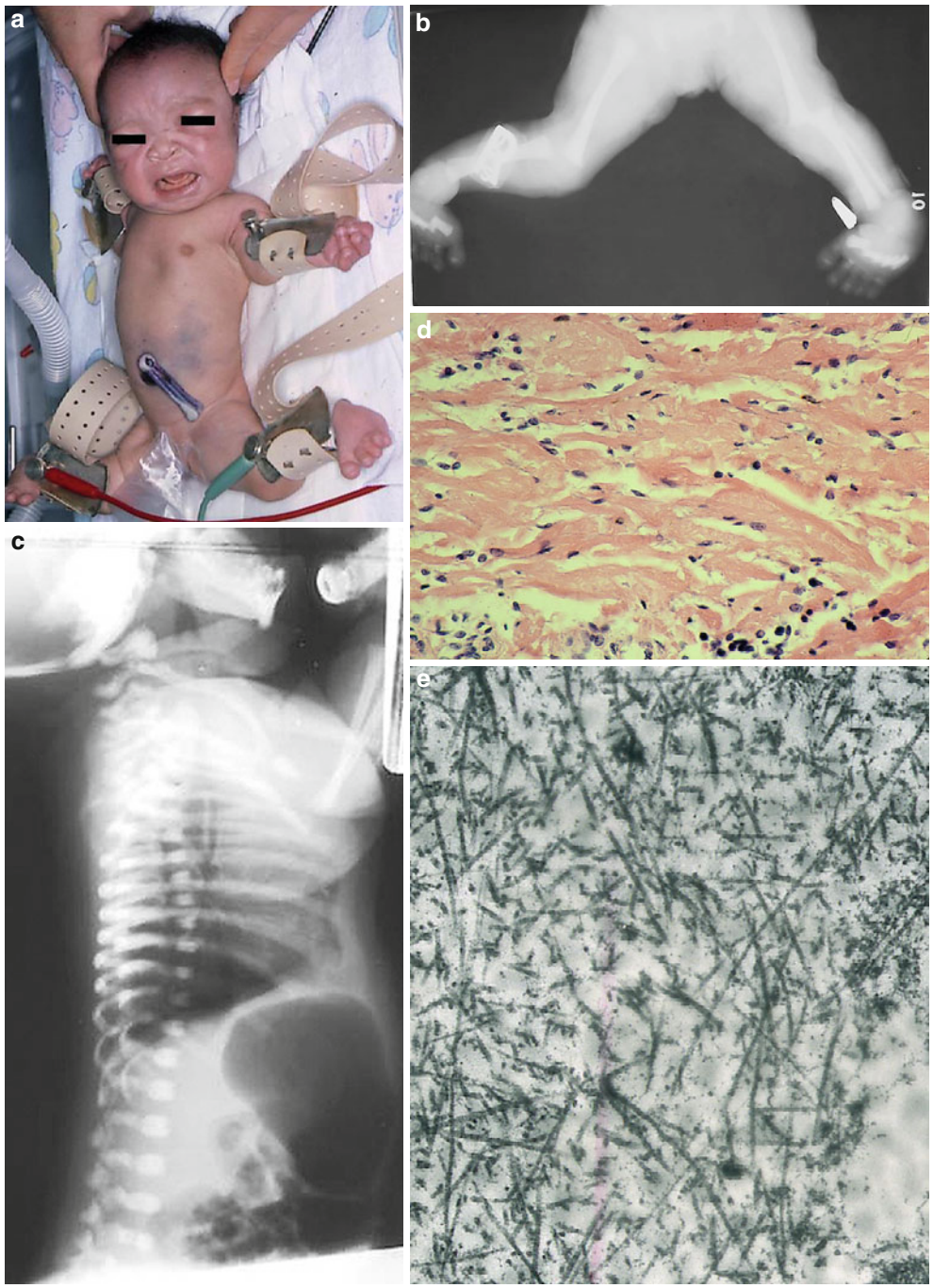

Fig. 5 (**a**–**e**) An infant with lethal, Larsen-like syndrome showing characteristic flat facies (prominent forehead, hypertelorism, depressed nasal bridge, micrognathia, and cleft palate); multiple dislocations involving shoulders, elbows, wrists, knees, ankles, and hips, and talipes equinovarus. The radiographs showed anterior dislocation of the tibia, lateral dislocation of the hips, hypoplasia of fibulae and of distal ends of the fibulae, cervical kyphosis with the apex at C-4, and coronal clefts of the lower lumbar vertebrae. Necropsy showed tracheomalasia. The dermal histology showed relatively broad and smudgy collagen bundles. The electron microscopic study showed a relative increase in small short fibers with a reduction of mature collagen fibers in the hyaline cartilage of the trachea

LEOPARD Syndrome

The acronym "LEOPARD syndrome," coined by Gorlin et al. (1969), is derived from clinical features which include *l*entigines, *e*lectrocardiographic conduction abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitalia, growth *r*etardation, and sensorineural *d*eafness. It is also known as multiple lentigines syndrome and Moynahan syndrome and classified as a cardiocutaneous syndrome of neural crest origin (Moynahan 1970).

Synonyms and Related Disorders

Cardiomyopathic lentiginosis; Multiple lentigines syndorme

Genetics/Basic Defects

1. Inheritance
   a. An autosomal dominant disorder with high penetrance and variable expressivity
   b. Allelic to Noonan syndrome
2. Caused by mutations in the protein tyrosine phosphatase nonreceptor type 11 (*PTPN11*) gene, mapped on chromosome 12q22-qter, which is known to be mutated in the Noonan syndrome (Digilio et al. 2002)
   a. Missense mutation (836A → G; Tyr279Cys) in exon 7
   b. Missense mutation (1403C → T; Thr468Met) in exon 12
   c. Both mutations affect the PTPN11 phosphotyrosine phosphatase domain, which is involved in <30% of the Noonan syndrome *PTPN11* mutations.
3. Also can be caused by mutations in the V-RAF-1 murine leukemia viral oncogene homolog 1 (*RAF1*) gene (mapped on chromosome 3p25)

Clinical Features

1. Cutaneous features (Abdelmalek et al. 2002)
   a. Lentigines
      i. Dark brown irregularly shaped macules ranging from pinpoint size to 5 cm in diameter
      ii. Noted in infancy or childhood
      iii. Continue to increase in number until puberty
      iv. Primarily on the face, neck, and upper trunk with some involvement of the extremities
      v. Less commonly on the palms, soles, genitalia, iris, and sclera, but sparing oral mucosa
      vi. Generalized symmetric distribution of lentigines
   b. Other cutaneous abnormalities
      i. Café au lait spots (38% of patients)
      ii. Café noir spots (a term proposed in 1971 by Gorlin et al.): by analogy to café au lait spots to describe larger and more pigmented lentigines in patients with LEOPARD syndrome (Bujaldón 2008)
      iii. Melanoma
      iv. Localized hypopigmentation
      v. Interdigital webs

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vi. Dermatoglyphic abnormalities
vii. Onychodystrophy
viii. Multiple granular cell myoblastomas
ix. Steatocystoma multiplex
x. Hyperelastic skin

2. Noncutaneous features
   a. Cardiac anomalies
      i. Valvular pulmonary stenosis: the most common cardiac anomaly (40% of cases)
      ii. Subaortic stenosis
      iii. Subpulmonic stenosis
      iv. Mitral valve involvement
      v. Hypertrophic obstructive cardiomyopathy
      vi. Left and right ventricular outflow tract obstructions
      vii. Atrial septal defect
      viii. Atrial myxomas
      ix. Variable conduction abnormalities
         a) Benign asymptomatic arrhythmia
         b) Malignant arrhythmias resulting in sudden cardiac death
      x. Cardiac symptoms
         a) Dyspnea on exertion
         b) Congestive heart failure
         c) Paroxysmal atrial tachycardia
         d) Sudden death
         e) Death at cardiac surgery
   b. Noncardiac anomalies
      i. Craniofacial features
         a) Ocular hypertelorism (25%)
         b) Epicanthic folds
         c) Ptosis
         d) Mandibular prognathism
         e) High-arched palate
         f) Dental abnormalities
         g) Low-set posteriorly rotated ears
      ii. Skeletal abnormalities
         a) Joint hypermobility
         b) Short webbed neck
         c) Winging of the scapula
         d) Pectus excavatum and carinatum
         e) Rib anomalies
         f) Cervical spine fusion
         g) Syndactyly
         h) Scoliosis
      iii. Genitourinary abnormalities (26% of cases)
         a) A small penis
         b) Cryptorchidism
         c) Hypospadias
         d) Ovarian disorders
      iv. Neurologic abnormalities
         a) Learning disability
         b) Mild mental retardation
         c) Sensorineural deafness
         d) Nystagmus
         e) Seizures
         f) Hyposmia
         g) Mild atrophy of the brain
      v. Retardation of growth (short stature)
      vi. Delayed puberty

3. Diagnostic criteria (Voron et al. 1976)
   a. Multiple lentigines plus two other features
   b. Immediate family member with LEOPARD syndrome plus at least three other features in the absence of lentigines

4. Differential diagnosis with other neuro-cardio-facial-cutaneous syndromes (Kalev et al. 2010)
   a. Noonan syndrome: please see chapter on Noonan syndrome
   b. Costello syndrome
      i. Causative genes: *HRAS*, *KRAS*, *BRAF*, and *MEK1*
      ii. Autosomal dominant
      iii. Phenotype
         a) Short stature
         b) Congenital heart defect
         c) Characteristic facies with more coarse features
         d) Mental retardation: more severe
         e) Distinctive skin involvement – curly, sparse hair; loose soft skin; and papillomata
   c. Cardio-facio-cutaneous syndrome
      i. Causative genes: *KRAS*, *BRAF*, *MEK1*, and *MEK2*
      ii. Autosomal dominant, de novo
      iii. Phenotype
         a) Short stature
         b) Congenital heart defect
         c) Cardiomyopathy
         d) Characteristic facies
         e) Mental retardation: more severe
         f) Distinctive features: hyperkeratotic dry skin; sparse, curly hair.
         g) Phenotype overlaps most with Noonan syndrome, but facial appearance tends to be coarse.
         h) Cardiac problems overlap mostly with LEOPARD syndrome.

d. Neurofibromatosis type 1: please see chapter on neurofibromatosis type 1

Diagnostic Investigations

1. ECG abnormalities (Torres et al. 2004)
   a. Left axis deviation
   b. Bundle branch block
   c. Abnormal P wave
   d. Prolongation of the P-R interval
   e. Right or left ventricular hypertrophy
   f. Infarction patterns
   g. Ischemic patterns with nonspecific ST and T wave changes
   h. Isolated ventricular ectopic beats
   i. Ventricular fibrillation
   j. Bradycardia
   k. Paroxysmal atrial fibrillation
2. Careful cardiac assessment including echocardiography
3. Hearing tests
4. Histology of lentigines
   a. Large membrane-bound accumulations of melanin granules within the Langerhans cells
   b. Giant melanosomes rarely seen within keratinocytes and melanocytes
5. Mutation screening of *PTP11* or *RAF1*: by direct sequencing of select exons or entire coding region

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: low unless a parent has the syndrome (possibility of germline mosaicism exists)
   b. Patient's offspring: 50%
2. Prenatal diagnosis
   a. Available clinically by mutation analysis of *PTPN11* or *RAF1* genes on fetal DNA obtained by amniocentesis or CVS, provided the disease-causing allele has been identified in an affected family member
   b. Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified.
3. Management
   a. Avoid strenuous physical exercise when outflow tract obstruction or significant cardiac dysrhythmias are present.
   b. β-adrenergic receptor or calcium channel blocking agents to reduce cardiac outflow tract obstruction and adrenergic responsiveness
   c. Amiodarone treatment in cases of life-threatening ventricular ectopy
   d. Surgery may be needed to relieve severe cardiac outflow tract obstruction.
   e. Surgery for cryptorchidism or severe skeletal deformity
   f. Hearing aids for sensorineural deafness
   g. Dermabrasion for cosmetic correction on the face

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Fig. 1 A lady (**a**, **b**) with LEOPARD syndrome showing ocular hypertelorism and generalized symmetric distribution of lentigines. Close views of lentigines (**c**–**e**) show variation in size and color. There is striking mottling of pigment within any one lentigo

Lesch–Nyhan Syndrome

In 1964, Lesch and Nyhan provided the first detailed clinical description of Lesch–Nyhan syndrome with a report of two brothers with hyperuricemia and a characteristic neurobehavioral syndrome that included motor dysfunction and self-injurious behavior. The prevalence of the syndrome is estimated to be approximately 1:380,000.

Synonyms and Related Disorders

Hypoxanthine guanine phosphoribosyltransferase 1 deficiency

Genetics/Basic Defects

1. Inheritance: X-linked recessive
2. Enzymatic defect: caused by deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT), which catalyzes the conversion of hypoxanthine to inosine monophosphate and guanine to guanine monophosphate in the presence of phosphoribosylpyrophosphate
3. Hypoxanthine-guanine phosphoribosyltransferase gene (*HPRT1*)
   a. Mapped to chromosome Xq26-q27.2
   b. The only gene known to be associated with Lesch–Nyhan syndrome
   c. Heterogeneous mutations
      i. Single base substitutions
      ii. Deletions
      iii. Insertions
      iv. Substitutions
4. Heterogeneity of clinical phenotype (Sarafoglou et al. 2010)
   a. An approximately inverse relationship exists between HPRT enzyme activity measured in intact cells and clinical severity (Page et al. 1981; Puig et al. 2001).
   b. Affected patients with classic Lesch–Nyhan disease, the most severe and frequent form, have the lowest HPRT enzyme activity (<1.5% of normal) in intact cultured fibroblasts, and the patients display the full spectrum of clinical abnormalities.
   c. Patients with partial HPRT deficiency, designated as Lesch–Nyhan variants (LNVs), have HPRT enzyme activity ranging from 1.5% to 8.0% (Nyhan 2008).
   d. Individuals with the intermediate form of LNV (also known as neurologic variants) have a variable clinical phenotype and, in most cases, are neurologically indistinguishable from patients with Lesch–Nyhan disease (Puig et al. 2001; Nyhan 2009).
   e. However, they do not have self-injurious behaviors, and their intelligence is normal or near normal. The least-affected patients with LNV have residual HPRT enzyme activity exceeding 8%, and their only manifestations have been attributed to hyperuricemia and include gout, hematuria, and nephrolithiasis.

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f. There is another LNV, HPRT Salamanca, that is characterized by spastic gait, mental retardation, and skeletal abnormalities (Nyhan 2008; Page et al. 1987).

5. Pathogenesis
   a. Metabolic basis of overproduction of uric acid: results from changes in the regulation of purine synthesis and degradation.
   b. Pathogenesis of neurologic and behavioral features remains incompletely understood. Growing evidence suggests that these features result from dysfunction of the dopamine transmitter systems of the basal ganglia (Baumeistger and Frye 1985).

Clinical Features

1. Normal prenatal and perinatal course.
2. Early developmental milestones.
   a. Hypotonia and developmental delay: most common presenting features evident by 3–6 months of age
   b. Failure to reach normal motor milestones, such as delayed in crawling, sitting, and walking
3. Within the first few years.
   a. Extrapyramidal involvement
      i. Dystonia
      ii. Choreoathetosis
      iii. Opisthotonus
      iv. Ballismus
   b. Pyramidal involvement
      i. Spasticity
      ii. Hyperreflexia
      iii. Extensor plantar reflexes
      iv. Ankle clonus
      v. Scissoring of the legs
4. Between 2 and 3 years.
   a. Impaired cognition
      i. Moderate to severe mental retardation in most patients
      ii. Varying degree of impairment
      iii. Difficult to obtain adequate assessments of cognitive abilities
   b. Compulsive behavioral disturbances
      i. Aggressiveness
      ii. Vomiting
      iii. Spitting
      iv. Coprolalia
      v. Copropraxis
      vi. Manipulative behavior
   c. Persistent self-injurious behavior: a hallmark of the disease
      i. Biting the fingers, hands, lips, and buccal mucosa
      ii. Banging the head or limbs
5. Overproduction of uric acid: hyperuricemia-related renal and articular symptoms. These symptoms are present in all HPRT-deficient patients and are not related to the severity of the enzyme defect (Torres and Puig 2005).
   a. Uric acid crystalluria noted as orange crystals in the diaper during the first weeks of life.
   b. Deposition of uric acid crystals or calculi in the kidneys, ureters, or bladder.
   c. Leading to nephrolithiasis, obstructive uropathy, and azotemia if untreated.
   d. Gouty arthritis develops later in the course of the disease.
   e. All characteristic findings associated with gout may be present (acute arthritis, tophi, nephrolithiasis or urolithiasis, and renal disease). However, nowadays, allopurinol treatment prevents the development of gouty manifestations.
6. Other features.
   a. Delayed growth and puberty
   b. Testicular atrophy in most affected males
   c. Associated orthopedic problems
      i. Hip subluxation or dislocation
      ii. Fractures
      iii. Autoamputation
      iv. Infections
      v. Minor scoliosis
      vi. Contractures
7. Life expectancy.
   a. Most surviving into the second or third decade of life if properly managed
   b. No evidence suggesting disease progression over time
   c. Complications
      i. Aspiration pneumonia
      ii. Chronic nephrolithiasis
      iii. Renal failure
      iv. Sudden unexpected death
8. Lesch–Nyhan syndrome in females.
   a. Extremely rare
   b. Female carriers
      i. Generally considered to be asymptomatic

ii. Have increased uric acid excretion
iii. Develop symptoms of hyperuricemia in later years

c. Affected females
i. Affected carrier females: considered to have nonrandom X chromosome inactivation or skewed inactivation of the normal *HPRT1* allele.
ii. The first female case reported was caused by a microdeletion of the maternally derived *HPRT* gene and nonrandom inactivation of the paternally derived X chromosome.
iii. Two additional cases were caused by a point mutation in one allele and markedly reduced mRNA expression from the other allele.

Diagnostic Investigations

1. EEG: nonspecific changes of slowing or disorganization (Nicklas et al. 2010).
2. CT and MRI of the brain: nonspecific changes of atrophy of the basal ganglia or cerebrum.
3. Positron emission tomography to demonstrate a selective decrease of 50–70% in dopamine transporters in the caudate and putamen.
4. Hyperuricuria or hyperuricemia (serum uric aids concentration >8 mg/dL): often present but not sensitive or specific enough for diagnosis.
5. 24-h uric acid excretion (>20 mg/kg): characteristic but not diagnostic.
6. Uric acid to creatinine ratio >2.0: characteristic for patients under 10 years of age.
7. In males: hypoxanthine-guanine phosphoribosyltransferase enzyme activity <1.5% of normal enzyme activity in cells from any tissue (blood, cultured fibroblasts, or lymphoblasts): establishes the diagnosis.
8. In females: measurement of HPRT enzyme activity for carrier detection is technically demanding and not widely used. Measurement of HPRT enzyme activity on hair bulbs from women at risk has had both false-positive and false-negative results.
9. Molecular genetic testing of the *HPRT1* gene (Nyhan et al. 2010).
   a. Purposes
      i. To define the mutation in the affected males
      ii. To determine carrier status in at-risk females: requires prior identification of the disease-causing mutation in the family
   b. Sequence analysis or mutation scanning to detect *HPRT1* mutations in males affected with Lesch–Nyhan syndrome: available on clinical basis
   c. Deletion/duplication analysis
      i. To detect exonic or whole-gene deletions
      ii. Between 21% and 24% of mutations in *HPRT1* are large deletions that cannot be detected in females by sequence analysis

Genetic Counseling

1. Recurrence risk.
   a. Patient's sib
      i. When the mother is not a carrier: not increased unless the mother has germ line mosaicism in which case there is an undetermined, but real, risk of having future affected sons or carrier daughters
      ii. When the mother is a carrier
         a) A 25% risk of having an affected male
         b) A 25% risk of having a carrier female
         c) A 50% risk of having an unaffected male or female
   b. Patient's offspring
      i. Severely affected males: not surviving to reproductive age
      ii. Less severely affected males: all of his daughters are obligatory carriers and none of his sons affected
2. Prenatal diagnosis available to at-risk pregnancies.
   a. Fetal sex determination by amniocentesis or CVS
   b. Confirmation of a previously known *HPRT1* disease-causing mutation in a male fetus
      i. Perform HPRT enzyme activity
      ii. Perform molecular genetic testing
   c. Assay of HPRT enzyme activity in cultured amniocytes or chorionic villus cells: the method of choice if the *HPRT1* mutation has not been identified in the family
   d. Preimplantation genetic diagnosis possible for a previously characterized disease-causing mutation (Ray et al. 1999)
3. Management (Nicklas et al. 2010).
   a. Hyperuricemia.
      i. Control hyperuricemia to reduce the risk of nephropathy, nephrolithiasis, and gouty arthritis

ii. Allopurinol
   a) To block the conversion of oxypurines into uric acid
   b) To prevent uric acid accumulation and subsequent arthritic tophi, renal stones, and nephropathy
   c) Has no effect on behavioral and neurologic symptoms

b. Renal stones.
   i. Lithotripsy
   ii. Surgery

c. Neurologic dysfunction.
   i. No medication known to be consistently effective in controlling the extrapyramidal motor features
   ii. Baclofen or benzodiazepine for spasticity

d. Neurobehavioral symptoms.
   i. No effective intervention available
   ii. Use behavioral modification techniques
   iii. Control self-injurious behavior
      a) Requires physical restraints
      b) Removal of teeth
      c) A noninvasive approach with a special appliance fabricated for the prevention of damage to oral and perioral soft tissues (Fardi et al. 2003)
      d) Carbamazepine to attenuate the behavioral manifestations

e. Surgery for orthopedic problems.

f. Bone marrow transplantation or red blood cell transfusions do not significantly ameliorate the neurologic disorder.

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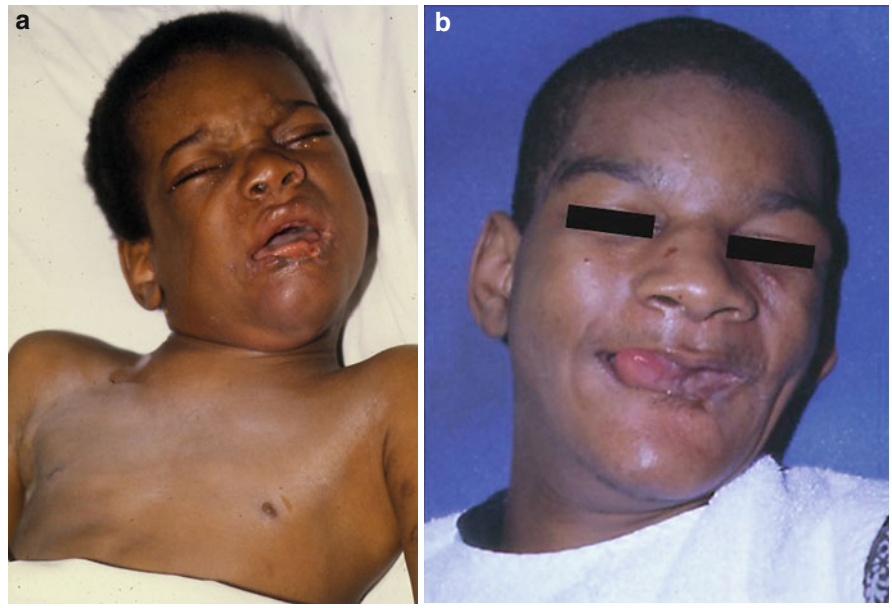

Fig. 1 (**a**, **b**) Two boys with Lesch–Nyhan syndrome showing severe mental retardation and self-mutilation of the lips and tongue

Lethal Multiple Pterygium Syndrome

Lethal multiple pterygium syndrome (LMPS) is a lethal hereditary disorder characterized by a distinct constellation of multiple anomalies, consisting of multiple pterygia, flexion contractures of multiple joints, characteristic facial appearance, cystic hygroma, hydrops, and pulmonary and cardiac hypoplasia.

Synonyms and Related Disorders

Chen syndrome; Gillin–Pryse–Davis syndrome; Herva syndrome; van Regemorter syndrome

Genetics/Basic Defects

1. Inheritance: possible heterogeneity
   a. Autosomal recessive inheritance
   b. Possible X-linked recessive inheritance (Tolmie et al. 1987; Meyer-Cohen et al. 1999)
2. Classification by Hall (1982; 1984) and Entezami et al. (1998)
   a. Based on the following concomitant abnormalities
      i. Age of onset of intrauterine growth retardation
      ii. Timing and extent of neck swelling
      iii. Presence or absence of bony fusions and bone modeling errors
   b. Type I (Gillin–Pryse–Davis syndrome)
      i. Multiple pterygia
      ii. Pulmonary hypoplasia
      iii. Genital anomalies
      iv. Facial anomalies
      v. Strongly flexed extremities with a reduced muscle mass
   c. Type II (Chen syndrome)
      i. Multiple pterygia
      ii. Hygroma colli
      iii. Facial anomalies
      iv. Shortened extremities
      v. Undermodeled long bones
      vi. Cartilaginous fusion of joints and bony fusion of the spinous processes of the vertebrae
      vii. Polyhydramnios
      viii. Hypoplastic lungs and heart
      ix. Diaphragmatic hernia
   d. Type III (van Regemorter syndrome)
      i. Multiple pterygia
      ii. Pulmonary hypoplasia
      iii. Facial anomalies
      iv. Thin extremities with reduced muscle mass
      v. Fusions of the long tubular bones
   e. Type IV (Herva syndrome)
      i. Multiple pterygia
      ii. Degeneration of the anterior horn cells of the spinal cord
      iii. Found particularly in Finland
3. Classification by de Die-Smulders et al. (1990a)
   a. Early LMPS
      i. A group with presumed genetic heterogeneity
      ii. Lethality in the second trimester
      iii. Hydrops fetalis
      iv. Cystic hygroma
   b. Late LMPS
      i. Survival into the third trimester
      ii. Absence of fetal hydrops
   c. Finnish-type LMPS
      i. Fetal hydrops from the 15th gestational week
      ii. Lethality at average gestation of 29 weeks

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   iii. Occasional pterygia of the neck and elbows
   iv. Distinct neuropathologic findings
4. Pathogenesis (Moerman et al. 1990)
   a. Combination of the following two sequences:
      i. Fetal akinesia deformation sequence
         a) Resulting from myoneural dysfunction (generalized amyoplasia) and/or intrauterine growth constraint leading to fetal akinesia
         b) Fetal akinesia, in turn, leading to growth retardation, pulmonary hypoplasia, short umbilical cord, limb positional defects, and facial anomalies
      ii. Jugular lymphatic obstruction sequence: delay in development of the connection between jugular lymph sacs and the internal jugular vein resulting in dilatation of tributary lymphatics and peripheral lymphedema
   b. Fragile collagen proposed as a possible pathogenesis (Hartwig et al. 1989)
5. A gene responsible for some cases of lethal MPS (LMPS) and Escobar variant of MPS has now been identified.
   a. Caused by mutation in the *CHRNG* gene (Hoffmann et al. 2006; Morgan et al. 2006)
   b. Caused by mutations in the *CHRNA1* and *CHRND* genes (Michalk et al. 2008)

Clinical Features

1. Prenatal history
   a. Nonimmune fetal hydrops
   b. Diminished fetal activity
   c. Maternal hydramnios
   d. Often presented with fetal demise
2. Characteristic facial features
   a. Ocular hypertelorism
   b. Antimongoloid slant of the palpebral fissures
   c. Epicanthal folds
   d. Markedly flattened nasal bridge with hypoplastic nasal alae
   e. Micrognathia
   f. Cleft palate
   g. Apparently low-set malformed ears
3. Neck
   a. Short
   b. Cystic hygroma
4. Chest
   a. Small chest
   b. Hypoplastic lungs
   c. Hypoplastic heart
5. Multiple pterygia
   a. Symmetrical
   b. Sites
      i. Chin-to-sternum
      ii. Cervical
      iii. Axillary
      iv. Antecubital
      v. Crural
      vi. Popliteal
6. Other limb anomalies
   a. Multiple contractures: always present
   b. Camptodactyly
   c. Calcaneovalgus foot deformities
7. Gastrointestinal anomalies
   a. Intestinal malrotation
   b. Short bowel
   c. Thin colon
   d. Colonic atresia
   e. Absent vermiform appendix
8. Genitourinary anomalies
   a. Hydronephrosis
   b. Unilateral renal dysplasia
   c. Cryptorchidism
9. Other associated anomalies
   a. Kyphoscoliosis
   b. Near-complete absence of diaphragmatic muscle
   c. Aortic coarctation
   d. Absent abdominal wall muscle
   e. Adrenal hypoplasia
   f. Short umbilical cord
   g. Rare cerebral anomalies
      i. Hydranencephaly
      ii. Holoprosencephaly
      iii. Dilated ventricles with intracerebral cyst

Diagnostic Investigations

1. Radiography
   a. Craniofacial abnormalities
      i. Scalp edema
      ii. Microbrachycephaly
      iii. Flattened mandibular angle

   b. Hypoplasia and undermodeling of the bones
      i. Thin crowded ribs
      ii. Markedly hypoplastic scapulae
      iii. Hypoplastic iliac wings, ischia and pubic bones
      iv. Lack of normal curvature at the cervico-thoracic junction
   c. Bony fusion
      i. Marked bony fusion of posterior spinous processes
      ii. Radioulnar synostosis
2. Histologic studies of the skeletal system
   a. Cartilaginous and bony fusion of the spinous processes
   b. Fusion of epiphyseal cartilages of distal humerus and proximal ulna
   c. Poorly developed joint space
   d. An abnormal growth plate
   e. Weak safranin staining of the resting cartilages
   f. Placenta
      i. Scalloped chorionic villi
      ii. Intravillous trophoblast invaginations
   g. Muscular and neural abnormalities
3. Chromosome analysis: normal

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal recessive inheritance: 25%
      ii. X-linked recessive inheritance: 50% risk of having an affected brother if the mother is a carrier
   b. Patient's offspring: a lethal entity not surviving to reproductive age
2. Prenatal diagnosis by ultrasonography: possible (Entezami et al. 1998)
   a. Nonimmune fetal hydrops
   b. Cystic hygroma
   c. Diminished fetal activity
   d. Short and fixed limbs
   e. Maternal hydramnios
   f. Other ultrasonographically detectable anomalies
      i. Diaphragmatic hernia
      ii. Scoliosis
      iii. Pterygia
   g. Ultrasonographic features at first trimester of pregnancy (Chen et al. 2005; Gundogan et al. 2006)
      i. Cystic hygroma
      ii. Generalized edema
      iii. Ascites
      iv. Markedly increased nuchal translucency
      v. No fetal movement
      vi. Flexed upper and lower limbs
      vii. Cutaneous webs across both elbow joints
      viii. Hypoplastic left heart
3. Management: a lethal entity

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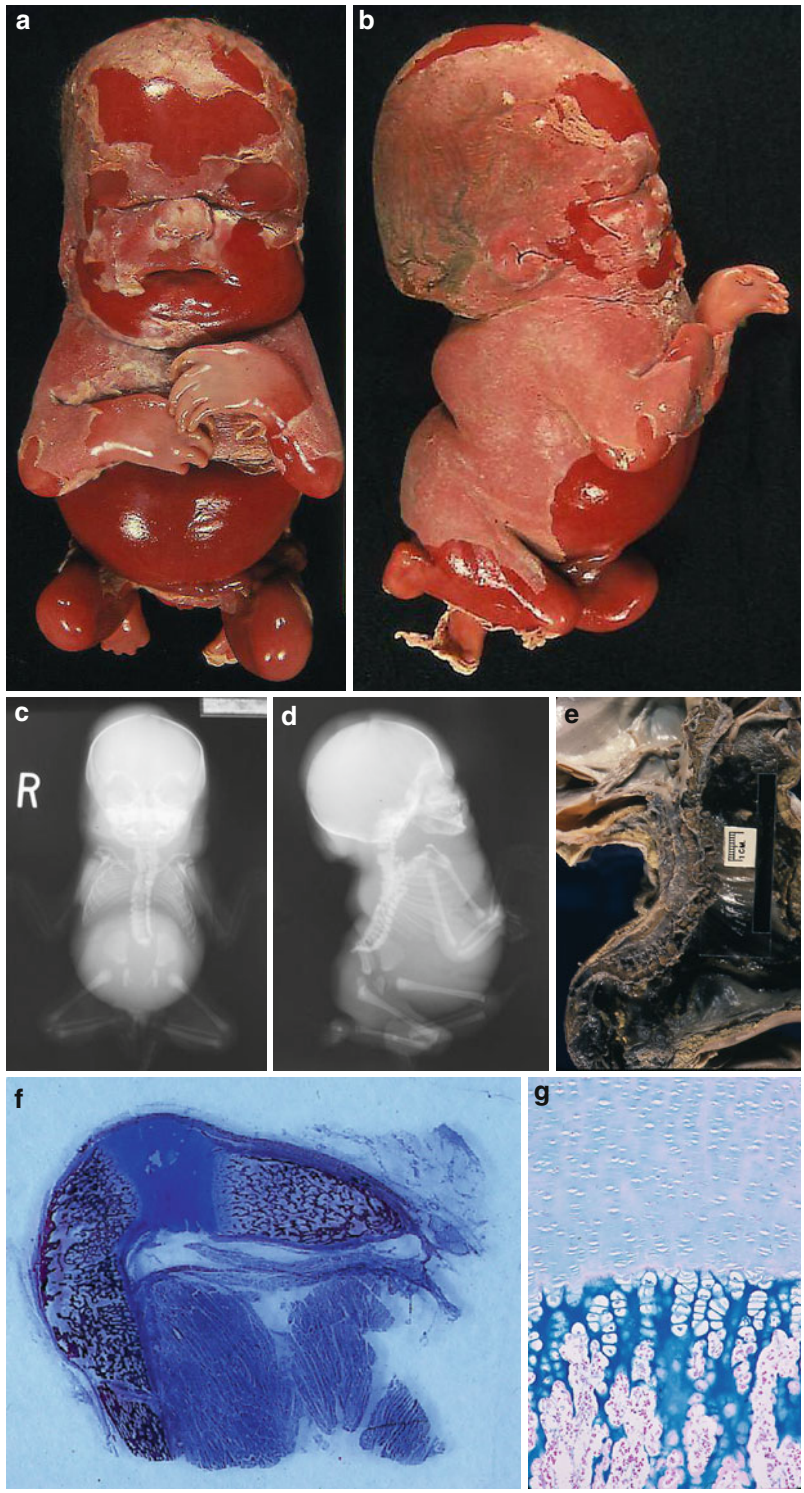

Fig. 1 The macerated 32-week stillborn (**a**, **b**) with Chen syndrome showing multiple pterygia involving the neck, axillae, antecubital, crural, popliteal, and interphalangeal areas, hygroma coli, and facial anomalies (hypertelorism, antimongoloid slant of the palpebral fissures, a shortened nose, depressed nasal bridge and tip of the nose, a long philtrum, a receding chin, apparently low-set and malformed ears). Contractures of the fingers were present with ulnar deviation of the hands. Polyhydramnios and fetal hydrops were noted by ultrasonography at 30 weeks of gestation. Autopsy showed hypoplastic lungs and heart and a large left diaphragmatic hernia (containing intestine, pancreas, and part of the stomach and ascites). Radiographs (**c**, **d**) and postmortem section (**e**) revealed a large cystic hygroma, hypoplastic vertebral bodies, fusion of the posterior elements extended from the cervical into the midthoracic spine, angulated cervicothoracic junction, and undermodeled long bones. Representative section of the elbow (**f**) showed fusion of epiphyseal cartilages of the distal humerus and proximal ulna resulting in bending of the proximal portion of the ulna and a deficient joint space. The resting cartilage (**g**) was distinctly demarcated from the physeal growth plate, which showed slightly retarded but normally arranged chondrocytic column

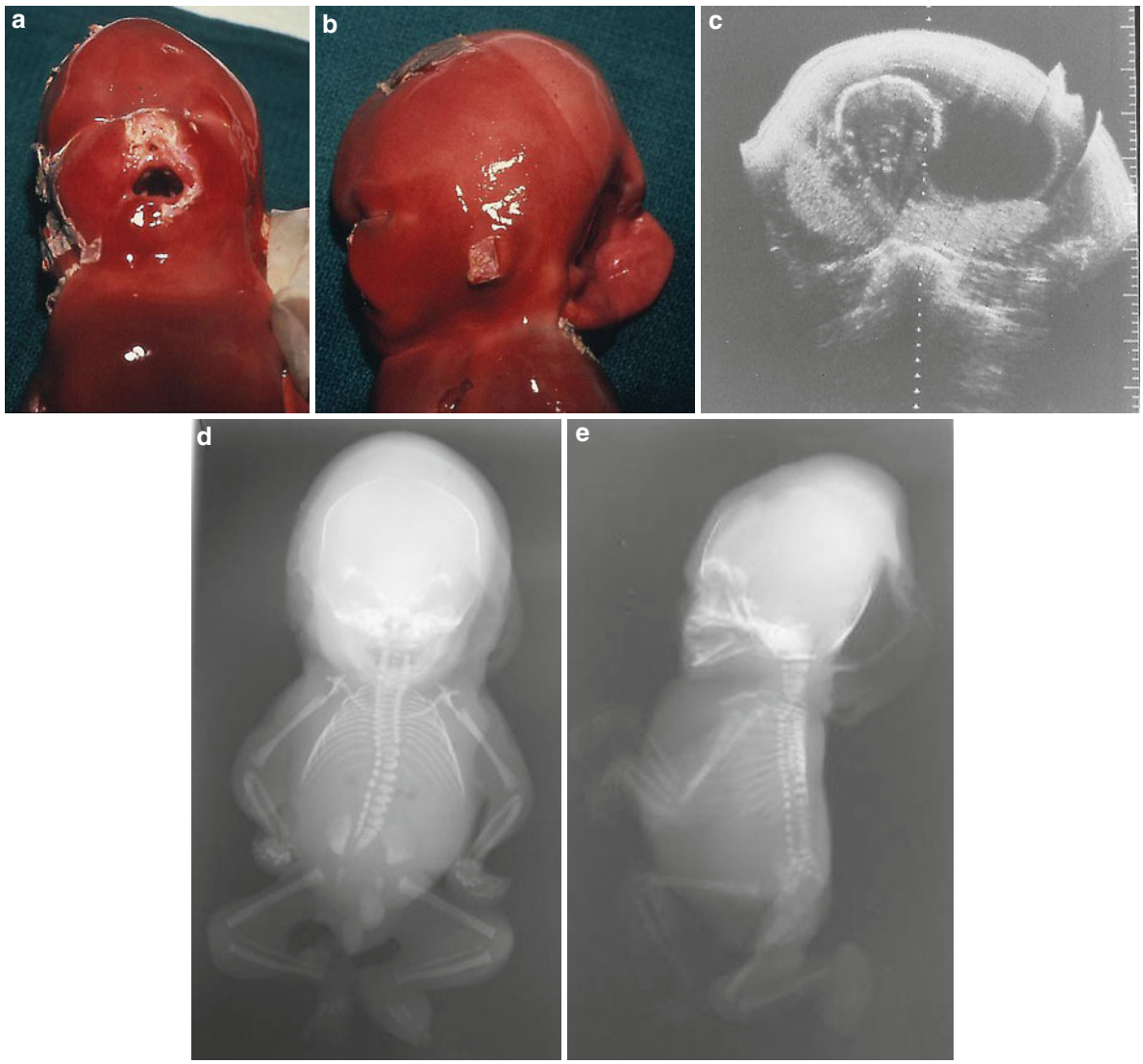

Fig. 2 A malformed macerated 28-week fetus (**a**, **b**) with Chen syndrome showing impressive skin webbing at the neck, axillae, antecubital, crural, and popliteal areas, and abnormal facies (markedly flattened nasal bridge with anteverted and hypoplastic nasal alae, low-set ears, and a small mouth with cleft soft palate). In addition, there were contractures of the hands and fingers and rocker bottom feet. The prenatal ultrasound at 25 weeks of gestation (**c**) showed a large cystic hygroma at the back of the head. Radiographs (**d**, **e**) revealed massive edema of the scalp contiguous with the neck pterygia, hypoplastic vertebral bodies, multiple fusions of the posterior elements of the cervical and lumbosacral spine bodies, and incipient fusion of the radius and ulna bilaterally. Post mortem study revealed markedly hypoplastic lungs and heart

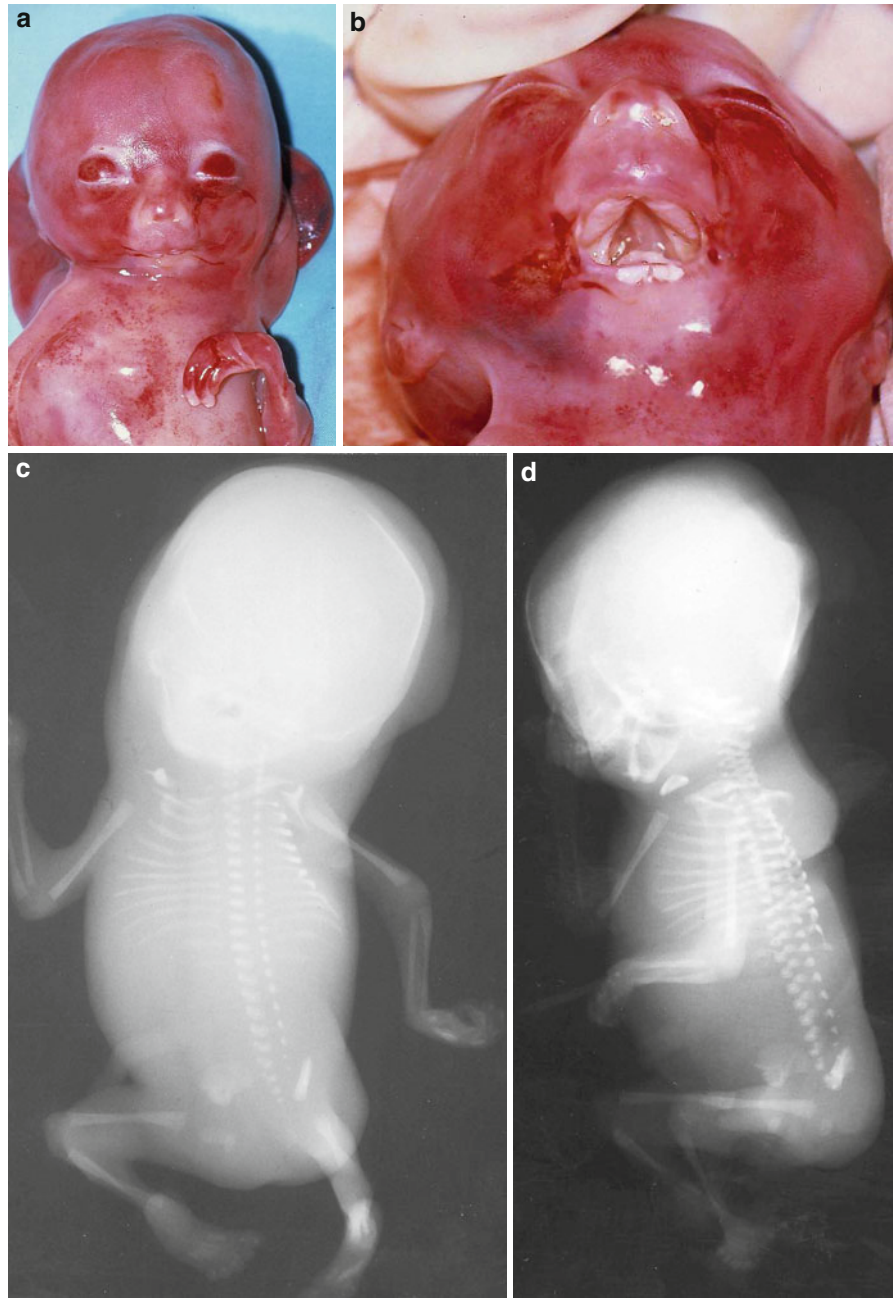

Fig. 3 A 19-week fetus with Chen syndrome (**a**, **b**) showing a large cystic hygroma, detected by prenatal ultrasonography, multiple pterygia involving neck, axillae, elbows, fingers, and knees with contractures, illustrated by radiographs (**c**, **d**). Distinctive facial features include hypertelorism, flat nasal bridge, cleft palate, and micrognathia. Postmortem study revealed hypoplastic lungs and heart, fusion of cartilage of the elbow joints, and hypoplastic cervical vertebral bodies with posterior elements beginning to come together but were not yet fused

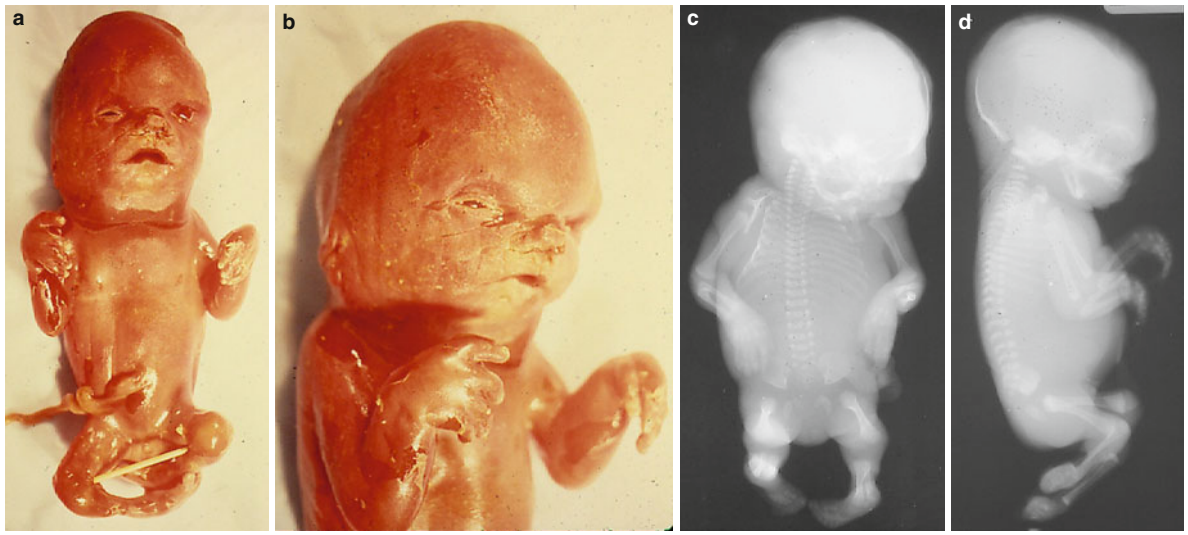

Fig. 4 A fetus with lethal multiple pterygium (**a**, **b**) syndrome showing multiple pterygia involving neck, axilla, elbows, and knees associated with multiple contractures, illustrated by radiographs (**c**, **d**). There were hypertelorism, small nose, micrognathia and micrognathia

Fig. 5 (**a**, **b**) A stillbirth with lethal multiple pterygium syndrome showing flexion of all four limbs with multiple pterygia involving neck, axillae, elbows, and knees; short neck; and cystic hygroma colli. There were antimongoloid slant of the palpebral fissures, hypertelorism, flat nasal bridge, micrognathia, and high-arched palate. The upper extremities were held in extreme flexion with ulnar deviation of both hands and camptodactyly. The lower limbs were rotated externally and flexed in a crossed position with bilateral calcaneus deformities of the feet. Postmortem findings include multiloculated cystic hygroma, hypoplastic lungs, and kyphoscoliosis

Loeys–Dietz Syndrome

Loeys–Dietz syndrome (LDS), a newly recognized connective tissue disorder, shares overlapping features with Marfan syndrome (MFS) and the vascular type of Ehlers–Danlos syndrome (EDS), including aortic root dilatation and skin abnormalities.

Synonyms and Related Disorders

Loeys-Dietz aortic aneurysm syndrome; TGFBR1-related Loeys-Dietz syndrome; TGFBR2-related Loeys-Dietz syndrome

Genetics/Basic Defects

1. An autosomal dominantly inherited disorder of connective tissue
2. Caused by heterozygous mutations in the gene encoding type I or II transforming growth factor beta (TGF-β) receptor
3. An altered signaling of the TGF-β cytokine family
   a. Plays an important role in cell proliferation and differentiation, apoptosis and extracellular matrix formation, underling both LDS and MFS
   b. Causes disarrayed elastic fibers and loss of elastin content in the aortic media, predisposing to dilatation and dissection of the aortic wall
   c. Disruption of the normal TGF-β signaling takes place at the level of the TGF-β receptors. Mutations in either the TGF-β receptor 1 or 2 genes have been identified in one third and two thirds of LDS patients, respectively. However, in MFS an abnormal fibrillin protein causes an increased activity of TGF-β, leading to the typical phenotypic characteristics of the MFS.
4. No differences in phenotype are observed between individuals with mutations in *TGFBR1* and *TGFBR2*
5. Marfan syndrome–related disorders and mutated genes
   a. Marfan syndrome: *FBN1*, *TGFBR*1, *TGFBR2*
   b. Neonatal Marfan syndrome: *FBN1*
   c. Familial thoracic aortic: aneurysms and dissections: *FBN1*, *TGFBR1*, *TGFBR2*
   d. Isolated ectopia lentis: *FBN*1
   e. Shprintzen–Goldberg craniosynostosis syndrome: *FBN1*, *TGFBR2*
   f. Autosomal dominant Weill–Marchesani syndrome: *FBN1*
   g. Loeys–Dietz syndrome: *TGFBR1*, *TGFBR2*

Clinical Features

1. Clinical types
   a. Type I (about 75% of cases): recognized by recognizable craniofacial characteristics (hypertelorism, bifid uvula, or cleft palate)
   b. Type II (about 25% of cases): absence of facial characteristics (However, certain common facial features have been recently observed in type II patients.)
   c. Generalized arteriopathy: the most salient feature in LDS whether in type I or type II
   d. Aortic root aneurysms are present in 98% of LDS patients.

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e. Dural ectasia has recently been observed in LDS patients.
f. Both types with interfamilial and intrafamilial phenotypic variability

2. LDS type I
   a. Overlapping features with MFS
      i. Aortic root dilatation/aneurysm
      ii. Arachnodactyly (long slender fingers)
      iii. Dolichostenomelia (thin body habitus and long extremities)
      iv. Pectus deformity
      v. Joint laxity
   b. Typical characteristics
      i. Aortic root aneurysm (98%)
      ii. Aneurysms of other vessels (52%)
      iii. Generalized arterial tortuosity (84%)
   c. Typical and easily recognizable facial characteristics
      i. Ocular hypertelorism (increased distance between the pupils) (90%)
      ii. Cleft palate or bifid uvula (90%)
      iii. Other facial features
         a) Blue sclera (40%)
         b) Malar hypoplasia (60%)
         c) Exotropia
         d) Proptosis
         e) Retrognathia (50%)
   d. Musculoskeletal manifestations
      i. Craniosynostosis (premature closure of cranial sutures) (48%)
         a) Premature fusion of the sagittal suture (resulting in dolichocephaly) most commonly involved
         b) Coronal suture synostosis (resulting in brachycephaly)
         c) Metopic suture synostosis (resulting in trigonocephaly)
      ii. Dolichostenomelia (18%)
      iii. Cervical spine instability
      iv. Pectus deformity (68%)
      v. Arachnodactyly (70%)
      vi. Scoliosis (50%)
      vii. Joint laxity (68%)
      viii. Talipes equinovarus (45%)
      ix. Camptodactyly (38%)
   e. Cutaneous manifestations
      i. Velvety skin (28%)
      ii. Translucent skin (32%)
   f. Congenital heart defects
      i. Patent ductus arteriosus (35%)
      ii. Atrial septal defect (22%)
      iii. Bicuspid aortic valve
      iv. Bicuspid pulmonary valve
      v. Mitral valve prolapse
   g. Developmental delay (15%)
   h. Absence of ectopia lentis (lens subluxation) (0%) and other ocular manifestations seen in MFS

3. LDS type II
   a. Aortic root aneurysm with dissection (100%)
   b. Other aortic aneurysm (73%)
   c. Arterial tortuosity (67%)
   d. Overlapping features with the vascular type of EDS
      i. Skin abnormalities
         a) Easy bruising (67%)
         b) Translucent skin (64%)
         c) Velvety skin (83%)
         d) Skin hyperextensibility (20%)
         e) Atrophic scars (50%)
      ii. Joint laxity (100%)
      iii. Rupture of visceral organs
         a) Vascular rupture during pregnancy (50%)
         b) Uterine rupture (33%)
         c) Splenic or bowel rupture (25%)
      iv. Uterine hemorrhage (17%)
      v. Inguinal hernia (36%)
   e. Facial features observed in most patients, although not exclusive to LDS II (Adès 2008)
      i. Dolichocephaly
      ii. A tall broad forehead
      iii. Frontal bossing
      iv. A high anterior hairline
      v. Hypoplastic supraorbital margins
      vi. A "jowly" appearance (particularly in the first 3 years of life)
      vii. Translucent and redundant facial skin (often most pronounced in the periorbital region)
      viii. Prominent upper central incisors in late childhood/adulthood
      ix. An open-mouthed myopathic face
      x. The adult faces appeared prematurely aged

4. Cardiovascular involvement
   i. Type I
      a) Mean craniofacial-severity-index score (scores range from 0 to 11 with higher scores indicating more severe abnormalities): 4.8 years

b) Mean age at first major event: 24.5 years
c) Age at death: 22.6 years (0.5–45.0)
d) Cause of death: thoracic aortic dissection (19%), abdominal aortic dissection (5%), subclavian artery dissection (0%), and cerebral bleeding (3%)
e) Age at first cardiovascular surgery 16.9 years (1.2–46.0)
f) Distribution of aneurysms: ascending aorta (84%), transverse aorta (5%), descending thoracic aorta (6%), abdominal aorta (8%), thoracic arterial branches (27%), head or neck arterial branches (11%), and abdominal arterial branches (3%)

ii. Type II
a) Mean craniofacial-severity-index score: 0.8 year
b) Mean age at first major event: 29.8 years
c) Age at death: 31.8 years (18.0–47.0)
d) Cause of death: thoracic aortic dissection (23%), abdominal aortic dissection (12%), subclavian artery dissection (4%), and cerebral bleeding (0%)
e) Age at first cardiovascular surgery: 26.9 years (14.0–38.0)
f) Distribution of aneurysms: ascending aorta (85%), transverse aorta (23%), descending thoracic aorta (19%), abdominal aorta (15%), thoracic arterial branches (8%), head or neck arterial branches (8%), and abdominal arterial branches (15%)

5. Differential diagnosis
a. Vascular type of Ehlers–Danlos syndrome (please see Atlas)
b. Marfan syndrome (please see Atlas)
c. Shprintzen–Goldberg syndrome (Marfanoid craniosynostosis syndrome)
i. Phenotypes overlapping with some LDS patients with mutations in TGFBR1 or TGFBR2
ii. Not associated with cleft palate, arterial tortuosity or risk of aneurysm, or dissection other than at the aortic root
iii. Most affected individuals have no vascular pathology.
iv. Sequencing of TGFBR1 and TGFBR2 in five individuals with classic SGS identified no mutations (data not shown). Nevertheless, given the extent of phenotypic overlap between SGS, MFS and selected individuals with mutations in either TGFBR1 or TGFBR2, the pathogenesis of SGS probably also relates to alteration in TGF-β signaling.
d. Children who present with diffuse hypotonia, joint laxity, and/or joint contractures and in whom a diagnosis of arthrogryposis, Larsen syndrome, or Beal syndrome is being entertained should undergo thorough genetic evaluation to rule out a *TGFBR1* or *TGFBR2* mutation.

Diagnostic Investigations

1. Diagnosis of LDS
a. Based on characteristic clinical findings in the proband and family members
b. Craniofacial examination for evidence of bifid uvula, cleft palate, and craniosynostosis
c. Ophthalmologic examination by an ophthalmologist with expertise in connective tissue disorders
i. Slit-lamp examination through a maximally dilated pupil for exclusion of lens subluxation or luxation
ii. Careful refraction and visual correction, especially in young children at risk for amblyopia
iii. Specific assessment for retinal detachment and blue sclerae
d. Magnetic resonance angiography (MRA) or CT scan with 3D reconstruction from head to pelvis: to identify arterial aneurysms and arterial tortuosity throughout the arterial tree
e. Radiographs to detect skeletal manifestations (e.g., severe scoliosis, cervical spine instability) that may require attention by an orthopedist
f. Molecular genetic testing of *TGFBR1* and *TGFBR2*, the only two genes known to be associated with LDS, available on a clinical basis
2. Genetic testing of relatives at risk
a. To clarify genetic status of family members at risk if the causal *TGFBR1* or *TGFBR2* mutation is known in the proband
b. To evaluate relatives at risk for signs of LDS, including echocardiography and extensive vascular imaging if the mutation is not known in the proband

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. If a parent of the proband is affected: the risk to the sibs is 50%
      ii. If parents are clinically unaffected: the risk to the sibs of a proband appears to be low but greater than that of the general population because of reported rare cases of somatic and germline mosaicism
   b. Patient's offspring
      i. A 50% chance of inheriting the mutation and the disorder
      ii. Since the penetrance of disease-causing *TGFBR1* and *TGFBR2* mutations is reported to be near 100%, offspring who inherit a mutant allele from a parent will have LDS, although the severity cannot be predicted.
2. Prenatal diagnosis
   a. Ultrasound examination in the first two trimesters: not sensitive in detecting manifestations of LDS although prenatal occurrence of aortic dilatation has been described
   b. Molecular genetic testing
      i. Prenatal diagnosis for pregnancies at increased risk for LDS is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15–18 weeks' gestation or chorionic villus sampling (CVS) at approximately 10–12 weeks' gestation
      ii. The disease-causing allele of an affected family member must be identified or linkage established in the family before prenatal testing can be performed.
      iii. Linkage analysis should be used with caution unless *TGFBR1* or *TGFBR2* marker alleles can be shown to cosegregate with disease in a large family.
      iv. Preimplantation genetic diagnosis: available for families in which the disease-causing mutations have been identified
3. Management
   a. Careful follow-up and aggressive surgical treatment mandatory because of the following reasons:
      i. Aortic dissection and rupture in LDS tend to occur at a young age vs. MFS.
      ii. Vascular pathology can be seen throughout the entire arterial tree.
   b. Echocardiographic assessment of the aortic root diameter and its growth
   c. MR angiography from head to pelvis to discover other possible aneurysms
   d. Surgical fixation of cervical spine instability to prevent spinal cord damage
   e. Standard treatment of clubfeet and severe pes planus
   f. Standard management of cleft palate and craniosynostosis, preferably by a craniofacial team
   g. Prevention of secondary complications: consider subacute bacterial endocarditis prophylaxis in those undergoing dental work or other procedures expected to contaminate the bloodstream with bacteria
   h. Initiate β-blockade therapy to reduce further aortic root dilatation or alternatively treat with angiotensin II receptor antagonist
   i. Indications for surgical intervention in Loeys–Dietz syndrome (Williams et al. 2007)
      i. Adults
         a) Aortic root >4.0 cm or expanding rapidly (>0.5 cm/year)
         b) Descending thoracic aorta >5.0 cm or expanding rapidly (>0.5 cm/year)
         c) Abdominal aorta >4.0 cm or expanding rapidly (>0.5 cm/year)
         d) Rapid expansion of peripheral aneurysms
      ii. Children
         a) Severe craniofacial features: aortic root z-score >3.0 or expanding rapidly (>0.5 cm/year), or mild craniofacial features: aortic root z-score >4.0 or expanding rapidly (>0.5 cm/year)
         b) Effort should be made to delay surgery until the annulus reaches 1.8 cm, allowing placement of a valve-sparing graft of sufficient size to accommodate growth.
         c) Large size or rapid expansion of the descending aorta or other vessels
   j. Situations and agents to avoid
      i. Contact sports
      ii. Competitive sports
      iii. Isometric exercise
      iv. Agents that stimulate the cardiovascular system including routine use of decongestants
      v. Activities that cause joint injury or pain

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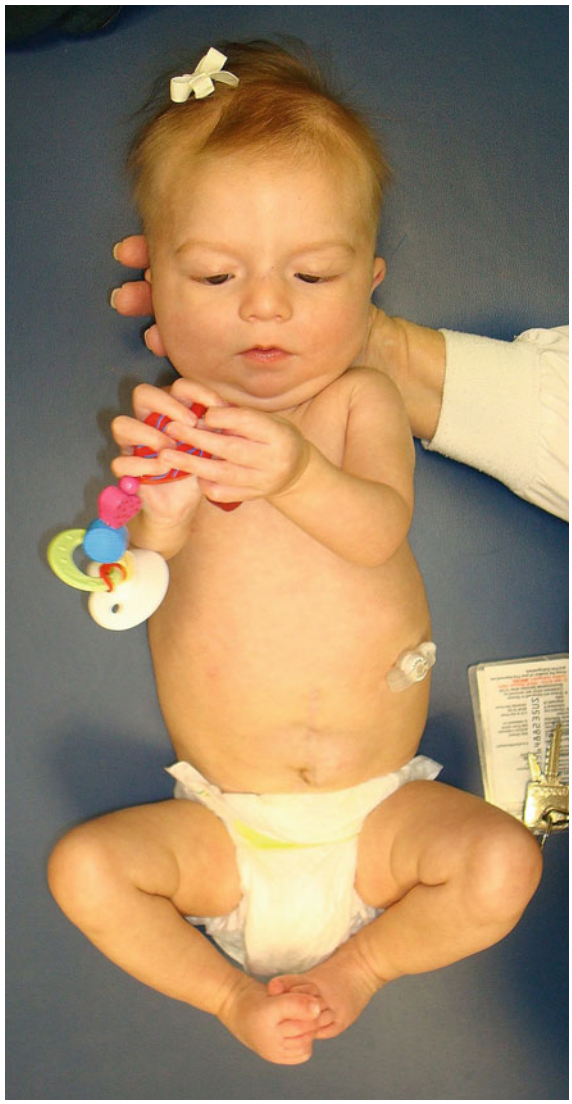

Fig. 1 A 5-month-old infant girl with molecularly confirmed Loeys–Dietz syndrome with *TGFBR1* exon 4 mutation c.722C>T (Ser241Leu). She was evaluated initially for possible neonatal Marfan syndrome because of very long fingers and toes. At 3 weeks of age, she was diagnosed to have intestinal malrotation which was surgically repaired and a Nissen fundoplication was performed. She had seizures since birth (eyes rolling up, occasional twitching and head pulling back for a very short period). MRI of the brain showed bilateral caudal thalamic groove cyst. At 3 months of age, she was noted to be abnormally pale and was found to have bleeding due to a ruptured wandering spleen in the pelvis which was surgically removed. She had a surgical incision hernia at the site of the first surgery in addition to her original inguinal hernia. Multiple echocardiograms showed no aortic root dilatation but the patient was put on β-blocker for aortic root dilatation prevention. Family history was noncontributory. Note the ocular hypertelorism, dolichostenomelia, and arachnodactyly

Fig. 2 Note the large incisional umbilical hernia

Fig. 3 Note the marked hypotonia and long and slender extremities

Fig. 4 Note the long toes

Lowe Syndrome

Lowe syndrome, also known as oculocerebrorenal syndrome, is a rare X-linked recessive disorder. It was initially recognized in 1952 by Lowe and colleagues who described the triad of congenital cataracts, mental retardation, and generalized aminoaciduria. In 1954, a renal Fanconi syndrome was recognized as being associated with the syndrome (Bickel & Thurshby-Pelnam 1954) and in 1965, an X-linked recessive pattern of inheritance was determined (Richards et al. 1965). Its prevalence is estimated to be several cases per 100,000 males.

Synonyms and Related Disorders

Dent-2 disease; Oculocerebrorenal syndrome

Genetics/Basic Defects

1. Inheritance
   a. X-linked recessive disorder predominantly affecting males, although several affected females have been reported
   b. New mutations in 31.6% of affected males
   c. Germline mosaicism in 4.5%
2. The gene involved (*OCRL1*)
   a. Map locus: Xq26.1, based on
      i. Balanced X-autosome translocations with a break-point in band Xq25-q26 in two unrelated female patients
      ii. Linkage analysis with RLFP in families with multiple affected individuals
   b. Mapped in 1977
   c. Cloned in 1992
   d. Encoding *OCRL1*, a 105-kD enzyme with phosphatidylinositol 4,5-bisphosphate 5-phosphatase (PtdIns-4,5-P_2) activity localized to the Golgi complex
      i. Loss or reduction of the enzyme demonstrated in affected males
      ii. Carrier status of OCRL in females not readily determined by assays of the enzyme due to the X-linked nature of *OCRL1* and random X inactivation
3. Mutations of *OCRL1* gene responsible for Lowe syndrome
   a. Nonsense mutations and deletions causing frameshifts and premature termination
   b. Deletions
   c. Missense mutations in domains conserved among all the known PtdIns(4,5)P_2 5-phosphatases
4. Carrier females with typical lens opacities
5. Affected females as a result of
   a. Unfavorable lyonization
   b. Turner syndrome
   c. X-autosome translocation through the relevant gene
6. Dent-2 disease (a mild variant of Lowe syndrome (Bökenkamp et al. 2009)
   a. Dent disease
      i. An X-linked tubulopathy characterized by low-molecular-weight proteinuria, hypercalciuria, and nephrolithiasis/nephrocalcinosis (1)
      ii. In more than half the patients, Dent disease is caused by mutations affecting the voltage-gated chloride channel and chloride/proton antiporter (ClC-5).

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b. Dent-2 disease
   i. In approximately 15% of patients with a Dent phenotype, mutations in the oculocerebrorenal syndrome of Lowe gene (*OCRL*) encoding a phosphatidylinositol 4,5-bisphosphate 5-phosphatase, have been found (Hoopes et al. 2005; Utsch et al. 2006; Sekine et al. 2007; Cho et al. 2008).
   ii. These patients are classified as having "Dent disease-2" to distinguish them from most patients with an *OCRL* mutation who have the more severe oculocerebrorenal syndrome of Lowe phenotype (Charnas et al. 1991) which is characterized by a proximal tubulopathy (Böckenhauer et al. 2008; Kleta 2008), congenital cataract, severe mental retardation, and behavioral disturbances.

Clinical Features

1. Variable age of onset and severity of clinical manifestations
2. Eye abnormalities
   a. Congenital cataracts (the hallmark of the disease)
      i. Developed prenatally
      ii. Always present prior to birth
   b. Congenital glaucoma with or without buphthalmos (50–60%)
   c. Microphthalmos
   d. Nystagmus
   e. Decreased visual acuity (blindness)
   f. Corneal scarring and keloid formation
      i. Develops spontaneously without trauma
      ii. Onset usually after age 5
      iii. Causes significant visual impairment
3. Renal abnormalities
   a. Fanconi syndrome of renal tubules (the cardinal features)
      i. Bicarbonaturia
      ii. Proximal tubular acidosis
      iii. Generalized aminoaciduria
      iv. Hyperphosphaturia leading to osteomalacia, renal rickets, and pathologic fractures
      v. Hypercalciuria
      vi. Proteinuria
      vii. Glycosuria (not a feature of the renal tubular dysfunction)
      viii. Impairment in urine-concentration (polyuria)
      ix. Carnitine wasting
   b. Variable age of onset and severity of the tubular dysfunction
      i. Failure to thrive
      ii. Recurrent infections
      iii. Metabolic collapse
      iv. Severe hypokalemia or hypocalcemia requiring replacement therapy in a minority of patients. This is probably a part of preterminal exacerbation of tubular dysfunction.
      v. Slowly progressive renal failure may occur in the second to fourth decade of life.
4. CNS (prominently involved organ) and behavioral abnormalities
   a. Cardinal features
      i. Neonatal/infantile hypotonia
      ii. Delay in motor milestones
      iii. Cognitive impairment
      iv. Areflexia by 1 year of age
   b. Mental retardation (common but not cardinal feature)
   c. Seizures
   d. Neuropathologic and neuroimaging abnormalities
   e. Stereotypic behaviors
      i. Temper tantrum (Lowe tantrum)
      ii. Aggression
      iii. Irritability
      iv. Stubbornness
      v. Rigidity of thought
      vi. Self injury
      vii. Repetitive nonpurposeful movements
5. Musculoskeletal abnormalities
   a. Secondary consequences of hypotonia, renal tubular acidosis, and/or hypophosphatemia
      i. Short stature
      ii. Joint hypermobility
      iii. Dislocated hips
      iv. Genu valgum
      v. Scoliosis
      vi. Kyphosis
      vii. Platyspondylia
      viii. Fractures
   b. Primary abnormality of excessive connective tissue growth
      i. Nontender joint swelling
      ii. Subcutaneous nodules

6. Typical facies
   a. Frontal bossing
   b. Characteristic deep-set eyes
   c. Inattentiveness
7. Other features
   a. Increased hemorrhagic risk (Lane et al. 2010)
   b. Cryptorchidism
8. Natural history
   a. Succumb to either severe renal insufficiency and dehydration or infection
   b. Survival to adulthood if metabolic abnormalities are adequately treated
9. Manifestation in the carriers
   a. Lens involvement
      i. Micropunctate cataracts clustered in a radial wedge pattern
      ii. Occasional dense posterior cortical cataract
   b. Sensitivity of carrier detection by slit-lamp examination (>90%), due to random inactivation of Lowe syndrome allele in the proportion of cells in the lens of female carriers
   c. Germ line or somatic mosaicism documented
   d. Positive family history of early cataracts in mother, maternal female relatives, and institutionalized maternal uncles

Diagnostic Investigations

1. Blood chemistry
   a. Blood gas for metabolic acidosis
   b. Electrolyte disturbances (likely absent in neonates and young infants)
2. Urine
   a. Aminoaciduria
   b. Hyperphosphaturia
   c. Low-molecular-weight (LMV) proteinuria: characterized by the excretion of proteins such as retinal binding protein and N-acetyl glucosaminidase, is seen in
      i. Lowe syndrome: LMW proteinuria can be seen early in life even in the absence of clinically significant aminoaciduria or other renal tubular abnormalities (Laube et al. 2004)
      ii. The allelic disorder Dent disease
      iii. Many other diseases associated with the Fanconi syndrome
   d. Glycosuria
   e. Low urine osmolality
   f. Elevated 24-h volume
3. Serum enzyme values
   a. Elevated CK
   b. Elevated SGOT
   c. Elevated LDH
   d. Elevated α2-globulin
4. Measurement of inositol polyphosphate 5-phosphatase OCRL1 activity in cultured skin fibroblasts (Lewis et al. 2008)
   a. Males: to confirm the diagnosis in affected males (Suchy et al. 1995; Zhang et al. 1995)
      i. Affected males have less than 10% normal activity of the enzyme.
      ii. Such testing is abnormal in more than 99% of affected males.
   b. Carrier females. The activity is not accurate for carrier detection because of lyonization (random X-chromosome inactivation), which results in a wide range of "normal" activity in females (Lin et al. 1999).
5. Karyotype. Translocations between an autosome and an X chromosome with a breakpoint through the OCRL locus (Xq26.1) have been observed (Hodgson et al. 1986; Mueller et al. 1991)
6. Radiography
   a. Rickets/osteoporosis
   b. Pathological fractures
   c. Frontal bossing
   d. Kyphoscoliosis
   e. Cervical spine anomalies
   f. Platyspondyly
   g. Hip subluxations/dislocation
7. Neuroimaging
   a. Cranial MRI
      i. Mild ventriculomegaly (33%)
      ii. Multiple tiny periventricular cysts (no clinical significance)
      iii. Two patterns of brain lesions (de Carvalho-Neto et al. 2009)
         a) Hyperintensities on T2-weighted images
         b) Periventricular cystic lesions
   b. Neuropathologic examination of the brain
      i. Normal in some cases
      ii. Diffuse or focal myelin pallor without myelin breakdown
      iii. Ventriculomegaly
      iv. Mild cerebral abnormalities

v. Isolated cases of subependymal cysts
vi. Mesencephalic porencephaly
vii. Postencephalitic changes
viii. Blunted and foreshortened frontal lobes
ix. Acute pontine necrosis
x. Cerebellar hypoplasia
xi. Aberrant neuronal migration
xii. Multiple tiny cysts without inflammatory changes

8. Affected male patients
   a. Biochemical assay of reduced activity (<10%) of PtdIns (4,5)P_2 5-phosphatase in cultured fibroblasts to confirm diagnosis of patients with OCRL. Peripheral blood cannot be tested since the enzyme is not present in lymphocytes.
   b. Molecular analysis to detect mutations in the *OCRL* gene in about 95% of affected males
      i. Sequence analysis
      ii. Fluorescence in situ hybridization analysis (FISH), with cosmid probes that span the entire *OCRL1* gene
9. Carrier females
   a. Karyotyping to rule out X-autosome translocation with a breakpoint through the *OCRL* locus
   b. Carrier detection
      i. Biochemical assay of reduced activity of PtdIns (4,5)P_2 5-phosphatase in cultured fibroblasts is not suitable for determining OCRL carrier status, since random X inactivation could result in a wide range of enzyme activity that may overlap with the normal range.
      ii. An obligatory carrier based on evaluation of the family pedigree
      iii. Slit-lamp examination for numerous punctate opacities, especially in prepubertal females, is a better method and it has a low false-negative rate.
      iv. By direct detection of mutations when the mutation is previously identified (in about 95% of carrier females)
      v. By mutation scanning of high-risk females by denaturing high performance liquid chromatography (DHPLC) when:
         a) The affected male is not available
         b) The diagnosis has been confirmed by enzyme analysis
      vi. By linked markers when the mutation is unknown

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. A 25% risk of having an affected boy and a 25% risk of having a carrier daughter if the mother is a carrier
      ii. A low but finite recurrence risk (estimated to be about 1.5%) in case of a new mutation due to possibility of nonpenetrance or gonadal mosaicism in the mother
   b. Patient's offspring: affected males not known to reproduce
2. Prenatal diagnosis available for pregnancies at risk
   a. Determine fetal gender by amniocentesis or CVS
   b. Biochemical assay for deficiency of PtdIns(4,5)P_2 5-phosphatase from cultured amniotic fluid cells or cultured CVS if the fetal karyotype shows 46,XY (not suitable for determining OCRL carrier status for females)
   c. Molecular analysis
      i. By direct detection of mutations when the *OCRL* disease-causing mutation in the family is known
      ii. By linked markers in informative families when the mutation is unknown
   d. Offer prenatal diagnosis by enzymatic analysis to every mother of a son with Lowe syndrome because of the relatively high rate (4.5%) of germline mosaicism, even with the following situations:
      i. Negative family history
      ii. Negative dilated slit-lamp examination
      iii. DNA testing showing that the mother is not a carrier
3. Management
   a. Ocular management
      i. Cataract extraction to avoid amblyopia
      ii. Refraction for aphakia
      iii. Control of glaucoma
      iv. Removal of corneal keloids: often with recurrence and enlargement of the lesions
   b. Speech and physical therapy for developmental delay
   c. Medications
      i. Anticonvulsants
      ii. Behavior-modifying medications if needed

d. Replacement/supplementation
   i. Phosphate and sodium-potassium citrate for renal tubular acidosis (urinary bicarbonate, water, and phosphate losses) and bone disease (rickets)
   ii. L-carnitine
   iii. Vitamin D supplements as indicated
e. Anesthetic risks
   i. Chronic metabolic acidosis
   ii. Existing hypokalemia, a risk for serious cardiac arrhythmia
   iii. A risk of glaucoma
   iv. Hypophosphatemic rickets causing fragility of bone structures
      1. Requires attention while positioning
      2. Difficulty in maintaining the airway due to craniofacial abnormalities and abnormal teeth structure

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Fig. 1 (**a**–**d**) One and half year-old boy with Lowe syndrome showing frontal bossing and deep-set eyes. He had a history of profound hypotonia, failure to thrive, cataracts, glaucoma, seizures, and generalized aminoaciduria. The diagnosis was confirmed by assay of markedly deficient phosphatidylinositol bisphosphate phosphatase activity in the cultured fibroblasts (0.05, control: 2–5 mmol/min/mg protein). The recent photos were taken at 6 and 9 years of age

Fig. 2 (**a**, **b**) A 10-year-old boy with Lowe syndrome showing short stature and visual impairment. The diagnosis was confirmed by assay of markedly deficient phosphatidylinositol bisphosphate phosphatase activity (0.05 with normal control of 2–5 nmol/min/mg protein) in the cultured fibroblasts

Marfan Syndrome

Marfan syndrome (MFS) is an inherited connective tissue disorder, noteworthy for its worldwide distribution, relatively high prevalence, clinical variability, and pleiotropic manifestations involving primarily the ocular, skeletal, and cardiovascular systems, some of which are life threatening. Its estimated frequency is 2–3 per 10,000 individuals.

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant
   b. New mutation in about 25–30% of the cases
   c. About 70–75% of individuals diagnosed with Marfan syndrome have an affected parent.
2. Caused by a wide variety of mutations in the fibrillin-1 (*FBN1*) gene located on chromosome 15q21.1
3. Molecular defects in the fibrillin gene are responsible for the impaired structural integrity of the skeletal, ocular, and cardiovascular systems.
4. Almost all mutations are specific (unique) to a particular individual or family.
5. *FBN1* mutation is helpful diagnostically only if it has been previously found in the person who independently meets the criteria for Marfan syndrome.
6. Criteria for causal *FBN1* mutation (Loeys et al. 2010)
   a. Mutation previously shown to segregate in Marfan family
   b. De novo (with proven paternity and absence of disease in parents) mutation (one of the five following categories)
   c. Nonsense mutation
   d. Inframe and out of frame deletion/insertion
   e. Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level
   f. Missense affecting/creating cysteine residues
   g. Missense affecting conserved residues of the EGF consensus sequence ((D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F) with m and n representing variable number of residues; D aspartic acid, N asparagine, E glutamic acid, Q glutamine, Y tyrosine, F phenylalanine)
   h. Other missense mutations: segregation in family if possible plus absence in 400 ethnically matched control chromosomes, if no family history absence in 400 ethnically matched control chromosomes
   i. Linkage of haplotype for $n \geq 6$ meioses to the FBN1 locus
7. No obvious correlation between location of mutation and phenotypic severity (except an apparent clustering of mutations associated with the most severe form of Marfan syndrome, i.e., neonatal Marfan syndrome)
8. Pathophysiological consequence of the elastic fiber degeneration: reduced distensibility in response to the pulse pressure wave or increased stiffness (Dean 2002)
9. Intrafamilial and interfamilial variability of clinical expression
10. Fibrillin-1 mutations also observed in related disorders of connective tissue (type I fibrillinopathies) (Dietz 2009; Loeys et al. 2010)
    a. Autosomal dominant ectopia lentis (bilateral ectopia lentis without the typical skeletal and

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cardiovascular manifestations of the Marfan syndrome)

b. Shprintzen-Goldberg syndrome
   i. Unclear inheritance pattern
   ii. Marfanoid habitus
   iii. Craniosynostosis
   iv. Mental retardation
   v. Rarely aortic root dilatation
   vi. Mitral valve prolapse
   vii. Majority of cases are not caused by *FBN1* mutations

c. Autosomal dominant Weill-Marchesani syndrome
   i. Ectopia lentis
   ii. Short stature

d. Familial ectopic lentis
   i. An autosomal dominant condition
   ii. Bilateral ectopia lentis
   iii. Scoliosis in some cases
   iv. No cardiovascular manifestations

e. Familial aortic aneurysm
   i. Ascending aortic aneurysm and dissection
   ii. No ectopia lentis
   iii. No specific skeletal findings

f. MASS phenotype
   i. An autosomal dominant condition
   ii. Acronym MASS stands for:
      a) *M*itral valve prolapse
      b) *A*ortic root dilation without dissection
      c) *S*keletal abnormalities
      d) *S*kin abnormalities

g. Mitral valve prolapse syndrome
   i. An autosomal dominant condition
   ii. Mitral valve prolapse
   iii. Associated with subtle skeletal features that are reminiscent of the Marfan syndrome

h. New variant of Marfan syndrome
   i. Skeletal features of Marfan syndrome
   ii. Joint contractures
   iii. Knee joint effusions
   iv. Ectopia lentis
   v. No cardiovascular manifestations

i. Marfan-like (Marfanoid) skeletal abnormalities
   i. Tall stature
   ii. Scoliosis
   iii. Pectus excavatum
   iv. Arachnodactyly

11. Other disorders overlap with Marfan syndrome (Dietz 2009; Loeys et al. 2010).
   a. Loeys-Dietz syndrome: please see the chapter on Loeys-Dietz syndrome
      i. An autosomal dominant condition
      ii. Shares many features of Marfan syndrome but ectopia lentis is absent
      iii. Unique features
         a) Craniofacial involvement (bifid uvula/cleft palate, hypertelorism, craniosynostosis)
         b) Skin: soft, velvety, and translucent
         c) Easy bruising
         d) Generalized arterial tortuosity and aneurysms
         e) Dissection throughout the arterial trees
      iv. Other features
         a) Clubfoot
         b) Cervical spine instability
      v. Caused by mutations in either the *TGFBR1* or *TGFBR2* gene (Loeys et al. 2005, 2006)
      vi. Loeys-Dietz syndrome types 1 and 2: designate those with and without severe craniofacial involvement respectively (Loeys et al. 2006)
   b. Congenital contractural arachnodactyly
      i. Caused by fibrillin-2 (*FBN2*) mutations (highly homologous to BBN1, mapped to chromosome 5q23-31)
      ii. Characteristic features
         a) Marfanoid habitus
         b) Arachnodactyly
         c) Camptodactyly
         d) Crumpled ears
         e) Mild contractures of the elbows, knees, and hips
         f) Mild muscle hypoplasia especially of the calf muscles
   c. Ehlers-Danlos syndrome: please see the chapter on Ehlers-Danlos syndrome
   d. Homocystinuria
      i. An autosomal recessive condition
      ii. Caused by cystathionine β-synthase deficiency resulting from mutations in the *CBS* gene
      iii. Characteristic clinical features

a) Variable mental retardation
b) Ectopia lentis and/or severe myopia
c) Skeletal abnormalities (including excessive height and limb length)
d) Excessive overlap with Marfan syndrome (a long and lean body habitus, pectus deformity, scoliosis, mitral valve prolapse, highly arched palate, hernia, and ectopia lentis)
e) A tendency for intravascular thrombosis and thromboembolic events: Thromboembolic events can be life threatening. Approximately half of affected individuals are responsive to pharmacologic doses of vitamin B6, highlighting the need to consider this diagnosis.

e. Stickler syndrome: please see the chapter on Stickler syndrome
f. Fragile X syndrome: please see the chapter on Fragile X syndrome

Clinical Features

Ghent criteria: For the diagnosis of Marfan syndrome in the first (index) case in a family, major criteria must be found in at least two different organ systems and minor criteria in a third body system. If a fibrillin-1 mutation is identified, a major criterion in one system and involvement of another system are required. In a relative of an individual with confirmed Marfan syndrome, a major criterion in one body system and involvement of another system are all that are needed for the diagnosis (Pyeritz 2000).

1. Skeletal system (requires at least two majors or one major plus two minors): Affected patients are usually tall and thin with respect to the family profile. Limbs are disproportionately long compared with the trunk (dolichostenomelia). Arachnodactyly is a very common feature.
   a. Major criteria (requires at least four manifestations)
      i. Pectus carinatum
      ii. Pectus excavatum requiring surgery
      iii. Reduced upper-to-lower body segment ratio (<0.85 in Caucasians and <0.78 in African descents) or arm span-to-height ratio greater than 1.05. Arms and legs may be unusually long in proportion to the torso.
      iv. Positive wrist (Walker-Murdoch) and thumb (Steinberg) signs for arachnodactyly. Two simple maneuvers may help demonstrate arachnodactyly. First, the thumb sign is positive if the thumb, when completely opposed within the clenched hand, projects beyond the ulnar border. Secondly, the wrist sign is positive if the distal phalanges of the first and fifth digits of one hand overlap when wrapped around the opposite wrist.
      v. Scoliosis ≥20 or spondylolisthesis. More than 60% of patients have scoliosis. Progression is more likely with curvature greater than 20° in growing patients.
      vi. Reduced extension of the elbows (<170°).
      vii. Medial displacement of the medial malleolus, resulting in pes planus
      viii. Protrusio acetabuli (intrapelvic protrusion of the acetabulum; abnormally deep acetabulum with accelerated erosion) of any degree (ascertained by pelvic radiograph). Prevalence is about 50%.
   b. Minor criteria
      i. Pectus excavatum of moderate severity
      ii. Joint hypermobility
      iii. High arched palate with dental crowding
      iv. Typical face
         a) Dolichocephaly
         b) Malar hypoplasia
         c) Enophthamos
         d) Retrognathia
         e) Down-slanting palpebral fissures
2. Ocular system (requires one major or at least two minors).
   a. Major criterion: ectopia lentis (usually superior temporal dislocation, almost always bilateral, occurs in up to 80% of affected individuals). This may present at birth or develop during childhood or adolescence.
   b. Minor criteria
      i. Abnormally flat cornea (measured by keratometry)

ii. Increased axial length of the globe (measured by ultrasound)
iii. Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis

3. Cardiovascular system (requires one major or one minor): the most serious problems associated with Marfan syndrome
   a. Major criteria
      i. Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva. The prevalence of aortic dilatation in Marfan syndrome is 70–80%. It presents at an early age and tends to be more common in men than women.
      ii. Dissection involving the ascending aorta
   b. Minor criteria
      i. Mitral valve prolapse with or without mitral valve regurgitation. The prevalence of mitral valve prolapse is 55–69%.
      ii. Dilatation of main proximal pulmonary artery in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, below the age of 40 years
      iii. Calcification of mitral annulus in patients less than 40 years of age
      iv. Dilatation or dissection of abdominal or descending thoracic aorta in patients less than 50 years of age
4. Pulmonary system (requires one minor)
   a. Major criterion: none
   b. Minor criteria
      i. Spontaneous pneumothorax: occurs in about 5% of patients
      ii. Apical blebs (on chest radiography)
5. Skin and integument (requires one minor)
   a. Major criterion: none
   b. Minor criteria
      i. Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy, or repetitive stress. Stretch marks are usually found on the shoulder, midback, and thighs.
      ii. Recurrent or incisional hernia
6. Dura (requires the major criterion)
   a. Major criterion: lumbosacral ectasia (ballooning or widening of the dural sac) by CT or MRI. Fewer than 20% of patients experience serious dural ectasia. Dural ectasia is thought to be caused by CSF pulsations against weakened dura.
   b. Minor criteria: none
7. Family history (requires one major)
   a. Major criteria
      i. Having a parent, child, or sibling who meets the diagnostic criteria independently
      ii. Presence of a mutation in *FBN1* known to cause the MFS
      iii. Presence of a haplotype around *FBN1*, inherited by descent, known to be associated with unequivocally diagnosed MFS in the family
   b. Minor criterion: none
8. Other features not in the Ghent criteria
   a. Ocular features
      i. Myopia (most common ocular feature)
      ii. At increased risk for retinal detachment, glaucoma, and early cataract formation
   b. Skeletal system
      i. Bone overgrowth
      ii. Disproportionately long extremities for the size of the trunk (dolichostenomelia)
      iii. Overgrowth of the ribs pushing the sternum in (pectus excavatum) or out (pectus carinatum)
      iv. Mild, severe, or progressive scoliosis
9. Natural history: age-related nature of some clinical manifestations and variable phenotypic expression
   a. At birth, early in life, and childhood
      i. Dolichostenomelia
      ii. Arachnodactyly
      iii. Manifestations of other organ systems usually not present at birth, making the diagnosis during neonatal period difficult in the absence of family history
      iv. Asthenic habitus
      v. Lens dislocation or lens subluxations (a hallmark feature) commonly diagnosed during the first year of life (not present at birth)
   b. Childhood and puberty
      i. Skeletal manifestations apparent during childhood
      ii. Pectus deformities and scoliosis worsen during puberty

iii. Upper normal or larger than normal aortic root size in early childhood
iv. Rapidly increasing magnitude of dilatation during puberty

c. Adulthood
i. Lumbosacral dural ectasia manifesting as progressive dilatation of the dura with consequent erosion of vertebral bone during adulthood
ii. Aortic disease as the major cause of cardiovascular morbidity and reduced life expectancy (initial life expectancy: 32 +/− 16 years)
iii. Increased life expectancy attributes to successive elective and emergent aortic surgery and to the use of β-adrenergic receptor antagonists for the prevention of the progression of aortic root dilatation (current life expectancy: 41 ± 18 years)

10. Revised Ghent nosology for the Marfan syndrome (Loeys et al. 2010)
a. Established by an international expert panel
b. Puts more weight on the cardiovascular manifestations in which aortic root aneurysm and ectopia lentis are the cardinal clinical features
i. In the absence of any family history, the presence of aortic root aneurysm and ectopic lentis is sufficient for the unequivocal diagnosis of MFS.
ii. In absence of either of aortic aneurysm or ectopic lentis, the presence of a bonafide *FBN1* mutation or a combination of systemic manifestations is required. The following new scoring system has been designed for systemic features: The score of ≥7 indicates systemic involvement (maximum total of 20 points).
a) Wrist and thumb sign: 3 (wrist or thumb sign: 1)
b) Pectus carinatum deformity: 2 (pectus excavatum or chest asymmetry: 1)
c) Hindfoot deformity: 2 (plain pes planus: 1)
d) Pneumothorax: 2
e) Dural ectasia: 2
f) Protrusio acetabuli: 2
g) Reduced US/LS and increased arm/height and no severe scoliosis: 1
h) Scoliosis or thoracolumbar kyphosis: 1
i) Reduced elbow extension: 1
j) Facial features (3/5): 1 (dolichocephaly, enophthalmos, down-slanting palpebral fissures, malar hypoplasia, retrognathia)
k) Skin striae: 1
l) Myopia >3 diopters: 1
m) Mitral valve prolapse (all types): 1
c. In this revised nosology, *FBN1* testing, although not mandatory, has greater weight in the diagnostic assessment.
d. Special considerations are given to the diagnosis of MFS in children and alternative diagnoses in adults.
e. These new guidelines may delay a definitive diagnosis of MFS but will decrease the risk of premature or misdiagnosis and facilitate worldwide discussion of risk and follow-up/management guidelines.

11. Neonatal Marfan syndrome
a. Diagnosed early in life because of striking and severe clinical manifestations
i. Two symptoms that are uncommon in severe Marfan syndrome presenting at birth but very common in neonatal Marfan syndrome (Hannekam 2005)
a) Congenital pulmonary emphysema
b) Mitral or tricuspid insufficiency (multivalvular involvement)
ii. Congestive heart failure
iii. Joint contractures
iv. Death usually within the first year of life
b. Characteristic aged facial appearance
i. Deep-set eyes
ii. Down-slanted palpebral fissures
iii. Crumpled ears
iv. High arched palate
c. Striking arachnodactyly of the fingers and toes
d. Pectus deformities
e. Scoliosis
f. Flexion contractures
g. Pes planus
h. Aortic root dilatation
i. Ectopia lentis
j. A cluster of mutations in exons 24–27 as well as in exons 31–32

Diagnostic Investigations

1. Annual physical examination including blood pressure measurement
2. Slit lamp examination for lens dislocation
3. Electrocardiogram for symptomatic palpitations, syncope or near-syncope, and conduction disturbance
4. Echocardiography and targeted imaging studies to carefully monitor the cardiovascular status
   a. Cross-sectional echocardiography for detecting aortic root dilatation
   b. Standard echocardiography for assessing mitral valve prolapse, left ventricular size and function, left atrial size, and tricuspid valve function
   c. Transesophageal echocardiography for visualizing the distal ascending and descending aorta and assessing prosthetic valves
   d. Doppler echocardiography for detecting and assessing the severity of aortic and mitral regurgitation
5. Radiography
   a. Chest X-ray for apical blebs, enlargement of cardiac silhouette, and detecting dissecting aneurysm of aorta
   b. Pelvic X-ray for additional diagnostic criteria of protrusio acetabuli
   c. Feet X-ray for medial displacement of the medial malleolus, responsible for pes planus
6. Computed tomography (CT) and magnetic resonance imaging (MRI)
   a. MRI: best choice for assessing chronic dissection of any region of the aorta
   b. CT or MRI of the lumbosacral spine for detecting dural ectasia
7. Aortograph: still considered by many to be the gold standard for diagnosing acute aortic dissection although sensitivity is not 100% and there are associated risks
8. Molecular analysis of *FBN1* mutations by sequence analysis, mutation scanning, deletion analysis, or linkage analysis (may be used to determine if an individual has inherited an FBN1 allele that is associated with Marfan syndrome in family members)
   a. Routine mutation detection not available clinically due to the large size and complexity of *FBN1* gene
   b. Mutations detected nearly always specific to each family
   c. *FBN1* mutations observed in 20–80% of patients depending upon the clinical selection of patients and the mutation detection method used
      i. Mutation scanning
      ii. Targeted mutation analysis
      iii. Sequencing of entire coding region
   d. Genotype-phenotype correlations (Pyeritz 2000)
      i. Little correlation observed in several hundred mutations reported to date
      ii. Severe MFS detected in infancy (inappropriately termed neonatal MFS) usually caused by point mutations or small deletions inframe in the epidermal growth factor (ECF)–like motifs in the middle third of the fibrillin-1 protein
      iii. Less severe phenotype, verging on the MASS phenotype, usually caused by chain-terminating mutations resulting in essence in null mutants
      iv. Marked variability among individuals with the same mutation
   e. *FBN1* mutations of various types reported
      i. Classic Marfan syndrome
      ii. Nonclassical Marfan related phenotypes
   f. Molecular diagnosis practical in the following two situations (Pyeritz 2000)
      i. Information about a known *FBN1* mutation in a person with MFS applied to relatives
      ii. Linkage analysis using sufficient intragenic and tightly linked polymorphisms to MFS families with several available and willing relatives
9. Histology of the aorta
   a. Elastic fiber fragmentation and disarray
   b. Paucity of smooth muscle cells
   c. Deposition of collagen and the mucopolysaccharide between the cells of the media

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Recurrence risk: small if neither parent is affected

ii. Gonadal mosaicism reported as the cause of multiple affected offspring being born to unaffected parents
iii. Fifty percent if one parent is affected

b. Patient's offspring
i. Fifty percent if the spouse is normal
ii. "Homozygous" MFS reported in case of an affected spouse
iii. "Compound heterozygosity" at the *FBN1* locus confirmed at the molecular level; the affected child had a severe phenotype leading to early death

2. Prenatal diagnosis
a. Ultrasonography insensitive in the first two trimesters for detecting a fetus with MFS
b. Fetal echocardiography with careful limb length measurements by level II ultrasonography for at-risk pregnancy during 20th–24th weeks of gestation
c. Main clinical cardiovascular features for the prenatal diagnosis of Marfan syndrome (Lopes et al. 2006)
i. Cardiomegaly
ii. Dilated great vessels
iii. Dysplastic atrioventricular valves with tricuspid regurgitation and aneurysms of the pulmonary artery and/or sinus of Valsalva
d. Prenatal diagnosis of Marfan syndrome can be confirmed in affected families by gene identification using chorionic villus sampling (Godfrey et al. 1993; Rantamaki et al. 1995).
i. Only if the family's mutation is known in an affected parent
ii. Neonatal Marfan syndrome, mostly sporadic, appears to be more severe than those in familiar forms (Gross et al. 1989). Inability to predict exons 24–32 mutation to be associated with "classic, atypically severe or neonatal" Marfan syndrome (Tieck et al. 2001)
iii. Presence of sufficient affected family members available for genetic linkage analysis if linkage with markers in and around the *FBN1* locus can be established
e. Preimplantation diagnosis accomplished but complicated by the potential for selective PCR amplification of the normal allele as with all autosomal dominant conditions

3. Management
a. Address patients' perceptions of Marfan syndrome and its associated pain, fatigue, and depressive symptoms to enhance patient adaptation.
b. Stress benefits of medication use (β-blockers or calcium-channel blockers to retard aortic root dilatation and dissection) and restriction of physical activities (to delay the onset of a severe cardiovascular event and prevent other syndrome-related problems such as lens dislocation).
i. β-Blockers
a) Should be considered in all Marfan patients, particularly in the younger age group
b) Not suitable for patients with asthma, cardiac failure, or bradyarrhythmias
ii. Other treatments aimed at reducing the ejection impulse
a) Calcium antagonists
b) Angiotensin converting enzyme (ACE) inhibitors
c. Lifestyle changes
i. Avoid competitive and collision/contact sports which are potentially dangerous due to underlying aortic weakness and dilatation, valvular insufficiency, ocular abnormalities, and skeletal problems.
ii. Avoid blows to the head such as boxing and high diving.
iii. Protect against blows to the globe (racquet sports) with cushioned spectacles.
iv. Avoid activities involving isometric work to prevent excessive elevations of systolic blood pressure and sudden death.
a) Weight lifting
b) Climbing steep inclines
c) Gymnastics
d) Water skiing
e) Pull-ups
v. Avoid rapid decompression associated with quick ascents in elevators, scuba diving, and flying in unpressurized aircraft to protect against pneumothorax.
vi. Favor noncompetitive, isokinetic activity performed at a nonstrenous aerobic pace.
a) Golfing
b) Walking
c) Fishing

d. Surgical intervention recommended for affected individuals with significantly dilated or dissected aortic roots
e. Management of scoliosis
   i. Bracing
   ii. Physical therapy
   iii. Surgery for severe scoliosis
f. Pectus repair
   i. Repair of pectus excavatum to improve respiratory mechanics: should be delayed until midadolescence to lessen the chance of recurrence
   ii. Repair of pectus carinatum performed mainly for cosmetic purpose
g. Pneumothorax
   i. Chest tube: an appropriate initial therapy
   ii. Bleb resection and pleurodesis recommended after one recurrence
h. Ocular management
   i. Removal of dislocated lens (pars plana lensectomy and vitrectomy), only in the following few instances, due to an increased risk of retinal detachment related to lens extraction
      a) Dislocation of a lens in the anterior chamber, especially when it touches the corneal endothelium
      b) Significant lens opacity
      c) Evidence of lens-induced uveitis and glaucoma
      d) Inadequate visual acuity that is not correctable by refraction and iris manipulation
      e) Imminent complete luxation of the lens
   ii. Lasers to restore a detached retina
i. Pregnancy in women with MFS
   i. Preconceptional counseling of maternal risks during pregnancy and risk of transmitting the condition to offspring
   ii. A significantly increased risk of cardiovascular complications during pregnancy, particularly risk of dissecting aortic aneurysm
   iii. A high risk of spontaneous abortion but no other adverse maternal or fetal effects
   iv. Need for close surveillance during pregnancy
   v. Avoid pregnancy if echocardiography suggests a high risk of life-threatening cardiovascular compromise. Pregnancy bears a 1% risk of fatal complication; the risk rises with increasing aortic root diameter.
   vi. β-Blockers recommended in pregnant women to prevent aortic dilatation
   vii. Caesarean section should be offered at 38 weeks gestation if aortic root diameter is greater than 4.5 cm (Child 1997).

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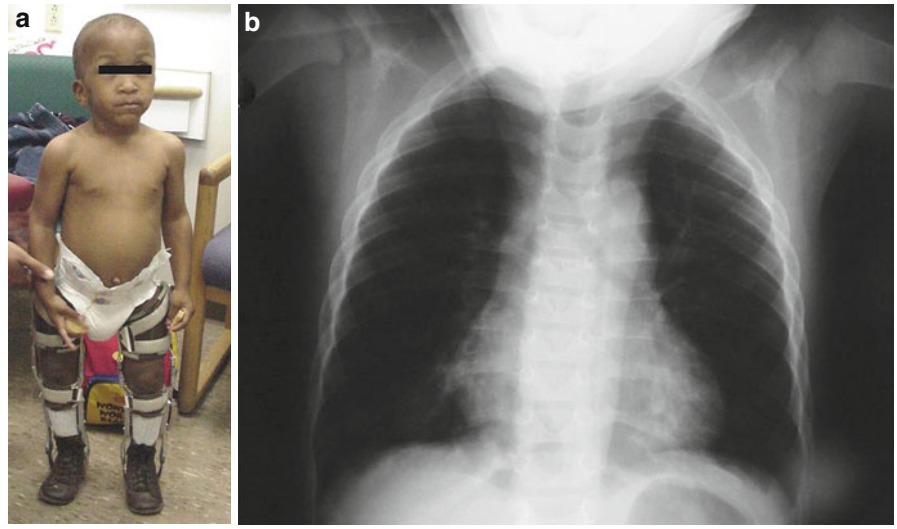

Fig. 1 (**a**, **b**) A boy with severe Marfan syndrome showing arachnodactyly, joint contractures, and aortic root dilatation, illustrated by the chest radiography

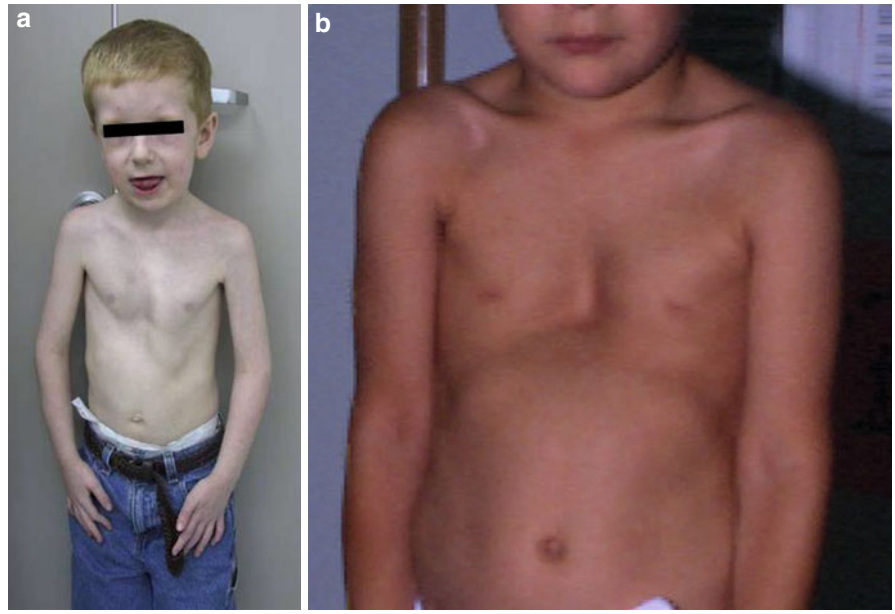

Fig. 2 (**a**, **b**) Two children with Marfan syndrome showing pectus and arachnodactyly. The first patient had dural ectasia detected by MRI. The second patient had aortic root dilatation and mitral valve prolapse

Fig. 3 A 4-year-old girl with Marfan syndrome showing pectus excavatum and the operation scar from surgical correction of marked aortic dilatation. She also has hyperextensible joints and scoliosis

Fig. 4 A 5-year-old boy with Marfan syndrome showing tall and slender body habitus. He was noted to have mitral valve prolapse and aortic root dilatation at age 2. In addition, he has bilateral lens dislocations and scoliosis

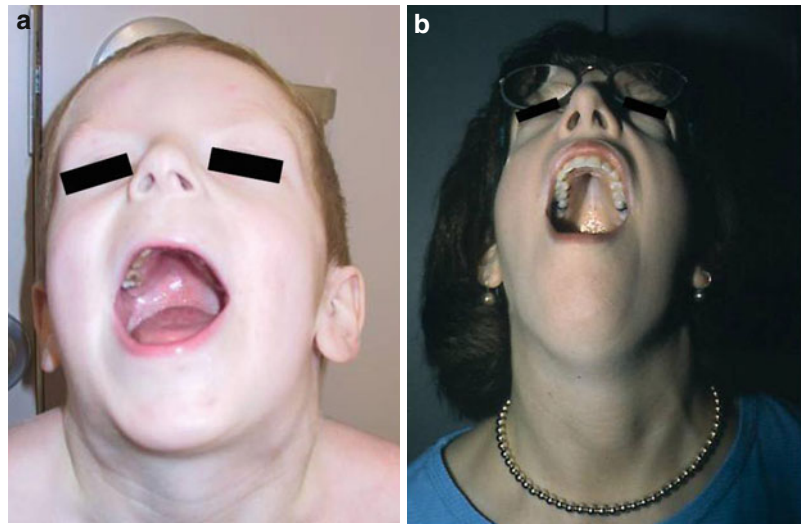

Fig. 5 (**a**, **b**) A child and an adult with Marfan syndrome showing high arched palate

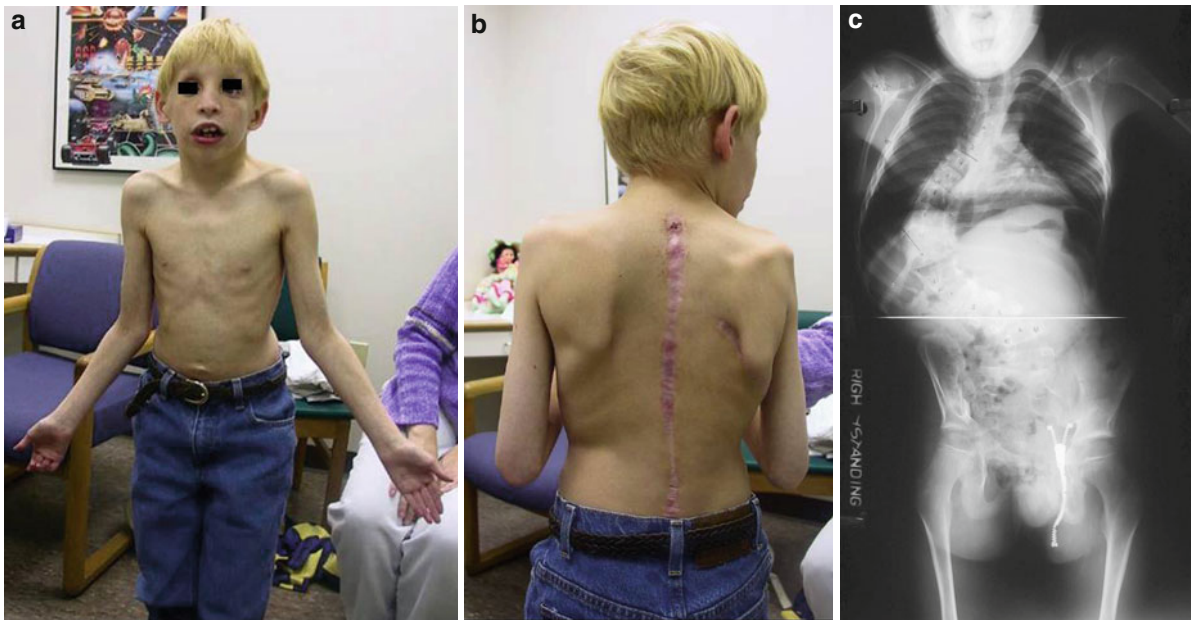

Fig. 6 (**a**–**c**) A child with Marfan syndrome showing cubitus valgus, arachnodactyly, and postsurgical spinal fusion for severe scoliosis (illustrated by radiograph)

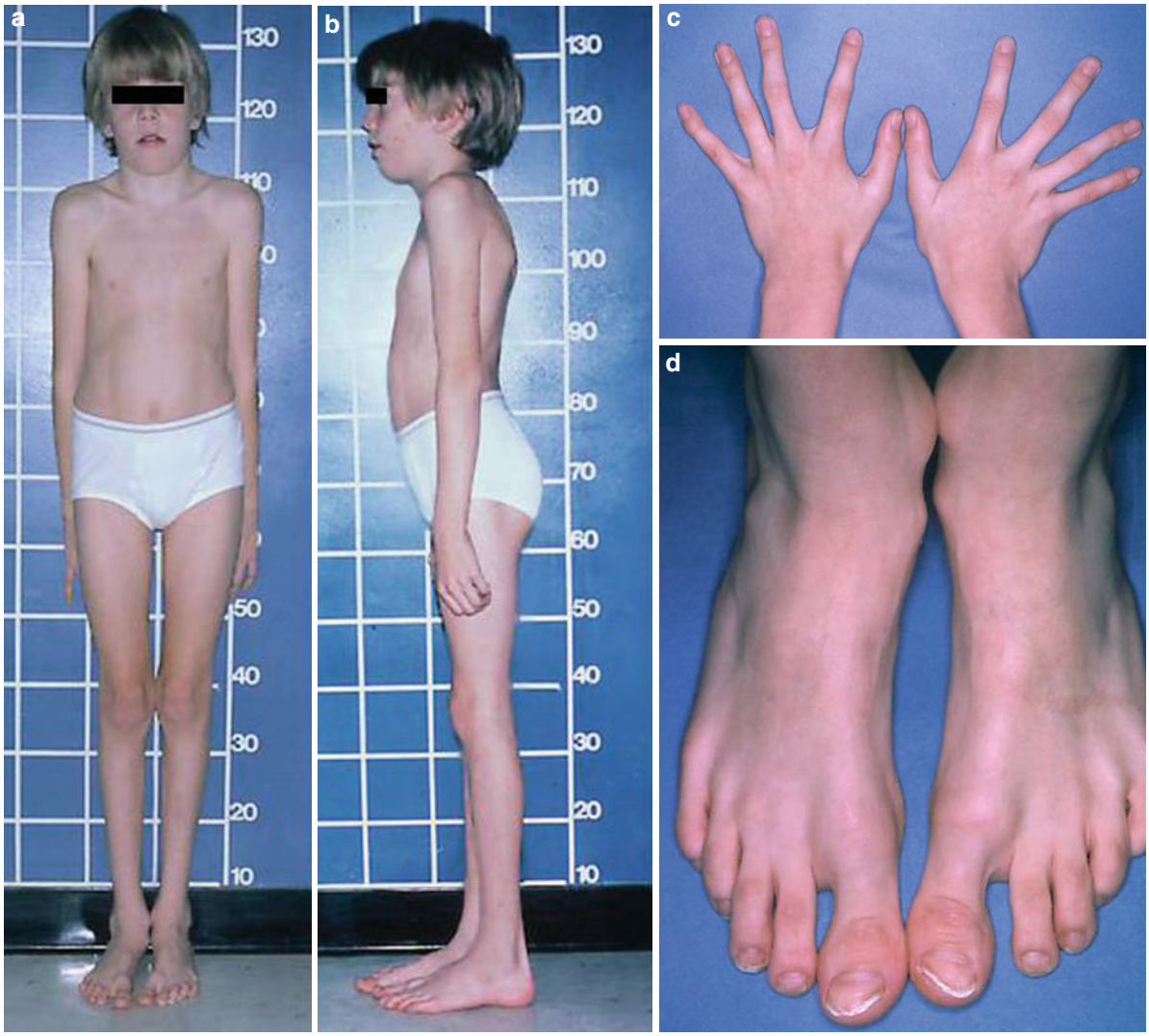

Fig. 7 (**a**–**d**) A boy with Marfan syndrome showing a slender/tall habitus and arachnodactyly

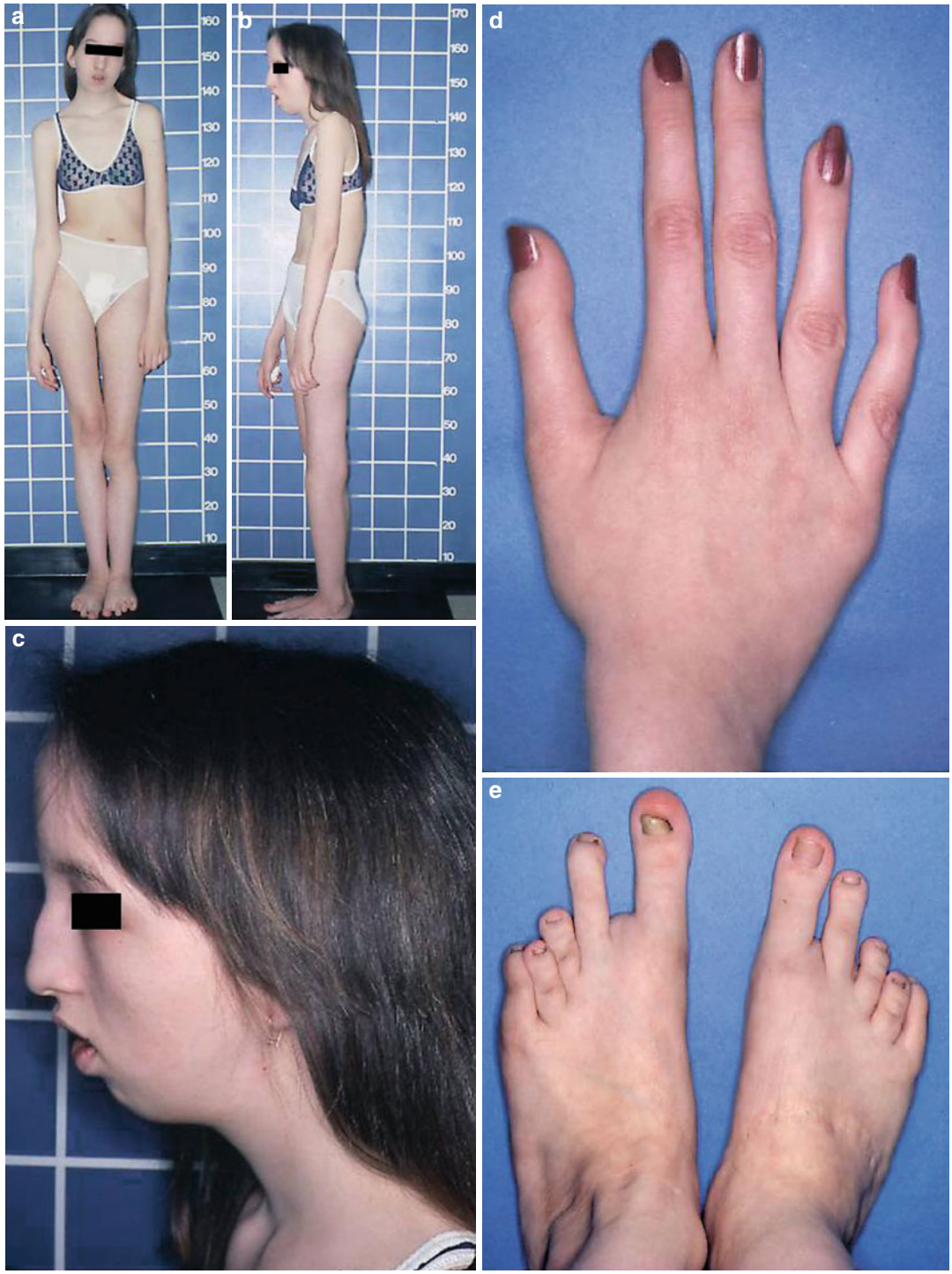

Fig. 8 (**a**–**e**) A girl with Marfan syndrome showing a slender/tall habitus, typical facies, arachnodactyly, and toe anomalies

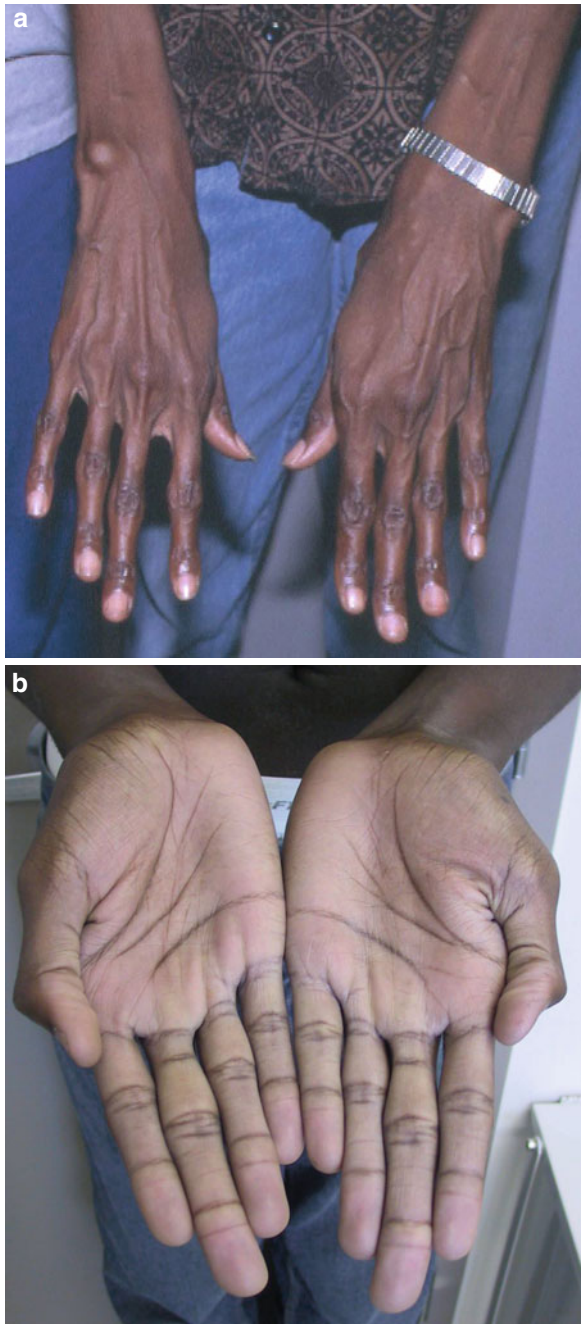

Fig. 9 (**a**, **b**) Arachnodactyly in two adult patients with Marfan syndrome

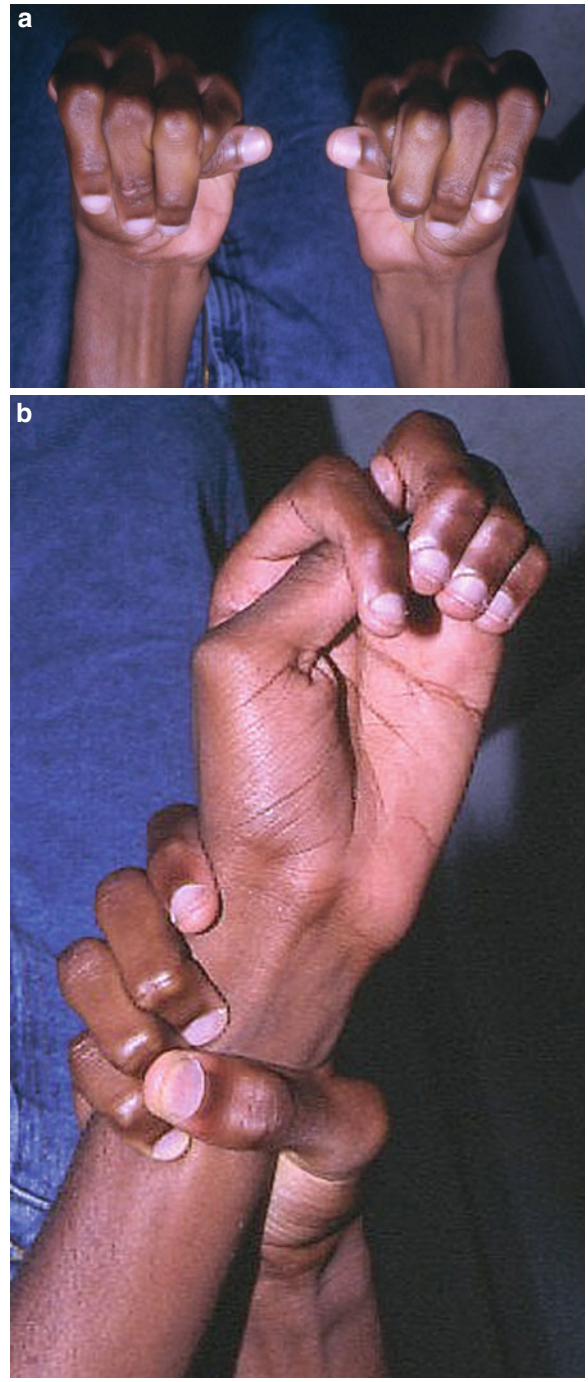

Fig. 10 (**a**, **b**) Thumb and wrist signs

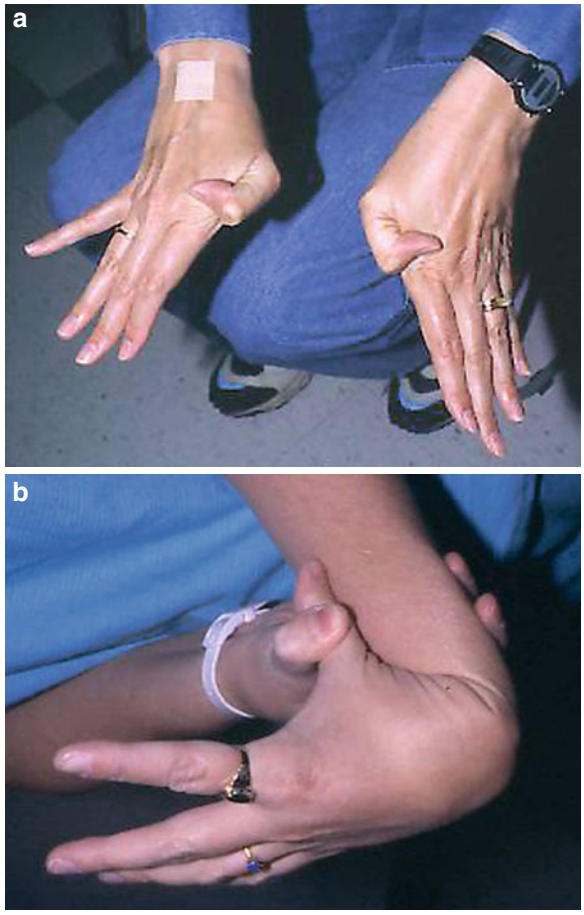

Fig. 11 (**a**, **b**) Hypermobile joints in two patients with Marfan syndrome

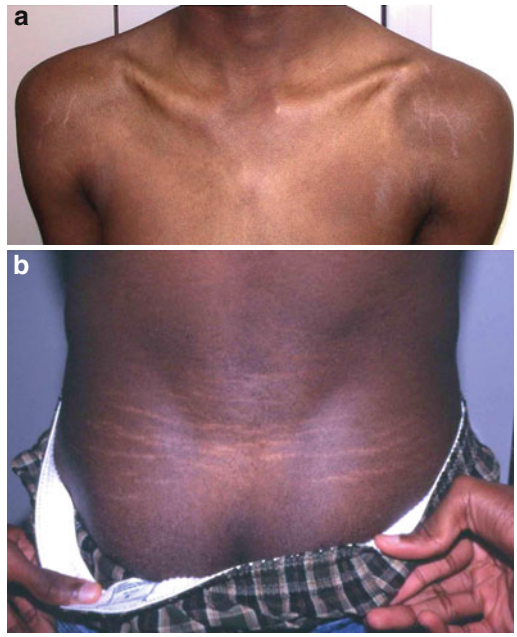

Fig. 12 (**a**, **b**) Stretch marks in the shoulders in one patient and in the buttock region in other patient with Marfan syndrome

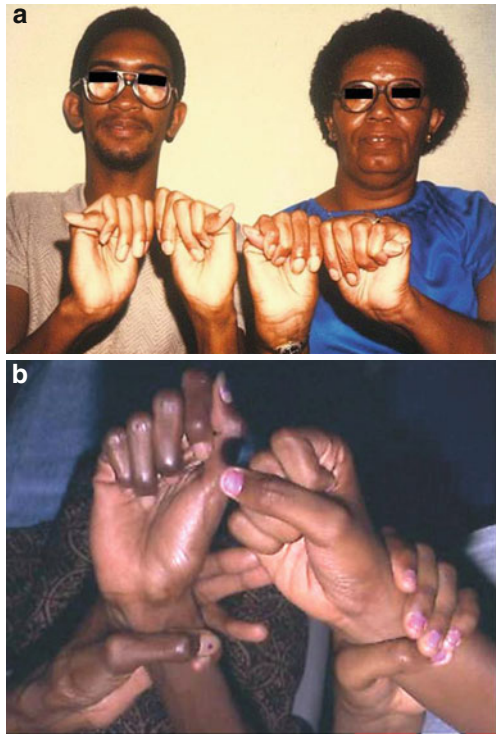

Fig. 13 (**a**, **b**) Familial Marfan syndrome in a mother and a son showing extreme myopia (lens dislocation) and thumb and wrist signs

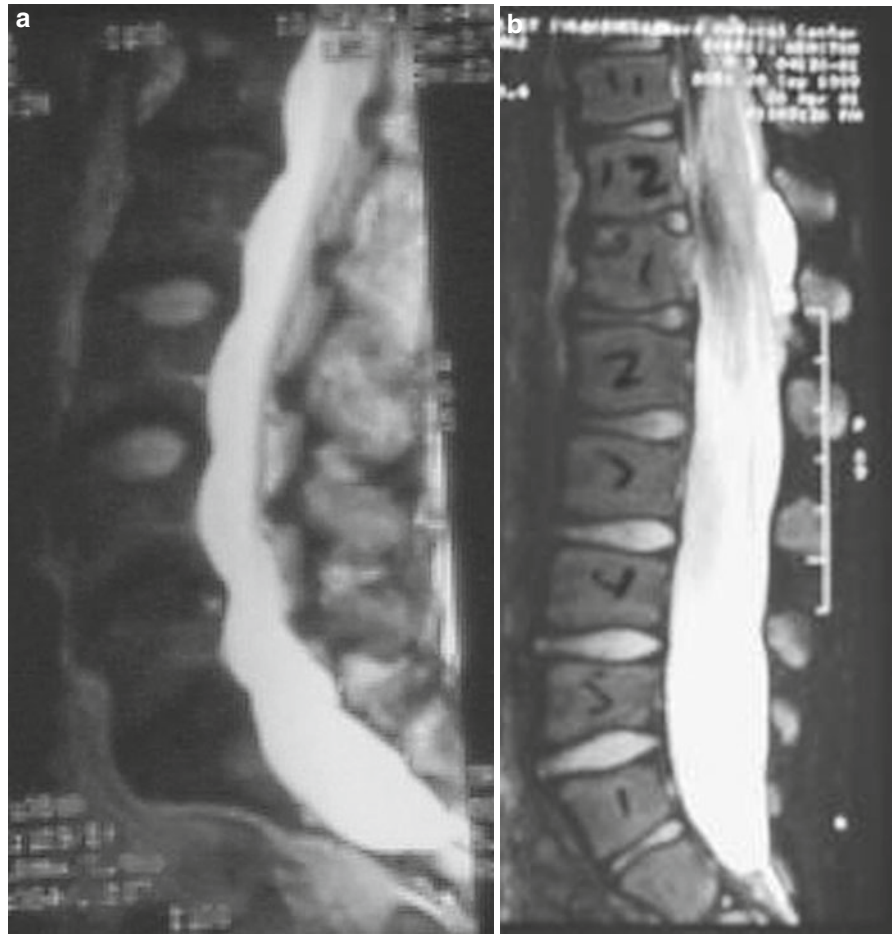

Fig. 14 (**a**, **b**) MRI of the lumbosacral spine in two patients showing dural ectasia

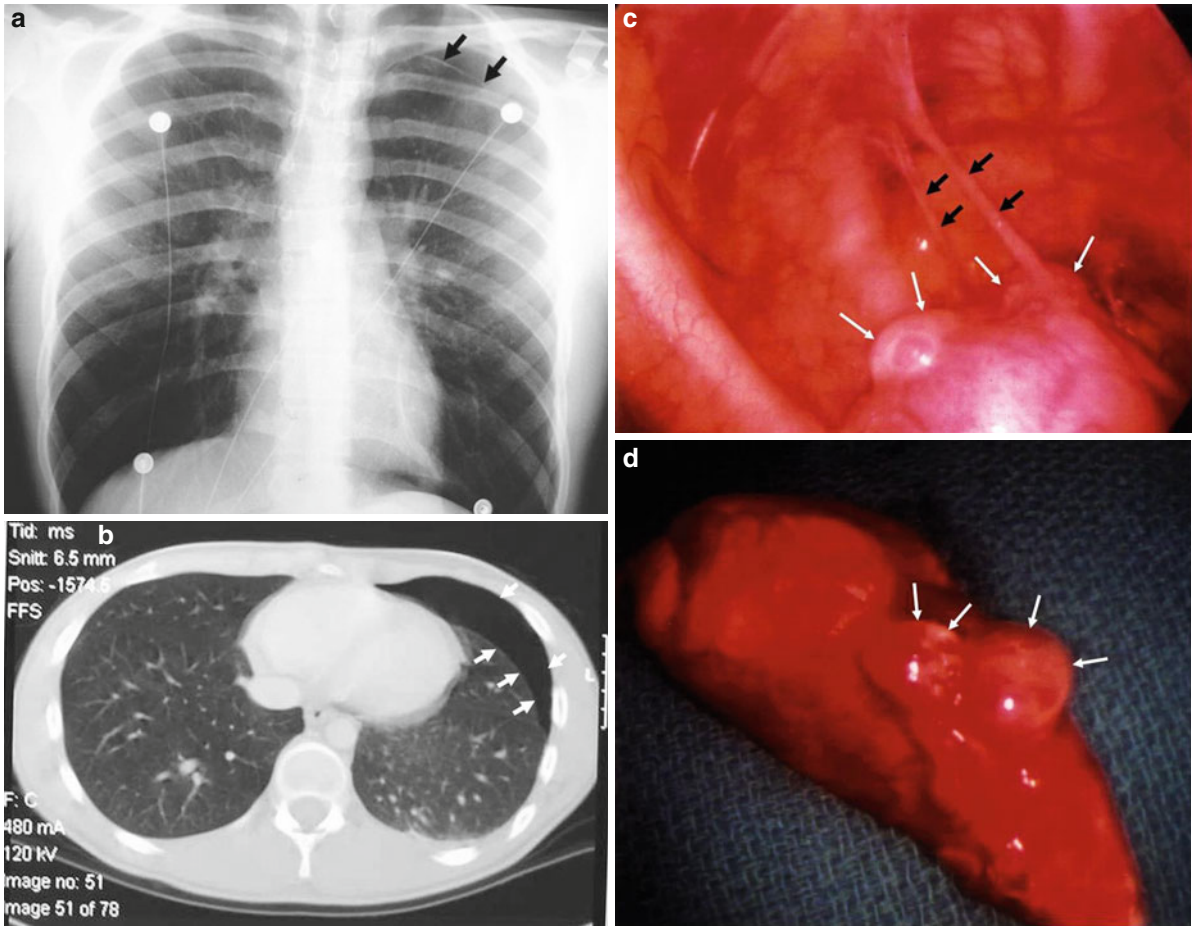

Fig. 15 (**a–d**) A 20-year-old male with Marfan syndrome with repeat spontaneous pneumothorax from ruptures of apical blebs. The chest X-ray shows collapsed left lung with pleural line (arrows). The CT of the chest shows pneumothorax on the right lung (*arrows*). Thoracoscope image from the right lung shows two bands representing the old adhesions due to previously ruptured apical blebs (*black arrows*) and two intact blebs (*white arrows*). The wedge biopsy specimen of the right apex shows two emphysematous blebs (*white arrows*) which were demonstrated in the previous figure

McCune-Albright Syndrome

McCune-Albright syndrome (MAS) consists of polyostotic fibrous dysplasia, precocious puberty, café-au-lait spots, and other endocrinopathies secondary to hyperactivity of various endocrine glands. It is a rare disease with an estimated prevalence between 1/100,000 and 1/1,000,000.

Synonyms and Related Disorders

Albright syndrome; Polyostotic fibrous dysplasia

Genetics/Basic Defects

1. Inheritance
   a. A sporadic condition
   b. Lack of genetic transmission in this syndrome
2. Molecular basis (Akintoye et al. 2002)
   a. Caused by a noninherited postzygotic somatic mutations in the guanine nucleotide-binding protein alpha subunit (*GNAS1*) gene coding for the alpha subunit of the stimulatory G protein ($G_s\alpha$).
   b. Mutations in *GNAS1* result in the constitutive activation of adenyl cyclase, which stimulates the synthesis of cAMP from ATP within cells.
   c. G proteins.
      i. Involved in transmitting hormone signals intracellularly by coupling cell surface receptors to intracellular signaling cascades.
      ii. Constitutively activated Gs protein stimulates autonomous cell proliferation in skin and bones and hormonal hypersecretion of gonads, hypophisis, thyroid, and adrenal glands.
      iii. Constitutive activation of these intracellular signaling cascades is caused by the specific mutations in the absence of hormone stimulation.
   d. Vast majority of $G_s\alpha$ mutations.
      i. Point mutations at the Arg201 position
      ii. Most being Arg201His or Cys
   e. The term *gsp* oncogene assigned to these mutations due to their association with certain neoplasms.
   f. Presence of somatic mosaicism is reflected by the identification of normal and mutated cells throughout the body.
   g. Timing of mutations.
      i. Early in embryogenesis: widespread involvement of the tissue and is likely lethal (accounts for the lack of autosomal dominant transmission of this disorder)
      ii. Late in embryogenesis: milder phenotype
      iii. Very late in tissue development after differentiation into a specific cell line
         a) Development of a single adenoma
         b) $G_s\alpha$-activating mutations reported in isolated hyperfunctioning thyroid nodules and in somatotroph adenomas

Clinical Features

1. Clinical features (Boston 2010)
   a. Extremely variable among affected individuals
   b. Consistent with a postzygotic somatic mutational event resulting in a mosaic distribution of the mutation

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c. Clinical triad
   i. Polyostotic fibrous dysplasia
   ii. Patchy cutaneous pigmentation (café-au-lait)
   iii. Gonadotropin-independent sexual precocity

2. Endocrine abnormalities
   a. Precocious puberty
      i. The most common endocrine feature and a central hallmark of MAS
      ii. Resulting from gonadotropin-independent autonomous ovarian or testicular function
      iii. Far more commonly observed in girls than boys (>50% of affected girls; only 15% of affected boys)
      iv. The signs of puberty (development of breasts, testes, pubic and axillary hair, body odor, menstrual bleeding, and increased growth rate) may appear before the age of 8 years in girls and 9 1/2 years in boys.
      v. Affected girls
         a) Breast development or vaginal bleeding as early as 4 months of age
         b) Premature development of secondary sex characteristics
         c) Excessive estrogen production, independent of gonadotropin activities, with development of ovarian cysts, sexual precocity, increased growth velocity, and markedly advanced skeletal maturity
      vi. Affected boys
         a) Premature testicular enlargement
         b) Premature spermatogenesis
         c) Premature development of secondary sex characteristics
   b. Hyperthyroidism (30%)
      i. The second most commonly associated endocrinopathy
      ii. Typically occurring in later childhood but occasionally within the first year of life
      iii. Primarily due to multinodular toxic goiter
      iv. Clinical effects
         a) Severe failure to thrive in infants and young children
         b) Decreased attention span
         c) Osteoporosis
         d) Tachycardia
   c. Acromegaly/gigantism
      i. Resulting from excess growth hormone secreted by somatotroph adenomas in the pituitary
      ii. Characteristic stigmata
         a) Coarsening of facial features, such as frontal bossing and prognathism
         b) Enlargement of hands and feet
         c) Arthritis
      iii. Complications
         a) Glucose intolerance
         b) Hypertriglyceridemia
         c) Hypertension
         d) Mild myopathy
   d. Cushing syndrome
      i. Adrenocorticotropic hormone (ACTH) independent
      ii. Caused by adrenal enlargement and excessive secretion of the adrenal hormone cortisol
      iii. Described mostly in infants and children
      iv. Clinical signs
         a) Cessation of growth
         b) Poor muscle tone
         c) Obesity of the face and trunk
         d) Weight gain
         e) Skin fragility
         f) Hypertension in infancy
         g) Death possible in long-term untreated hypercortisolism
   e. Gonadotropinomas
   f. Hyperprolactinemia
   g. Hyperparathyroidism
   h. Gynecomastia

3. Nonendocrine abnormalities
   a. Skin pigmentation (café-au-lait spots)
      i. Flat brown patches of pigmentation with irregular contour (coast of Maine) of varying size.
      ii. Frequently evident at birth.
      iii. Involved area may be extensive.
   b. Fibrous dysplasia
      i. The invariable component of the syndrome
      ii. Bone lesions usually evident by age of 10 years, often presenting with a limp, leg pain, or fractures
      iii. Polyostotic in nature
         a) Affecting any bones

b) Most commonly involving the femur, tibia, pelvis, phalanges, ribs, and the base of the skull

iv. Size and extent of involvement: ranging from small asymptomatic areas to markedly disfiguring lesions resulting in limping deformities
a) Leg length discrepancy
b) Coxa vara
c) Shepherd's crook deformity of the femur (a characteristic sign of the disease)
d) Bowing of the tibia
e) Harrison's groove
f) Protrusio acetabuli
g) Frequent pathologic fractures
h) Impingement on vital nerves

v. Craniofacial form (50% of the polyostotic form)
a) Involvement of orbital and periorbital bones resulting in hypertelorism, cranial asymmetry, facial deformity such as leontiasis ossea, visual impairment, exophthalmos, and blindness
b) Involvement of the sphenoid wing and temporal bones resulting in vestibular dysfunction, tinnitus, and hearing loss
c) Involvement of cribriform plate resulting in hyposmia or anosmia

vi. Low risk of malignant degeneration (0.4%)

vii. Fibrous dysplasia associated with single or multiple intramuscular or juxtamuscular myxomas (Mazabraud syndrome)

c. Hypophosphatemia
i. Resulting from decreased reabsorption of phosphate in the renal tubule
ii. Causing rickets and short stature
iii. Normal parathyroid hormone levels

d. Chronic liver disease
i. Mild cases: mild elevation of hepatic transaminases
ii. Severe cases: neonatal jaundice and chronic cholestasis

e. Persistent tachycardia: rare sudden death presumably due to cardiac arrhythmias

f. Associated malignancies (rare)
i. Osteosarcomas (most common)
ii. Chondrosarcomas
iii. Fibrosarcomas
iv. Liposarcomas
v. Breast cancer
vi. Thyroid cancer

Diagnostic Investigations

1. Elevated estradiol levels and suppressed or undetectable gonadotropins: diagnostic of gonadotropin-independent precocious puberty (Boston 2010).
2. Suppressed or undetectable levels of LH and FSH after administration of luteinizing hormone-releasing hormone: consistent with the diagnosis.
3. Elevated liver enzymes or hyperbilirubinemia even after normalization of cortisol or thyroxine levels suggests presence of G_s α activating mutations in the liver.
4. Hypophosphatemia (rickets and osteomalacia) results from increased urinary phosphate excretion.
5. Elevated thyroxine levels and suppressed TSH levels: consistent with hyperthyroidism.
6. Generally suppressed ACTH levels despite elevated cortisol levels since the glucocorticoid secretion is ACTH independent.
7. Elevated cortisol levels after dexamethasone suppression test: suggestive of Cushing syndrome.
8. Elevated 24-h urine-free cortisol levels: suggestive of Cushing syndrome.
9. Elevated serum growth hormone and insulin-like growth factor 1 levels in individuals with somatotroph adenomas due to G_s α activating mutations.
10. Biopsy of fibrous dysplasia lesions: can confirm the diagnosis if doubt remains after review of the radiographs.
11. Histology.
a. Fibrous dysplasia:
i. Caused by hyperproliferation of preosteoblastic cells
ii. Replacement of normal bones by irregular masses of fibroblasts
b. Ovarian cyst: generally large, unilateral, and follicular in nature
c. Thyroid nodules: ranging from multinodular hyperplasia to colloid goiter

d. Adrenal hyperplasia
e. Somatotroph adenoma
f. Liver: ranging from normal hepatocytes with some fatty infiltration to focal nodular hyperplasia with fibrosis and chronic cholestasis

12. Pelvic ultrasound to detect ovarian cysts.
13. Isotopic bone scan.
    a. The most sensitive tool for detecting the presence of fibrous dysplasia lesions
    b. To detect asymptomatic fibrous dysplasia sites
    c. Often useful, especially at the initial evaluation, for determining the extent of the disease and predicting functional outcome
14. Skeletal survey (Anand 2011).
    a. Plain radiographs (Dumitrescu and Collins 2008)
        i. Often sufficient to make the diagnosis of fibrous dysplasia.
        ii. Plain radiographs, demonstrating the classic ground-glass appearance, are usually sufficient for the diagnosis of fibrous dysplasia in the axial and appendicular skeleton. (The axial skeleton is comprised of bones of the skull, hyoid bone, vertebra, sternum, and ribs; the appendicular skeleton includes the hip, pelvic bone, and the shoulder girdle (clavicle and scapula).
    b. Advanced skeletal maturation
    c. Premature closure of growth plates resulting in short stature
    d. Polyostotic fibrous dysplasia
        i. Often unilateral
        ii. More frequently involved sites
            a) Lower extremities: femur (91%), tibia (81%)
            b) Pelvis (78%)
            c) Skull and facial bones (50%)
            d) Ribs
            e) Upper extremities
            f) Spine
            g) Shoulder girdle
    e. Pathological fractures (up to 85%)
        i. X-rays are often unable to detect new, small microfractures.
        ii. When new focal pain develops in a fibrous dysplasia lesion and no fracture is evident on plain radiograph, CT and/or MRI can be useful for detecting subtle fractures.
        iii. The classic lesion of the proximal femur in FD, the shepherd's crook deformity is common.
    f. Long and short tubular bones
        i. Lucent lesions in the diaphysis or metaphysis
            a) With endosteal scalloping
            b) With or without bone expansion
            c) Absence of periosteal reaction
            d) Usually smooth and relatively homogeneous matrix of the lucency, described as a ground-glass appearance
            e) Presence of irregular areas of sclerosis with or without calcification
            f) The ring sign (a lucent lesion with a thick sclerotic border)
        ii. Extension of lesions into the epiphysis observed only after fusion
            a) Premature fusion of the ossification centers resulting in adult dwarfism
            b) Dysplastic bone undergoing calcification and endochondral bone formation
    g. Skull and facial bones
        i. Sclerotic skull base. Diffuse sclerosis of the base of the skull often involves the sphenoid, sella turcica, roof of the orbit, thickening of the occiput, and obliteration of the paranasal sinuses
        ii. Mixed radiolucent and radiopaque pattern of maxillary and mandibular bones
            a) Displacement of the teeth
            b) Distortion of the nasal cavities
    h. Pelvis and ribs
        i. Common cystic lesions characterized by a diffuse ground-glass appearance and ring lesions
        ii. Protrusio acetabuli
    i. Spine
        i. Well-defined, expansile, and radiolucent lesions with multiple internal septa or striations involving the vertebral body and, occasionally, the pedicles and arches
        ii. Kyphotic deformity
        iii. Spinal cord compression
        iv. Rare paraspinal soft tissue extension and vertebral collapse
    j. Radiographic features suggestive of malignant degeneration
        i. A rapid increase in the size of the lesion

ii. A change from a previously mineralized bony lesion to a lytic lesion

15. Bone scintigraphy: valuable in early detection of the bone lesions.
16. CT scan.
    a. CT scan of the skull: the most useful test for diagnosis of craniofacial fibrous dysplasia
    b. CT scan of the abdomen to demonstrate bilateral enlargement of the adrenal glands in infantile Cushing syndrome
17. Whole-body MRI can be used for evaluation and follow-up of polyostotic fibrous dysplasia (Ferreira et al. 2010).
18. Mutation detection (Akintoye et al. 2002).
    a. Standard PCR-based amplification
    b. Followed by sequencing of the appropriate region of the *GNAS1* gene

Genetic Counseling

1. Recurrent risk
    a. Patient's sib: not increased since MAS is due to a somatic mutation
    b. Patient's offspring: not increased since a germ line–activating mutation in the G_s α gene might be lethal
2. Prenatal diagnosis: not been reported
3. Management (Boston 2010)
    a. Precocious puberty
        i. Medical care
            a) Difficulty to treat precocious puberty.
            b) The biosynthetic forms of gonadotropin-releasing hormone such as deslorelin, histrelin, and Lupron which suppress LH and FSH are not effective in most girls with MAS.
            c) Provera, a progesterone-like hormone, for cessation of vaginal bleeding but not effective in slowing the rapid rates of growth and bone development and may have unwanted effects on adrenal functioning.
            d) Ketoconazole, aimed at interrupting adrenal steroid biosynthesis, for cessation of vaginal bleeding.
            e) Testolactone and fadrozole (aromatase inhibitors, to block the conversion of testosterone to estradiol, thus lowering circulating estrogen levels) for halting pubertal progression.
            f) A multicenter trial of tamoxifen (an estrogen agonist/antagonist) treatment of precocious puberty in girls resulting in a reduction of vaginal bleeding and significant improvements in growth velocity and rate of skeletal maturation.
        ii. Surgical care: ovarian cystectomy or oophorectomy not typically warranted because of the likelihood of cyst recurrence in residual ovarian tissue
    b. Hyperthyroidism
        i. Medical care: propylthiouracil or methimazole, drugs which block thyroid hormone synthesis, for patients with excessively high thyroid hormone levels
        ii. Surgical care: thyroidectomy or hemithyroidectomy for hyperthyroidism associated with a goiter
    c. Infantile Cushing syndrome
        i. Medical care
            a) Treat with drugs that block cortisol synthesis
            b) Adequate adrenal steroid (hydrocortisone, Florinef) replacement after bilateral adrenalectomy
        ii. Surgical care: surgical removal of the affected adrenal glands
    d. Acromegaly/gigantism
        i. Medical care: treat with synthetic analogs of the hormone somatostatin to suppress growth hormone secretion (Bhansali et al. 2003)
        ii. Surgical care: surgical removal of the area of the pituitary which is secreting the pituitary growth hormone
    e. Early detection and treatment of patients with excess growth hormone to prevent morbidity related to the craniofacial form of the fibrous dysplasia (50% of polyostotic form)
        i. Morbidity
            a) Hearing loss
            b) Blindness
        ii. Therapy
            a) Cabergoline
            b) Long-acting octreotide therapy
    f. Hypophosphatemic rickets: treat with oral phosphates, supplement with vitamin D

g. Fibrous dysplasia
   i. Medical care (Isaia et al. 2002)
      a) Monitor vision and hearing closely if lesions are located near or around the orbits.
      b) Avoid contact sports to minimize the risk of pathologic fractures.
      c) Bisphosphonates used to inhibit bone absorption by osteoclast activity through apoptosis induction and protein prenylation inhibition.
      d) Pamidronate, a second generation aminobisphosphonate for reduction in bone pain and markers of bone turnover.
   ii. Surgical care: grafting, pinning, and casting to surgically correct fractures and deformities

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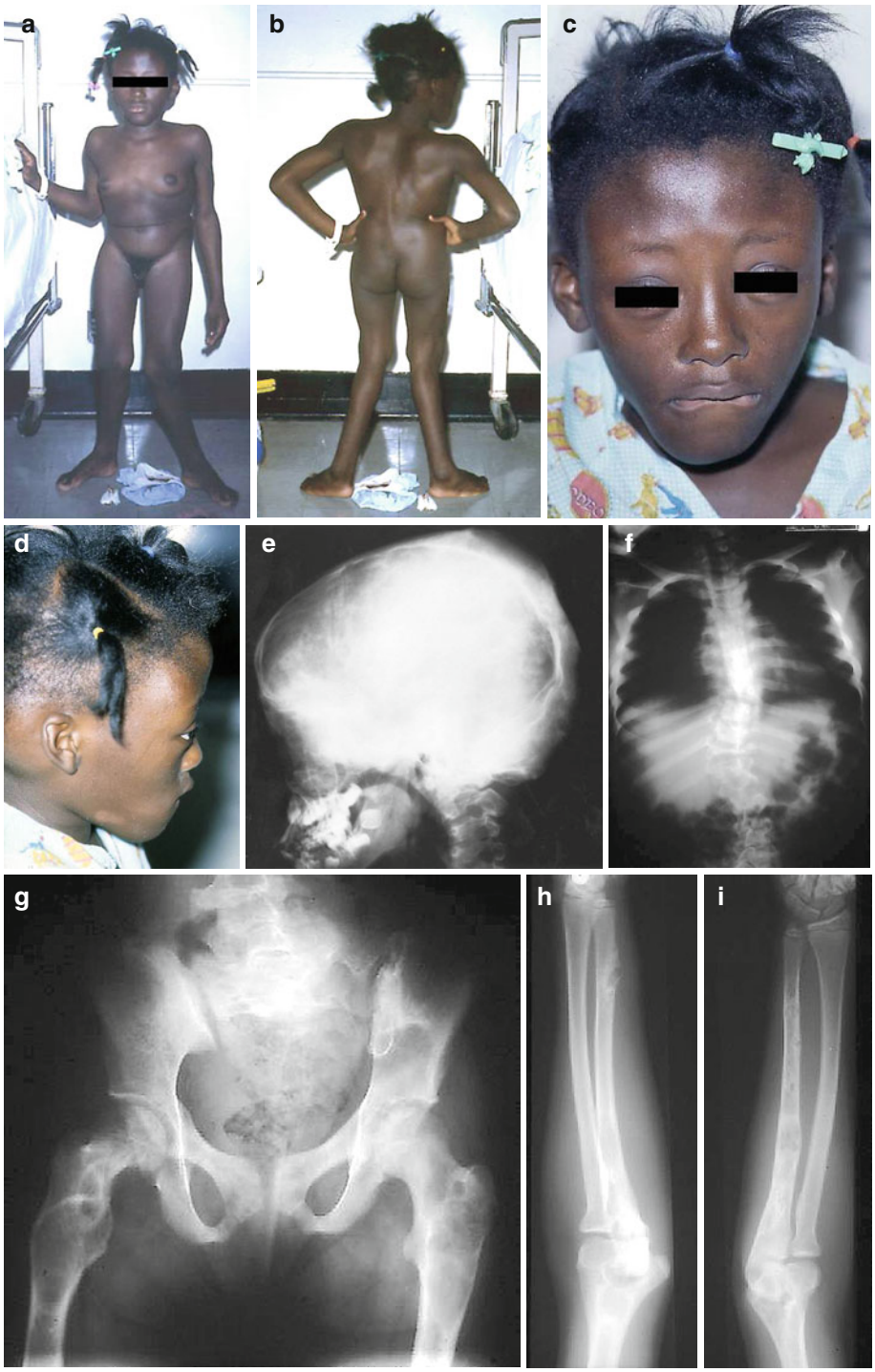

Fig. 1 (**a**–**i**) A girl with McCune-Albright syndrome showing precocious puberty, hyperpigmentation, and fibrous dysplasia affecting many bones shown by radiographs

Meckel–Gruber Syndrome

Meckel–Gruber syndrome (MKS) is a rare, lethal, and autosomal recessive disorder, characterized by occipital encephalocele, cystic dysplastic kidneys, and postaxial polydactyly. The incidence is estimated to be 1/13,250 (in USA) and 1/149,000 (in Great Britain) live births. The incidence in North African and Finnish populations is much higher at 1/3,500 and 1/9,000 respectively. Meckel–Gruber syndrome is considered the most frequent syndromic cause of neural tube defects (Paetau et al. 1985; Morgan et al. 2002).

Synonyms and Related Disorders

Dysencephalia splanchnocystica; Guber syndrome; Meckel syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Genetic (locus) heterogeneity (Morgan et al. 2002; Jayakar et al. 2011)
   a. *MKS1* locus to 17q21-24 in Finnish kindreds
   b. *MKS2* locus to 11q13 in North African-Middle Eastern cohorts
   c. *MKS3* to 8q21.3-q22.1 in Indian sub-continent cohorts: *MKS3* mutation also cause Jubert syndrome (Baala et al. 2007)
   d. *MKS4* to 12q21.31-q21.33 in a Kosovar Albanian family with two affected male fetuses
   e. *MKS5* to 16q12.2
   f. *MKS6* to 4p15.3 in 11 Finnish families

Clinical Features

1. Major clinical features
   a. Clinical triad (Nyberg et al. 1990)
      i. Occipital encephalocele (85%)
         a) Extrusion of rhombic roof elements (cerebellar vermis, caudal third ventricle, distended fourth ventricle) through a widened posterior fontanelle
         b) Protruding CNS structures covered by a dural sac
         c) Medial occipital cortex occasionally included in the sac formed by the dilated caudal third ventricle
      ii. Dysplastic kidneys (100%)
         a) Result in oligohydramnios
         b) Lead to fetal pulmonary hypoplasia
      iii. Postaxial polydactyly (55%)
   b. Microcephaly
   c. Oral clefts
      i. Cleft lip
      ii. Cleft palate
   d. Ambiguous genitalia
2. Other clinical features
   a. CNS abnormalities
      i. Absent olfactory lobe
      ii. Absent pituitary gland (hypopituitarism)
      iii. Hydrocephalus
      iv. Dandy–Walker malformation
   b. Craniofacial features
      i. Sloping forehead
      ii. Microphthalmia/anophthalmia
      iii. Micrognathia
      iv. Malformed tongue
      v. Abnormal ears

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c. Short neck
d. Hypoplastic thyroid
e. Congenital heart defect
f. Gastrointestinal abnormalities
   i. Omphalocele
   ii. Malrotated bowel
   iii. Fibrotic or cystic liver
g. Absent or small adrenals
h. Accessory spleen
i. Urinary tract anomalies
j. Short limbs
k. Abnormal palmar creases
l. Club feet
m. Syndactyly

3. Lethal outcome
   a. Abortions
   b. Stillborns
   c. Neonatal deaths
   d. Rare survivals till 2 years of age

Diagnostic Investigations

1. Ultrasonography
   a. CNS anomalies
   b. Cystic dysplastic kidneys
2. MRI of the brain for CNS anomalies
3. Echocardiography for congenital heart defect
4. Radiography (Seppänen and Herva 1983)
   a. Microcephaly with an occipital bone defect and encephalocele or hydrocephaly
   b. Short upper extremities
   c. Bell-shaped thorax with abdominal distension
   d. Postaxial polydactyly in the hands and feet
5. Necropsy
   a. Renal anomalies
      i. Cystic dysplastic kidneys
      ii. Hypoplastic kidneys/ureters/bladder
      iii. Rectovesical fistula
   b. Triad of CNS malformations (Herman and Siegel 1996)
      i. Prosencephalic dysgenesis (Ahdab-Barmada and Claassen 1990)
         a) Agenesis of olfactory bulbs and tracts (arhinencephaly)
         b) Complete holoprosencephaly
         c) Hypoplasia of optic nerves and chiasm
         d) Microphthalmia
         e) Agenesis of the corpus callosum
         f) Fused thalami
         g) Hypoplasia of the third ventricle
         h) Small or absent pituitary gland
         i) Microcephaly
         j) Cleft/high arched palate
         k) Micrognathia
      ii. Occipital encephalocele
         a) Displacement of rhombic roof elements including caudal third ventricle, cerebellar vermis and fourth ventricle
         b) Extruded through an enlarged posterior fontanelle rather than through an occipital cranium bifidum
         c) Often associated with a variant of Dandy–Walker cyst with Chiari malformation
      iii. Rhombic roof dysgenesis
         a) Absent brain stem tectum
         b) Agenesis/dysgenesis cerebellar vermis
         c) Elongated brain stem
         d) Aqueduct stenosis
   c. Histologic features of the CNS (Paetau et al. 1985)
      i. Polymicrogyria
      ii. Heterotopias
      iii. Characteristic neuroepithelial rosettes
   d. Hepatic dysgenesis
      i. Consistent features
      ii. Arrested development of the intrahepatic biliary system
         a) Reactive biliary bile duct proliferation
         b) Bile duct dilatation
         c) Portal fibrovascular proliferation
   e. Lung hypoplasia
   f. Gastrointestinal anomalies
      i. Pancreatic cyst
      ii. Malrotated bowel
      iii. Anal atresia
   g. Genital anomalies
      i. Hypoplastic genitalia
      ii. Bicornuate uterus
      iii. Persistent urogenital sinus

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not surviving to reproductive age

2. Prenatal diagnosis
   a. Ultrasonography: diagnosis more difficult in the second trimester because of oligohydramnios secondary to poor renal output impairing visualization
      i. Occipital encephalocele
      ii. Renal anomalies (large cystic kidneys, renal agenesis, renal hypoplasia, and ureteral duplication)
      iii. Polydactyly
      iv. Oligohydramnios
      v. Dandy–Walker malformation
      vi. Cerebellar hypoplasia
   b. MRI, a valuable complement to ultrasonography in assessing fetal anomalies in the presence of severe oligohydramnios
   c. Elevated serum α-fetoprotein
   d. Amniocentesis
      i. Elevated amniotic fluid α-fetoprotein
      ii. Normal karyotype
3. Management
   a. No specific treatment
   b. Supportive care for lethal cases
   c. Operative excision of a small encephalocele
   d. Ventriculoperitoneal shunt for hydrocephalus

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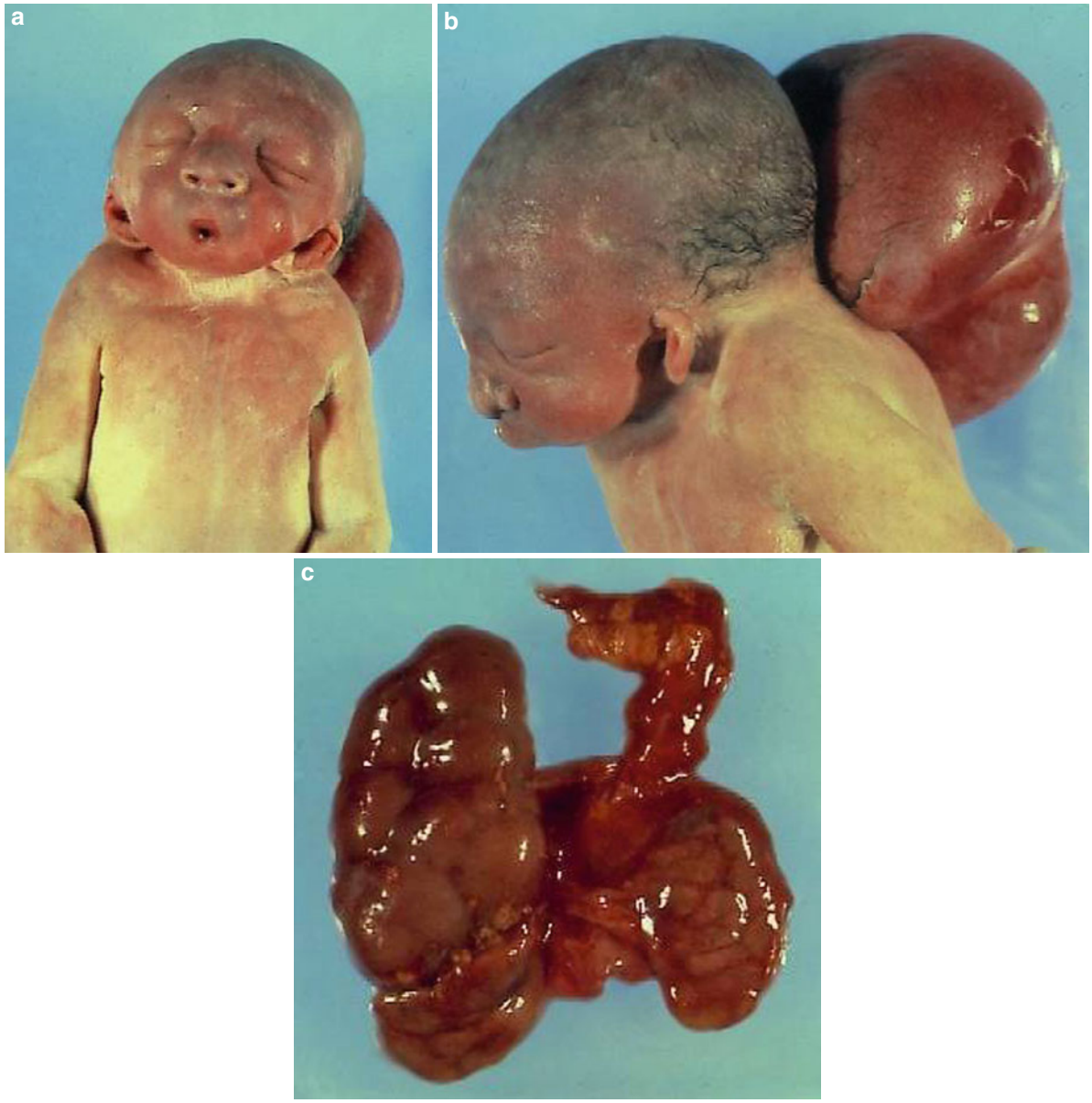

Fig. 1 (**a**–**c**) A neonate with Meckel–Gruber syndrome showing a large occipital encephalocele, microcephaly, sloping forehead, micrognathia/retrognathia, low-set malformed ears, and short neck. The infant also had post-axial polydactylies. Necropsy showed unilateral renal dysgenesis. Contralateral renal cystic dysplasia was present

Fig.2 (**a**–**e**) Another neonate with Meckel–Gruber syndrome showing a large occipital encephalocele, microcephaly, sloping forehead, micrognathia/retrognathia, low-set malformed ears, short neck and post-axial polydactylies

Megalencephalic Leukoencephalopathy with Subcortical Cysts

In 1995, van der Knaap et al. described a syndrome of cerebral leukoencephalopathy and megalencephaly with infantile onset in eight children, including two siblings. These children had normal or near-normal neurologic status despite evidence of severe white matter disease. The syndrome is currently termed megalencephalic leukoencephalopathy with subcortical cysts.

Synonyms and Related Disorders

van der Knaap Disease

Genetics/Basic Defects

1. An autosomal recessive disorder suggested by parental consanguinity and affected siblings
2. Caused by mutation in the *MLC1* gene which is expressed predominantly in astrocytes, located on 22qt13.33, encoding a putative membrane protein with eight predicted transmembrane domains
3. Genetically determined homozygous or compound heterozygous cases have been documented in almost all racial groups throughout the world and in both sexes equally.
4. Although the disease is considered rare, a higher frequency is observed in populations where consanguinity remains a common cultural practice.
   a. Among the Agarwals of India, almost all documented cases test positive for a homozygous insertional mutation (135insC) owing to founder effect.
   b. G59E mutation appears to be common among Libyan Jews.
   c. S93L mutation appears to be somewhat among in the Japanese.
5. Marked clinical intrafamilial and interfamilial variability in mutation-proven cases
6. A broad spectrum of pathogenetic mutations (missense, splice site, insertion, and deletions) identified in the *MLC1* gene, enlarging the spectrum of allelic variants without a straightforward genotype–phenotype correlation

Clinical Features

1. Clinical findings of 122 patients reviewed by Riel-Romero et al. (2005)
   a. Clinical presentation
      i. Accelerated head growth beginning in the first year of life, resulting in extreme macrocephaly (48%)
      ii. Mild developmental delay (25%)
   b. Gradually increasing spasticity (pyramidal findings) (86%) and ataxia (78%)
   c. Seizures (66%)
   d. Loss of ambulation (38%)
   e. Dysarthria (15%)
   f. Hypotonia (11%)
   g. Dysmetria (9%)
   h. Tremor (7%)
   i. Dysonia (5%)
   j. Dysphagia (5%)
   k. Choreoathetosis (3%)
2. Clinical course: Although progressive in its nature, MLC is characterized by a relatively mild clinical

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course (discrepantly mild cognitive impairment) compared with the severity of the neuroradiological findings

3. Differential diagnosis: infantile megalencephalic leukoencephalopathies (neurologic disorders characterized by progressive deterioration and severe impairment of neurological function resulting in marked disability and a shortened life span, leukodystrophic changes on neuroimaging, and megalencephaly)
   a. Alexander disease
      i. A rare neurological disorder that follows a progressive and usually fatal course
      ii. Does not share the relatively benign course of MLC
      iii. The most common infantile form: characterized by loss of developmental milestones, inexorable psychomotor retardation, megalencephaly, spasticity, seizures, ataxia, hyperreflexia, and pyramidal signs, with a lifespan of a few months to early childhood
      iv. Considered a leukodystrophy because myelin changes are invariably observed while sparing the axons
      v. *GFAP* as the causative gene for Alexander disease
      vi. MRI findings
         a) Abnormal enhancement of caudate nuclei, anterior columns of the fornices and periventricular areas
         b) Frequent hydrocephalus
         c) Cavitations in the frontal deep white matter
   b. Canavan disease
      i. Does not share the relatively benign course of MLC
      ii. MRI findings: Frequent involvement of the globus pallidus and thalami which are not involved in MLC
      iii. The white matter may be cystic in Canavan disease, but the typical subcortical cysts seen in MLC are lacking.
      iv. N-acetyl aspartate is elevated in urine and blood.
      v. Deficiency of the enzyme aspartoacylase can be demonstrated in cultured fibroblasts
   c. Glutaric aciduria I: presence of biochemical abnormalities (glutaric acid, 3-OH-glutaric acid in the urine, glutarylcarnitine in the blood)
4. Other differential diagnosis
   a. Merosin-deficient congenital muscular dystrophy
      i. Typical subcortical cysts are generally lacking, although the white matter disease most clearly resembles that observed in MLC.
      ii. Prominent weakness and hypotonia in affected individuals, not shared by individuals with MLC
      iii. Diagnosis: confirmed using muscle biopsy and staining for merosin
   b. Infantile GM gangliosidosis
      i. GM1 gangliosidosis
         a) Demonstration of deficiency of beta-galactosidase activity in leukocytes or cultured fibroblasts confirms the diagnosis.
         b) MRI features in infantile GM1 gangliosidosis very similar to those of GM2 gangliosidosis
      ii. Infantile GM2 gangliosidosis
         a) MRI: characterized by prominent involvement of the basal ganglia and thalami in addition to the white matter abnormalities
         b) Definitive diagnosis: established by assaying hexosaminidase A and B in serum, leukocytes, or cultured skin fibroblasts

Diagnostic Investigations

1. Brain imaging (CT, MRI)
   a. Diffusely abnormal and swollen white matter of the cerebral hemispheres
   b. Presence of subcortical cysts in the anterior temporal and frontoparietal region with preservation of gray matter structures
2. Quantitative proton MRS
   a. Underlines the MRI evidence of a white-matter disorder without cortical involvement
   b. Most striking MRS features: marked decrease in tNAA, tCr, and Cho, with normal Ins in abnormal-appearing hemispheric white matter
3. Technetium-99m-ethyl cysteinate dimer SPECT
   a. Hypoperfusion in the cerebral whitematter (shown high signal intensity on magnetic resonance imaging (MRI) T2 images)

   b. Hypoperfusion found unexpectedly in the frontal cortices (corresponded clinically to a low score on the frontal assessment battery), which showed no abnormalities on MRI.
   c. Decreased GABA receptor density as suggested by ^{123}I-Iomazenil SPECT provided further evidence of cortical neuron dysfunction.
   d. Findings suggest that SPECT can be used to non-invasively monitor in vivo cortical function in this disease.
4. Histopathology
   a. Splitting of the outer most lamellae of the myelin sheaths consistent with an edematous process, with sparing of the axons
   b. Cavitating spongiform leukoencephalopathy with vacuoles in the outermost lamellae of myelin sheaths
   c. Intense fibrillary astrogliosis of subcortical white matter with well preserved myelinated axons
   d. Normal cortical neuronal structure
5. Molecular genetic testing
   a. *MLC1* gene mutations determination clinically available
   b. Sequence analysis of *MLC1* gene mutations detects approximately 70% of cases whose MRI and clinical picture are consistent with the diagnosis of MLC, implying that at least one other gene may be responsible for the remaining 30% of cases.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Twenty five percent chance of inheriting both mutation alleles and being affected
      ii. Two thirds chance of being carriers in unaffected sibs
   b. Patient's offspring: recurrence risk not increased unless the spouse is a carrier, in which case 50% of offspring will be affected; otherwise, all offspring of the affected parent will be carriers who will be asymptomatic
2. Prenatal diagnosis for pregnancies at increased risk and carrier testing for relatives at risk: possible if both *MLC1* disease-causing alleles have been identified in the family
3. Management: largely supportive
   a. Antiepileptic drugs for seizure control
   b. Physical therapy to improve motor function
   c. Occupational therapy
   d. Speech therapy as needed
   e. Special education
   f. Antibiotic treatment for infections
   g. Attention to general care and nutritional requirements
   h. Prevention of head trauma: protective helmet suggested

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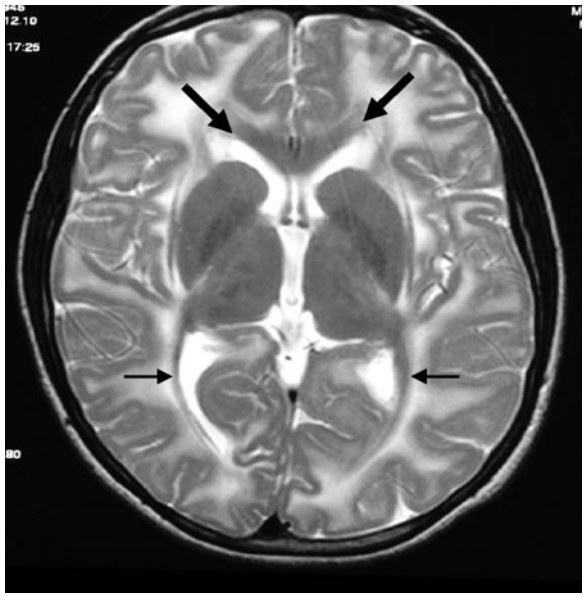

Fig. 1 A 15-year-old Caucasian female was evaluated for megalencephaly and possible leukodystrophy. Early developmental status was normal except for the presence of macrocephaly. She had a bicycle accident with trauma to her head, followed by a generalized tonic-clonic seizure 7 months later. At 15 years of age, she had striking macrocephaly (head circumference of 65 cm), receiving special education, and was found to have mild bilateral clonus Axial Tj-weighted scan demonstrates hyperintensity throughout cerebral white matter with sparing of the genu of the corpus callosum (*large arrowheads*), middle portion of the internal capsule, and the geniculocalcarine tracts (*small arrows*). Sequence analysis of the *MLC1* gene revealed two novel mutations, One mutation was inherited from the mother and was characterized by the substitution of adenine for guanine at nucleotide position 366 in exon 3. This mutation resulted in a change in the corresponding amino acid from arginine to histidine at amino acid position 84 (R84H). The other mutation was inherited from her father; it is in the canonical splicing site following exon 5 (538+1g → a) and is expected to cause the transcription of a variant messenger ribonucleic acid (RNA) that can be translated into an altered protein. A 12-year-old brother was noted to have macrocephaly, seizures, significant learning difficulty, behavioral problems, increasing difficulty in ambulation, hyperreflexia, spasticity with positive Babinski reflexes, sustained clonus and difficulty with tandem gait. His MRI showed a markedly increased T2-weighted signal throughout the supratentorial white matter with cysts in both temporal lobes in a pattern virtually identical to his sister's. Sequencing of the MLC1 gene revealed the same mutations identical to his older sister

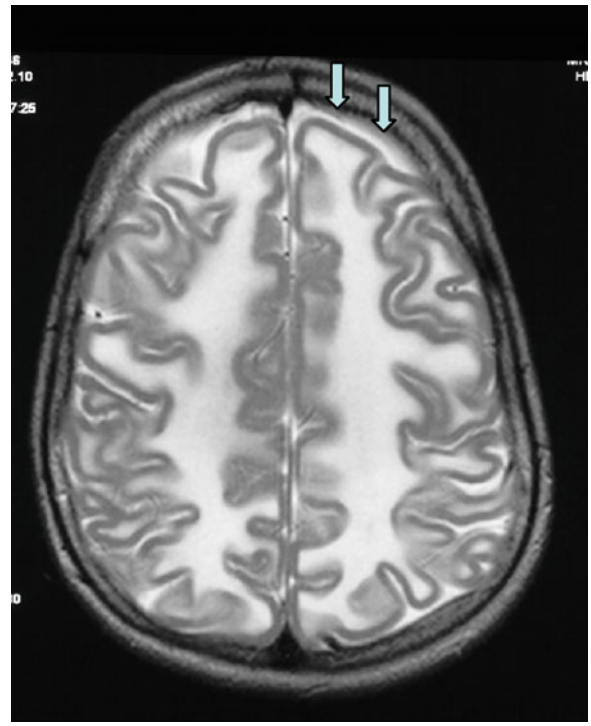

Fig. 2 Axial T-weighted scan at a more rostral level shows that the cortical U fibers are also hyperintense and therefore not spared (*arrows*)

Fig. 3 Anterior temporal regions show homogeneous white matter hyperintensity within the cysts, which expand and smooth the convolutions of the temporal poles – typical findings in megalencephalic leukoencephalopathy with subcortical cysts

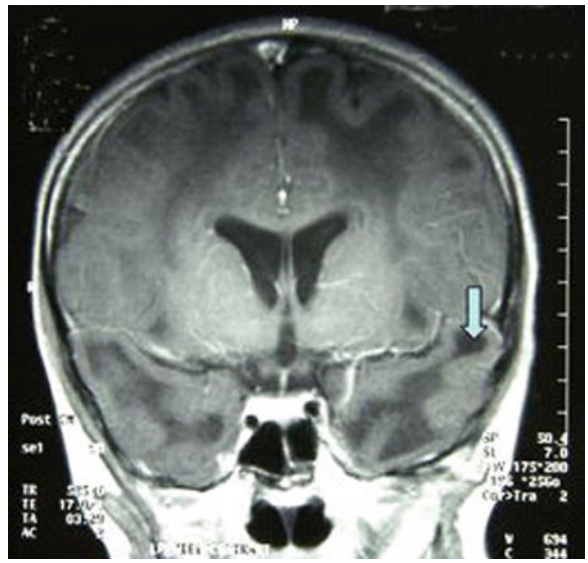

Fig. 4 Gadolinium-enhanced T-weighted coronal slice through the anterior temporal lobes demonstrates absence of abnormal enhancement in the white matter or elsewhere and hypointensity within a subcortical cyst (*arrowhead*)

Menkes Disease

Menkes and colleagues described Menkes disease in 1962 that reported five male infants in a family affected with a distinctive syndrome of neurologic degeneration, peculiar hair, and failure to thrive. Menkes disease is also called "kinky or steely hair disease." The incidence of Menkes disease is estimated to be 1/100,000–1/250,000 live births.

Synonyms and Related Disorders

ATP7A-related copper transport disorders; ATP-related distal motor neuropathy; Kinky hair syndrome; Occipital horn syndrome

Genetics/Basic Defects

1. Inheritance
   a. An X-linked recessive disorder of copper metabolism (Tümor 1998)
      i. Recognized to segregate as an X-linked recessive trait when it was described by Menkes et al. in 1962
      ii. Observation of two different cell populations (normal fibroblasts and mutant cells with increased copper accumulation) in cultured fibroblasts of female Menkes carriers, suggesting that the Menkes disease gene was subject to random X-inactivation and also confirming the X-linked recessive inheritance of the disease
   b. New mutations in one third of cases
2. Menkes gene mapped to chromosome Xq13.3
   a. Physical evidence of the location of the Menkes disease gene (*ATP7A*; *MNK*) suggested by observation of a female patient with a de novo balanced X:2 translocation (X break point at Xq13) and a male patient with X chromosome rearrangements with a breakpoint at Xq13.3 (Kodama and Murata 1999)
   b. The Xq13.3 breakpoint subsequently shown to be at the *MNK* locus by fluorescence in situ hybridization (FISH) analyses
   c. MNK belongs to a large family of cation-transporting P-type ATPases.
3. Cause: Mutations in *ATP7A* gene, which encodes a transmembrane copper-transporting P-type adenosine triphosphatase (ATPase) protein, leading to deficiencies of copper absorption in intestinal absorption and in intracellular processing of copper in the central nervous system and connective tissues, whereby enzymes requiring copper as a cofactor no longer function properly
4. Mutation spectrum
   a. Cytogenetic abnormalities (Tümor 1998)
      i. Visible cytogenetic abnormalities comprising about 1% of the underlying genetic defect in Menkes disease
      ii. Four female patients reported to have balanced X-autosomal translocations
      iii. A male patient reported to have a unique rearrangement of the X chromosome where the long arm segment Xq13.3-q21.2 was inserted into the short arm

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b. Gross deletion mutations (20%)
c. Point mutations (remaining genetic defects)
   i. Splice site (23%)
   ii. Nonsense (20.7%)
   iii. Missense (17.2%)
   iv. Small insertions/deletions (39.1%)

5. Genetic defect/pathogenesis
   a. Failure of copper transport to the affected fetus resulting in copper deficiency in utero; compounded by impairment of copper absorption and ineffective copper transport into the central nervous system after birth
   b. Decreased copper transport across cellular compartments, particularly the gut
   c. Decreased availability of copper for cuproenzymes
   d. Dysfunction of numerous copper-dependent enzyme systems (decreased enzyme activities)
      i. Dopamine β-hydroxylase
         a) Severe neurodegeneration
         b) Hypothermia
         c) Abnormalities in serum catecholamines
      ii. Ascorbate oxidase: skeletal deformities
      iii. Cytochrome c oxidase
         a) Hypothermia
         b) Severe neurodegeneration
         c) Impaired myelination
         d) Muscle weakness
         e) Mitochondrial abnormalities
      iv. Lysyl oxidase: decreased strength of collagen and elastin
         a) Frayed/split internal elastic layer of arteries
         b) Bladder diverticula
         c) Loose skin and joints
      v. Monamide oxidase
         a) Kinky hair
         b) Reduced pigmentation of hair and skin
         c) Severe neurodegeneration
      vi. Tyrosinase
         a) Depigmentation of hair
         b) Skin pallor
      vii. Sulfhydryl oxidase: pili torti (Kodama and Murata 1999)
      viii. Ceruloplasmin: decreased levels of circulating copper
      ix. Copper-zinc superoxide dismutase
         a) Failure of free radical detoxification, contributing to profound Purkinje cell loss
         b) Cytotoxic effects
6. Loss of function of specific cuproenzymes resulting in the clinical features of Menkes disease
   a. Abnormal hair and pigmentation
   b. Laxity of the skin
   c. Metaphyseal dysplasia
   d. Cerebellar degeneration
   e. Failure to thrive
7. Favorably skewed X-inactivation accounts for neurological sparing in female carriers of Menkes disease (Desai et al. 2011)
8. Allelic heterogeneity resulting in milder forms of the disease, occipital horn syndrome, also known as X-linked cutis laxa or Ehlers-Danlos syndrome type IX (Tümor 1998)
   a. Clinical resemblances to Menkes disease with milder manifestations
   b. Biochemical resemblances to Menkes disease
      i. Patients typically have between 20% and 35% residual copper transport function and far less severe neurodevelopmental abnormalities, even in the absence of early diagnosis and treatment (Kaler et al. 1994)
      ii. Low serum copper and ceruloplasmin
      iii. Increased copper accumulation and markedly low lysyl oxidase activity
      iv. Impairment of *MNK* in patients with occipital horn syndrome (base-pair substitution mutations affecting the normal mRNA splicing) giving a direct molecular evidence for the allelic relationship between the two diseases
9. *ATP7A*-related distal motor neuropathy
   a. Another allelic variant of Menkes disease
   b. Caused by mutations in the copper-transporting P-type ATPase gene, *ATP7A*
   c. Males with *ATP7A* mutations have even greater quantity of residual copper transport activity and manifest a late-onset syndrome restricted to progressive distal motor neuropathy, without overt signs of systemic copper deficiency (Kennerson et al. 2010).

Clinical Features

1. Phenotype: considerable variability in the severity of clinical expression encompassing the severe classical form (90–95% of patients) to the mild occipital horn syndrome
2. Distinctive clinical features present by 3 months of age, often manifested by:
   a. Loss of early developmental milestones
   b. Poor weight gain (failure to thrive)
3. Neonatal hypothermia
4. Neonatal hypoglycemia
5. Hyperbilirubinemia
6. Poor feeding
7. Impaired weight gain (failure to thrive)
8. CNS abnormalities
   a. Profound (truncal) hypotonia
   b. Abnormal head control
   c. Hyperactive reflexes
   d. Generalized seizures
      i. Myoclonic
      ii. Occasional tonic-clonic
   e. Developmental delay
   f. Severe mental retardation
9. Abnormal and characteristic hair, responsible for the synonyms of "kinky hair disease" or "steely hair disease" in the past
   a. Depigmented, short, sparse, coarse, and twisted scalp hair: a striking and pathognomonic feature
   b. Fragile, frequently broken hair
   c. Twisted strands reminiscent of steel wool cleaning pads
   d. Eyebrows
      i. Unusual appearance
      ii. Scant
   e. White or gray hair lacking pigment secondary to absence of tyrosinase activity
10. Characteristic face
    a. "Jowly," "pudgy," or "cherubic" face
    b. Sagging cheeks
    c. Large-appearing ears
    d. High-arched palate
    e. Delayed tooth eruption
11. Ocular abnormalities
    a. Retinal hypopigmentation
    b. Retinal vessel tortuosity
    c. Macular dystrophy
    d. Congenital cataracts
    e. Partial optic nerve atrophy
    f. Decreased retinal ganglion cells
    g. Microcysts in the pigment epithelium of the iris
12. Connective tissue abnormalities secondary to loss of lysyl oxidase activity
    a. Loose skin (cutis laxa)
    b. Pectus excurvatum
    c. Umbilical and/or inguinal hernias
    d. Diverticula of the bladder, uterus, and other organs
    e. Vascular complications including aortic aneurysms commonly present
    f. Tortuosity of the intracranial blood vessels by neuroimaging techniques
    g. Radiographic evidence
       i. Wormian skull bones
       ii. Osteoporosis
       iii. Metaphyseal dysplasia including anterior flaring and fracture of the ribs
13. Progressive neurologic deterioration
    a. Usually death by 3 years of age
    b. Rare survival beyond childhood in some children with profound neurologic deficits
    c. Long survival, especially with copper therapy, to teens and people in their twenties
14. Patients with milder or atypical manifestations than "classical" Menkes disease
    a. Milder phenotype
       i. Mild intellectual delay
       ii. Ataxia
    b. Later onset of symptoms
    c. Less severe clinical course
    d. A longer life span
15. Occipital horn disease: a very mild allelic form of Menkes disease
    a. A connective tissue disorder caused by a secondary deficiency of the cuproenzymes, lysyl oxidase
    b. Milder phenotypic manifestations
    c. Connective tissue abnormalities
       i. Hyperelastic and easily bruisable skin
       ii. Bladder diverticula
       iii. Varicosities
       iv. Hypermobile joints

d. Skeletal abnormalities
   i. Short broad clavicles
   ii. Fused carpal bones
   iii. Thoracic malformations
   iv. Bony exostosis of the occiput (occipital horn) secondary to calcifications of the muscle at the insertion sites
e. Occasional mild neurologic impairment
f. Any male infant with connective tissue abnormalities and mental retardation should be evaluated for the possibility of Menkes disease because of somewhat atypical presentation of these milder phenotypes.

Diagnostic Investigations

1. Biochemical phenotype
   a. Low levels of copper in serum, liver, and brain resulting from impaired intestinal absorption (Kaler 2010)
   b. Low serum ceruloplasmin levels
   c. Diagnosis of Menkes disease is confirmed by decreased serum copper and ceruloplasmin. Interpretation of these values is difficult in the first months of life. In such cases, the following analysis may be helpful in confirming the diagnosis.
      i. Copper accumulation in the placenta or chorionic villi
      ii. Copper accumulation in the cultured skin fibroblasts
   d. Low activities of numerous copper-dependent enzymes (Kaler 2010)
      i. Dopamine β-hydroxylase
         a) Temperature instability
         b) Hypoglycemia
         c) Eyelid ptosis
         d) Pupillary constriction
      ii. Peptidylglycine α-amidating monooxygenase (reduced bioactivity of many neuroendocrine peptides)
      iii. Cytochrome c oxidase (impaired myelination, muscle weakness)
      iv. Copper-zinc superoxide dismutase (diminished protection against O_2 free radicals, possible motor neuron damage)
      v. Tyrosinase (reduced pigmentation of hair and skin)
      vi. Diamine oxidase (reduced histamine degradation)
      vii. Lysyl oxidase (decreased strength of collagen and elastin)
      viii. Ceruloplasmin (decreased circulating copper levels)
   e. Paradoxical accumulation of copper in certain tissues, such as duodenum, kidney, spleen, pancreas, skeletal muscle, and placenta
2. Light microscopy of hair (Chang 2009)
   a. Pathognomonic pili torti (180° twisting of the hair shaft)
   b. Trichoclasis (transverse fracture of the hair shaft)
   c. Trichoptilosis (longitudinal splitting of the shaft)
   d. Trichorrhexis nodosa (small, beaded swelling with fractures at regular intervals)
   e. Monilethrix elliptica (swelling with intervening tapered constrictions)
3. MRI/MRA of the brain
   a. White matter abnormalities reflecting impaired myelination
   b. Progressive degeneration of gray matter
   c. Cortical encephalomalacia
   d. Diffuse cerebral atrophy
   e. Cerebellar atrophy
   f. Ventriculomegaly
   g. Tortuosity (corkscrew appearance) of cerebral blood vessels
   h. Subdural hematoma (common in infants)
   i. Cerebrovascular accidents in older patients
4. Cerebral angiogram for tortuous winding vessels
5. Variable electroencephalogram (normal, moderately to severely abnormal)
   a. Hypsarrhythmia after 5 months of age
   b. Low amplitude or absent evoked potentials
6. Echocardiography
   a. Dysplastic coronary vessels
   b. Vascular complications including aortic aneurysms
7. Pelvic ultrasound to detect diverticula of the urinary bladder
8. Renal ultrasound
   a. Hydronephrosis
   b. Hydroureter
   c. Bladder diverticula

9. Radiography
   a. Skull radiograph
      i. Wormian bones in the lambdoidal and posterior sagittal sutures
      ii. "Occipital horn"
   b. Metaphyseal spurring of long bones
   c. Diaphyseal periosteal reaction
   d. Anterior flaring or multiple fractures of ribs
   e. Scalloping of the posterior aspects of the vertebral bodies
   f. Osteoporosis seen after 6 months of age
10. Histologic examination of torturous cerebral blood vessels
   a. Thinning of the connective tissue
   b. Disruption of the elastic lamina
11. Cytogenetic studies using traditional chromosome banding techniques verified by FISH using yeast artificial chromosomes spanning the gene
   a. Mainly carried out in affected females for identification of possible X:autosome translocation at Xq13.3
   b. Rare chromosome abnormality in male patients
12. Molecular diagnosis
   a. Molecular diagnosis of Menkes disease: complicated by the heterogeneity at this locus
   b. Almost all mutations detected in the Menkes disease gene are unique to an affected family.
   c. About 20% of these mutations involve rearrangements or partial gene deletions that can be identified by Southern blot analysis.
   d. Molecular diagnosis (superior to biochemical information) when the mutation in a given family is known, especially in cases of prenatal diagnosis
   e. Carrier diagnosis is best done with mutation analysis and is readily accomplished when the specific mutation is known. In families where the mutation has not been identified, polymorphic markers and intragenic repeats have been used to facilitate carrier diagnosis.
13. Female carrier determination
   a. Measurement of copper (^{64}Cu) accumulation in fibroblasts: difficult to interpret negative results because of random X inactivation of one of the X chromosomes. Normal results do not completely exclude carrier status (Tümor 1998).
   b. Presence of pili torti in the hair: a positive clinical indicator, but its absence does not eliminate the possibility
   c. Heterozygote detection by mutation detection in a given family with a known mutation (Kaler 2010)
      i. Allele-specific PCR
      ii. Restriction enzyme analysis
      iii. Heteroduplex analysis
      iv. SSCP followed by DNA sequencing
      v. Southern blot analysis
   d. Linkage studies using intragenic polymorphic markers helpful in carrier detection, prenatal diagnosis, and genetic counseling where the mutation has not been identified (Tümor 1998)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Carrier mother: 50% of brothers affected, 50% of brothers normal; 50% of sisters carriers, 50% of sisters normal
      ii. Noncarrier mother: instances of recurrence reported due to gonadal mosaicism
   b. Patient's offspring: not surviving to reproduction
2. Prenatal diagnosis of a male fetus at risk
   a. 1st trimester: measurement of total copper content in chorionic villus samples
   b. Second trimester: copper (^{64}Cu) accumulation and kinetic studies in cultured amniotic fluid cells
   c. Mutation detection in a given family with a known mutation
3. Management
   a. No definitive therapeutic options currently available
   b. Oral copper treatment not effective
   c. Early parenteral administrations of cupric acetate
      i. Normalizes serum copper and ceruloplasmin levels but not CNS copper levels
      ii. Improves seizure control
      iii. Will not interrupt the progression of neurologic manifestations

d. Early subcutaneous injections of copper-histidine with encouraging results (Christodoulou et al. 1998)
   i. Normalizes serum copper, ceruloplasmin, dopamine, and norepinephrine levels after 3 months of treatment
   ii. May be able to cross the blood-brain barrier and thus disrupt the progression of neurological symptoms including decreased seizures
   iii. Prolong survival, especially if treatment started within 1 month of life
   iv. Does not prevent the connective tissue complications because lysyl oxidase may not incorporate copper-histidine well

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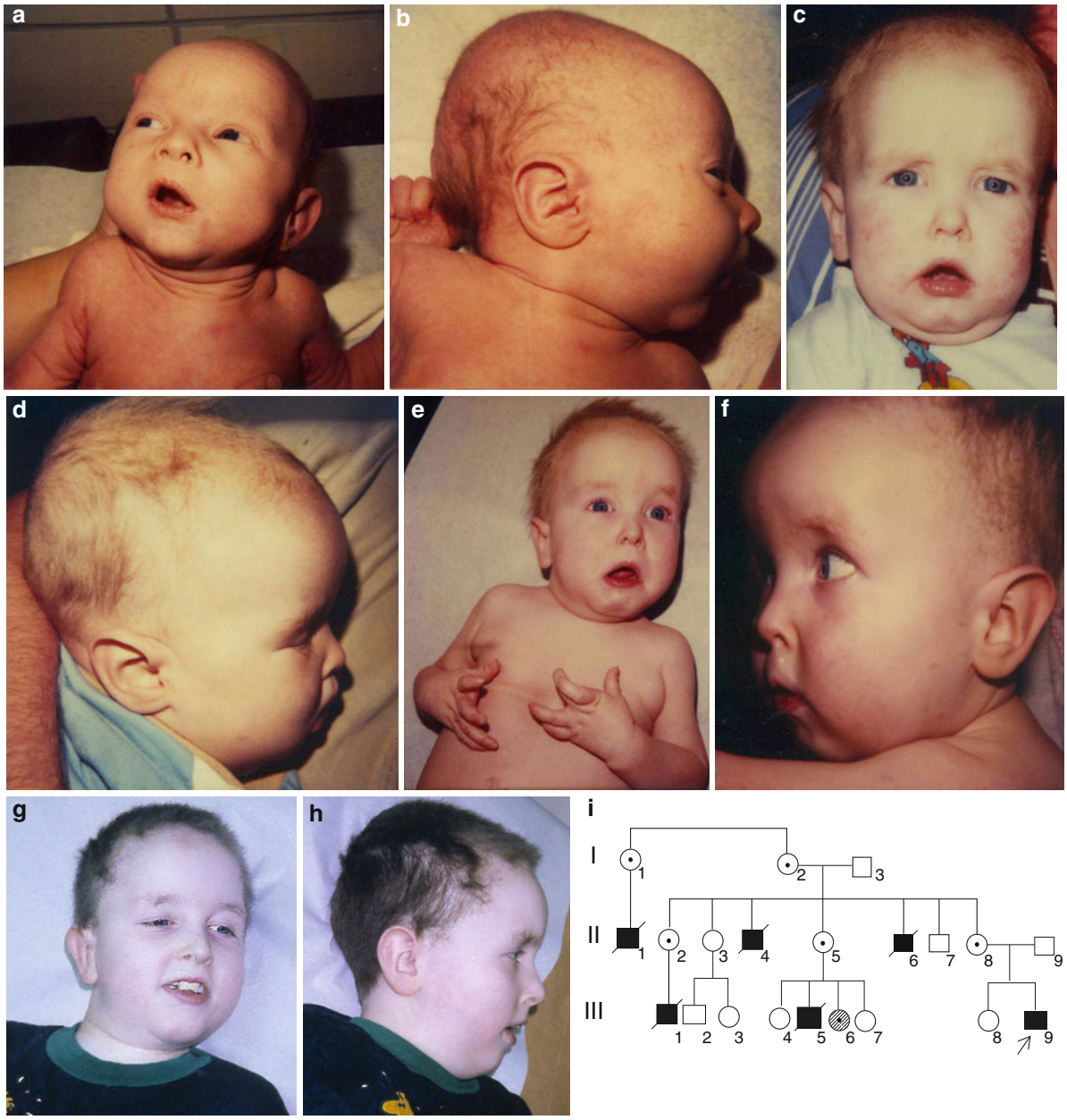

Fig. 1 (**a**–**i**) A boy with Menkes disease at 1 month, 9 months, 1 year, 27 months, and 9 years showing sparse, coarse, twisted hair; sagging cheeks; large-appearing ears; and pectus excurvatum. The boy was treated with cuprous sulfate and survived to his twenties. The pedigree is shown here illustrating X-linked recessive mode of inheritance

Fig. 2 (**a**–**b**) A cousin of the previous child with Menkes disease at 3 years of age showing coarse/twisting hair, sagging cheeks, and large-appearing ears

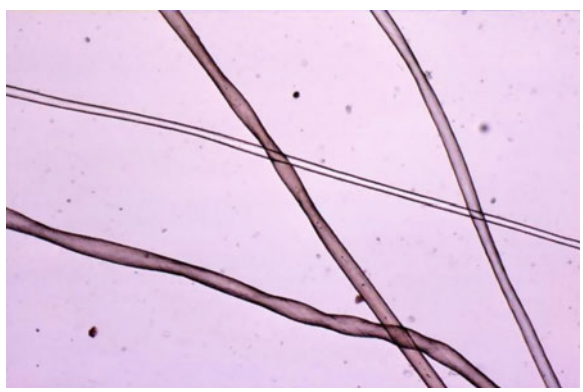

Fig. 3 Hairs showing pili torti (moderate variation in diameters; two hair shafts are twisted) in an 8-month-old male infant affected with Menkes disease

Metachromatic Leukodystrophy

Metachromatic leukodystrophy (MLD) is a lysosomal storage disease resulting from the deficient arylsulfatase A activity and the accumulation of sulfatides. The incidence among Caucasian is estimated to be about 1 in 40,000 births. The name of MLD originated from the metachromatic staining of the stored substance in histological sections.

Synonyms and Related Disorders

Arylsulfatase A deficiency; Cerebroside sulfatase deficiency; Metachromatic leukoencephalopathy

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Caused by deficiency of arylsulfatase A (ASA) activity
   a. Resulting in accumulation of the enzyme substrate sulfatide (cerebroside sulfuric ester) in
      i. Oligodendrocytes and Schwann cells
      ii. Visceral organs such as kidneys (sulfatide excreted in high amounts in the urine)
   b. Leading to severe myelin breakdown
      i. Resulting in demyelination of the white matter of the brain, spinal cord, and peripheral nerves
      ii. Providing the pathophysiologic basis for the deterioration and eventual premature demise
3. Arylsulfatase (*ARSA*) gene
   a. Mapped to 22q13.31
   b. MLD caused by *ARSA* mutations (Gieselmann 2008): more than 11 different mutations have been identified in the *ASA* gene (Missense mutations are by far the most frequent type of defect found.)
      i. Two most common mutations observed in Europe are (Berger et al. 1997)
         a) 459+1G>A
         b) A missense mutation causing a Pro426Leu substitution (accounts for about 25% of all alleles among European patients) (Polten et al. 1991)
      ii. A missense mutation causing an Ile179Ser substitution (accounts for about 12% of all defective alleles) (Berger et al. 1997)
      iii. All other mutant alleles have only been found in a few or single patients (Schestag et al. 2002).
   c. ASA pseudodeficiency (ASA-PD) caused by *ARSA* mutation
      i. Originally described in healthy individuals
      ii. Low ASA activity
      iii. Normal urinary sulfatide levels
      iv. The pseudodeficiency, in most cases, is caused by homozygosity for the arylsulfatase A pseudodeficiency (ASA-PD) allele (Polten et al. 1991).
      v. MLD mutations also known to occur within this allele: 1–2% of PD alleles are estimated to have a disease-causing mutation (Rafi et al. 2003).
   d. Chromosomal deletion unmasking a recessive disease: 22q13 deletion syndrome and metachromatic leukodystrophy (Bisgaard et al. 2009)
      i. One patient had a pathogenic mutation in the *ARSA* gene and succumbed to MLD.
      ii. Another patient had a pseudoallele which did not lead to MLD.

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e. Pathophysiology (Ikeda et al. 2010)
   i. Inability to degrade sulfated glycolipids, especially the galactosyl-3-sulfate ceramides, characterizes metachromatic leukodystrophy.
   ii. A deficiency in the lysosomal enzyme sulfatide sulfatase (arylsulfatase A) is present in metachromatic leukodystrophy.
   iii. Some patients with clinical metachromatic leukodystrophy have normal arylsulfatase A activity but lack an activator protein that is involved in sulfatide degradation.
   iv. Both defects result in the accumulation of sulfatide compounds in neural and in nonneural tissue, such as the kidneys and gallbladder.
   v. These defects may result from a number of different mutations, and many new causative mutations have been identified (Anlar et al. 2006; von Figura et al. 2001).

Clinical Features

1. Three main clinical forms based on the age of onset of the disease
   a. Late-infantile form (50–60% of cases)
   b. Juvenile form (20–30% of cases)
   c. Adult form (15–20% of cases)
2. Late-infantile form (Clark et al. 1979)
   a. The most common form
   b. Onset of the disease: between the ages of 15 months and 2 years
   c. Clinical symptoms
      i. Loss of acquired motor skills
      ii. Flaccid weakness and hypotonia
      iii. Ataxic gait with absent tendon reflexes
   d. Progression of the disease
      i. Quadriplegia
      ii. Speech disturbances
         a) Dysarthria
         b) Aphasia
         c) Speech deterioration leading to loss of speech
      iii. Difficulty in feeding (dysphagia) with bulbar and pseudobulbar palsies
      iv. Irritability
      v. Muscle wasting
      vi. Peripheral neuropathy
      vii. Ataxia
      viii. Ophthalmic features
         a) Nystagmus
         b) A cherry-red spot in the macula in some patients (Crumrine 2001)
         c) Optic atrophy leading to blindness
      ix. Epileptic seizures usually occur at advanced stages of the disease.
      x. Mental deterioration progresses with the disease until the patients are no longer able to establish any contact with their surroundings.
      xi. Death generally occurs 1–7 years after onset.
3. Juvenile form
   a. Clinical symptoms usually develop between the ages of 4 and 12 years.
   b. Progression of the illness similar to that of the infantile form
   c. Clinical characteristics
      i. Loss of developmental milestones by the end of the first decade
      ii. Gross motor
         a) Incoordination
         b) Clumsiness
         c) Ataxia with progressive gait disturbance leading to loss of ambulation
         d) Progressive hypertonia with tremor, postural abnormalities, and/or leg scissoring
         e) Diminished deep tendon reflexes
      iii. Speech and language
         a) Slurred speech
         b) Speech deterioration
      iv. Cognitive and behavioral changes
         a) Abnormal and bizarre behavior
         b) Daydreaming
         c) Difficulty in following directions
         d) Emotional difficulties
         e) Intellectual decline
         f) Mental deterioration
      v. Ophthalmologic features: optic atrophy leading to blindness
      vi. Other CNS manifestations
         a) Pseudobulbar palsy
         b) Epileptic seizures usually occur at advanced stages of the disease.
         c) Mental illness with features of psychosis, dementia, and emotional disorders in older children
         d) Progressive neurological problems but less severe than in the late-infantile form

d. Prognosis
   i. Fatal in majority of cases
   ii. Course of disease may last more than 20 years in a few cases.
4. Adult form
   a. Wide range of onset: from 19 to 46 years
   b. Very rare occurrence
   c. Slow progression of the disease
   d. Survival of 5–10 years common
   e. Cognitive and behavioral changes: the first symptoms in many cases
      i. Personality changes
         a) Anxiety
         b) Apathy
         c) Bewilderment
         d) Emotional instability
         e) Psychosis
      ii. Poor school or job performance
         a) Decreased mental alertness
         b) Defective visual-spatial discrimination
         c) Disorganized thinking
         d) Poor memory
   f. Mental deterioration
      i. Often the first symptom
      ii. Loss of professional abilities leading to total incapacity
      iii. Progressive deterioration eventually leading to dementia
   g. Rare epileptic seizures
   h. Ophthalmologic features
      i. Horizontal nystagmus
      ii. Optic atrophy leading to blindness
   i. Final stages
      i. Lose of speech
      ii. Immobility
      iii. Incontinence
5. Arylsulfatase pseudodeficiency
   a. Low arylsulfatase activity in healthy individuals
   b. Allelic variant metachromatic leukodystrophy
6. Nonallelic variants of MLD (Fluharty 2008)
   a. Multiple sulfatase deficiency (Austin variant of MLD)
      i. Caused by a defect in processing of an active site cysteine to formylglycine (alanine-semialdehyde), a proenzyme activation step common to most sulfatases (Dierks et al. 2005; Zafeiriou et al. 2008)
      ii. Findings suggesting a diagnosis of multiple sulfatase deficiency include
         a) Reduced activity of other sulfatases including arylsulfatase B, arylsulfatase C, iduronate sulfatase (the enzyme that is deficient in Hunter syndrome, and heparan-N-sulfamidase in leukocytes or cultured cells)
         b) Presence of mucopolysaccharides (glycosaminoglycans) as well as sulfatides in the urine
      iii. Although clinical variability of multiple sulfatase deficiency is great, features of both MLD and a mucopolysaccharidosis (MPS) may be present (Macaulay et al. 1998).
      iv. More severe forms of multiple sulfatase deficiency resemble late-infantile MLD. In other cases, MPS-like features such as coarse facial features and skeletal abnormalities may be evident in infancy and early childhood, with MLD-like symptoms becoming evident in later childhood.
      v. Eventually, the disease course resembles MLD with demyelination dominating the clinical picture (von Figura et al. 2001). Ichthyosis, common to arylsulfatase C deficiency, is also often present.
      vi. A defect in the formylglycine-generating enzyme (FGE) is causative (Dierks et al. 2005) and is responsible for the activation of most sulfatases, and a variable degree of arylsulfatase A deficiency occurs in many tissues in its absence.
   b. Sphingolipid activator protein B deficient MLD (saposin B deficiency)
      i. A defect in the glycolipid-binding protein saposin B, which is needed to solubilize sulfatides before they can be hydrolyzed by arylsulfatase A, causes an MLD-like disorder.
      ii. While a number of other glycolipid degradative processes are disrupted in saposin B deficiency, it is the failure in sulfatide catabolism that dominates the clinical picture.
      iii. Age of onset is variable, with too few cases having been reported to delineate a typical clinical picture.

iv. An MLD-like clinical presentation, leukodystrophy on MRI, normal arylsulfatase A enzyme activity, and evidence of excess urinary sulfatide excretion and/or sulfatide storage suggest activator deficiency.
v. Diagnosis depends on depressed sulfatide degradation by cultured cells, immunochemical assessment of saposin B levels, or sequence analysis of the gene encoding prosaposin (Sandhoff et al. 2001).

Diagnostic Investigations

1. Diagnosis suspected in individuals with progressive neurologic dysfunction and MRI evidence of a leukodystrophy.
2. Demonstration of decreased (<10% of normal controls) or absence ASA enzyme in the urine, leukocytes, or cultured skin fibroblasts (Gieselmann 1991)
   a. Low ASA activity also observed in
      i. Individuals with multiple sulfatase deficiency
      ii. Individuals with copies of pseudodeficiency (PD) allele
   b. Low ASA activity is seen in individuals without MLD due to the high frequency of the common PD allele in the general population.
   c. Differentiation of ASA pseudodeficiency from MLD
      i. Inability to reliably distinguish MLD and ASA pseudodeficiency, based solely on enzyme activity determinations
      ii. Cerebroside sulfate loading test
         a) Exposure of the cells to radioactively labeled cerebroside sulfate, the natural substrate of arylsulfatase A
         b) Cultured cells from pseudodeficient individuals will degrade this substrate at normal rates, whereas those from MLD patients do not.
         c) Disadvantages: require experienced investigator, noncommercially available substrate, and tissue culture facilities
      iii. PD allele mutations studies using allele specific amplification
3. Urinalysis showing metachromatic granules in the urine sediment
4. Urine chemistry showing markedly increased sulfatide levels
5. Sulfatide loading of fibroblast cultures and subsequent measurement of hydrolysis of added substrate: The differences in hydrolysis of added sulfatide provide a functional test that separates late-infantile, juvenile, and adult forms (Krivit et al. 1995).
6. Absence of gallbladder function on a cholecystography (Crumrine 2001)
7. Abnormal brain stem auditory, visual, and somatosensory evoked potentials
8. Elevated CSF protein levels
9. Brain imaging shows progressive loss of white matter due to demyelination (Faerber et al. 1999).
   a. Symmetric diffuse high-intensity signal on proton density and T2-weighted images throughout the white matter consistent with demyelination
   b. Hypointense signal abnormalities in the white matter of the centrum semiovale with following two distinct appearances
      i. A radiating pattern ("tigroid" appearance) of linear tubular structures or horizontal linear hypodensity indicative of spared perivascular white matter
      ii. Areas of relatively normal-appearing white matter: a punctate appearance to the linear structures ("leopard-skin" appearance) within the demyelinated centrum semiovale
   c. Cerebral atrophy with ventricular enlargement
10. Nerve conduction studies show decreased nerve conduction velocities.
11. Nerve biopsies show metachromasia of Schwann cells.
12. Molecular studies of ASA mutations (Fluharty 2008)
   a. Targeted mutation
      i. *ARSA*-mild alleles
      ii. *ARSA*-PD alleles
   b. Sequence analysis/mutation scanning
   c. Deletion/duplication analyses

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Recurrence risk: 25%
      ii. Younger siblings in the same family with an older sibling who is clinically affected by MLD (Krivit et al. 1995)
         a) Require appropriate and rapid evaluation
         b) May be affected but clinically presymptomatic
         c) Therapy with bone marrow transplantation in affected but asymptomatic sibling may be curative.
         d) Sibling with very low levels of white blood cell arylsulfatase A may not indicate the presence of disease because of the combination of the pseudodeficient gene with a metachromatic leukodystrophy gene.
   b. Patient's offspring
      i. Do not survive into reproductive age in late-infantile and juvenile forms
      ii. Not increased in adult form unless the spouse is a carrier
2. Carrier detection (Gieselmann 1991)
   a. Individuals with about 50% of arylsulfatase A
      i. Suspected to be carriers of a MLD allele and have genetic risk for MLD
      ii. Likely to be carriers of a pseudodeficiency allele and have no genetic risk for MLD
   b. Enzyme activity determination: impossible to distinguish heterozygotes of a pseudodeficiency allele from heterozygous of an MLD allele
   c. Mutation detection of the pseudodeficiency allele in the DNA to facilitate the differential diagnosis of MLD and pseudodeficiency
3. Prenatal diagnosis for couples at risk
   a. Demonstration of the absence of arylsulfatase A in cultured chorionic villi or amniocytes
   b. A combination of biochemical and molecular tests performed on chorionic villus samples or cultured amniotic fluid cells
   c. Demonstration of the disease-causing mutation previously identified in the proband on fetal DNA obtained from amniocentesis or CVS
   d. Preimplantation genetic diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.
4. Management
   a. Primarily supportive
      i. Currently, no available treatment can reverse the fatal outcome of the devastating MLD.
      ii. Nasogastric or G-tube feeding for dysphagia of bulbar and pseudobulbar palsies
      iii. Multidisciplinary approach
   b. Bone marrow transplantation
      i. For individuals who are presymptomatic or have only mild neurologic manifestations
      ii. Significant risks associated with this procedure
      iii. Highly dependent on the availability of adequately matched donors
      iv. Appears to slow the progression of the disease and improve the quality of life
      v. Successful treatment of metachromatic leukodystrophy using bone marrow transplantation of HoxB4 overexpressing cells in the mouse model (Miyake et al. 2010)

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Fig. 1 A 28-month-old boy with late-infantile form metachromatic leukodystrophy showing extreme hypotonia. At about 15 month of age, he stopped talking and showed muscle weakness. MRI of the brain demonstrated demyelination. Arylsulfatase A activity was absent in the cultured fibroblasts. Urinary excretion of excess sulfatides confirmed the diagnosis of metachromatic leukodystrophy. DNA analysis shows no copies of the pseudodeficiency allele or the common late-infantile mutation. Mutation screening of the entire coding sequence of the arylsulfatase A gene revealed the mutation E253K which was inherited from the mother and the second mutation P192R which was inherited from the father. The E253K mutation has been described as a disease-causing mutation in the literature. The second mutation P192R most likely is a disease causing mutation

Fig. 2 A 3-year-old girl presented with progressive muscle weakness in the lower limbs for 2–4 months. The low leukocyte arylsulfatase A at 0.4 (control: $\geq$2.5) was consistent with diagnosis of metachromatic leukodystrophy

Miller–Dieker Syndrome

In 1963, Miller reported two siblings with a specific pattern of malformations in which lissencephaly was a key feature. Later in 1969, Dieker et al. described a similar condition. Jones et al. in 1980 further characterized the phenotype and suggested the designation Miller–Dieker syndrome to distinguish it from other lissencephaly syndromes. At present, Miller–Dieker syndrome is known to be a contiguous gene disorder caused by haploinsufficiency of a gene or genes having a major role in the development of the brain and the face (Alvarado et al. 1993).

Synonyms and Related Disorders

Chromosome 17p13.3 deletion syndrome; Miller-Dieker lissencephaly syndrome

Genetics/Basic Defects

1. Genetics: a contiguous gene deletion syndrome involving chromosome 17p13.3 (Chitayat et al. 1997)
   a. Association of Miller–Dieker syndrome and del (17)(p13)
      i. First reported by Dobyns et al. in 1983
      ii. Familial cases reported by Miller (1963) with affected members being carriers of an unbalanced rearrangement from t(15;17)(q26.1;p13.3)
      iii. Family reported by Dieker et al. (1969) with affected members being carriers of an unbalanced rearrangement from t(12;17)(q24.31;p13.3)
   b. A microdeletion in a critical 350-kb region of chromosome 17p13.3 observed in familial and sporadic cases, detected by high-resolution banding
   c. Southern blot analysis of restriction fragment length polymorphism with several different DNA markers in 17p13.3, and later FISH analysis using different DNA probes of this segment
      i. Observed in >90% of patients with Miller–Dieker syndrome
      ii. Observed in 38% of patients with isolated lissencephaly
2. Mutations and large deletions of the lissencephaly gene (*LIS1*)
   a. Deletions involving *LIS1*: more common than mutations
   b. *LIS1* deleted in Miller–Dieker syndrome
   c. *LIS1* mutations observed in patients with isolated lissencephaly sequence
      i. Missense mutations
      ii. Nonsense mutations
      iii. Small deletions or insertions
      iv. Splice site mutations
      v. Partial deletions
   d. Phenotype-genotype correlations (Cardoso et al. 2002)
      i. Most severe LIS phenotypes observed in patients with large deletions of 17p13.3
      ii. Milder phenotypes observed in patients with intragenic mutations
      iii. Mildest phenotypes observed in patients with missense mutations
3. Classification of lissencephaly (Dobyns et al. 1984; Spalice et al. 2009)
   a. Lissencephaly type I (classical)
      i. Isolated lissencephaly sequence

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   ii. Miller–Dieker syndrome
   iii. Subcortical band heterotopia
   iv. Nonclassified forms
  b. Lissencephaly type II (cobblestone)
   i. Walker–Warburg syndrome
   ii. Fukuyama congenital muscular dystrophy
   iii. Muscle-eye-brain disease
   iv. Non-unclassified forms
  c. Rare forms
   i. Neu–Laxova syndrome
   ii. Cerebro-cerebellar syndrome
4. Cytogenetic mechanisms in Miller–Dieker syndrome (Dobyns et al. 1991)
  a. De novo abnormalities (44%)
   i. Deletion (terminal or interstitial) (36%)
   ii. Dicentric translocation (4%)
   iii. Ring chromosome (4%)
  b. Familial rearrangement (12%)
   i. Reciprocal translocation (8%)
   ii. Pericentric inversions (4%)
  c. Normal karyotype (44%)
   i. Submicroscopic deletion (36%)
   ii. No deletion detected (8%)
5. Molecular explanation for Miller–Dieker syndrome (Toyo-oka et al. 2003)
  a. Heterozygous deletions of 17p13.3 result in the human neuronal migration disorders.
   i. Isolated lissencephaly sequence
   ii. More severe Miller–Dieker syndrome
  b. Mutations in *PAFAH1B1* (the gene encoding LIS1): responsible for isolated lissencephaly sequence and contributing to Miller–Dieker syndrome
  c. The gene encoding 14-3-3ϵ (YWHAE), one of a family of ubiquitous phosphoserine/threonine-binding proteins: always deleted in individuals with Miller–Dieker syndrome, providing a molecular explanation for the differences in severity of human neuronal migration defects with 17p13.3 deletions

Clinical Features

1. Prenatal and neonatal history
  a. Polyhydramnios
  b. Prenatal growth deficiency
  c. Neonatal resuscitation
  d. Neonatal jaundice
  e. Postnatal growth deficiency
2. CNS anomalies
  a. Type I (classical) lissencephaly: can occur either in association with the Miller–Dieker syndrome or as an isolated finding, termed "isolated lissencephaly sequence."
   i. Agyria (absent gyration of the cerebral cortex)
   ii. Pachygyria (unusually thick convolutions of the cerebral cortex)
  b. Absent or hypoplastic corpus callosum
  c. Cavum septi pellucidi
  d. Midline calcification
  e. Ventricular dilatation
  f. Abnormal positioning of the olivary nuclei in the midbrain
  g. Occasional mild cerebellar vermis hypoplasia
  h. Microcephaly
  i. Seizures usually by age 9 weeks
  j. Cerebral palsy
  k. Profound mental retardation
3. Craniofacial features
  a. High, prominent, and wrinkled forehead
  b. Bitemporal narrowing
  c. Furrowed brow
  d. Epicanthal folds
  e. Broad nasal bridge
  f. Short and pointed nose with anteverted nostrils
  g. Long prominent upper lip with thin upper vermilion border
  h. Micrognathia
  i. High-arched palate
  j. Low-set and malformed ears
4. Congenital heart defects
5. Omphalocele (Chitayat et al. 1997)
6. Hands and fingers
  a. Clinodactyly
  b. Camptodactyly
  c. Transverse palm crease
7. Sacral dimple
8. Cryptorchidism
9. Prognosis: often die within the first few months of life
10. Differential diagnosis
  a. Isolated lissencephaly sequence (Dobyns et al. 1984)
   i. Brain abnormalities
    a) Lissencephaly (type I)
    b) Numerous heterotopias
    c) Failure of opercularization

d) Enlarged ventricles (usually colpocephaly)
e) Probable hypoplasia of the corpus callosum

ii. Neurologic abnormalities
a) Profound mental retardation
b) Decreased spontaneous activity
c) Early hypotonia
d) Subsequent hypertonia
e) Poor feeding
f) Seizures

iii. Craniofacial features
a) Microcephaly
b) Bitemporal hollowing
c) Prominent occiput
d) Micrognathia

iv. Occasional abnormalities
a) Prenatal polyhydramnios, decreased fetal movement
b) Postnatal: may require resuscitation at birth
c) Neurological: infantile spasms

v. Chromosome studies
a) Normal chromosomes by conventional studies
b) Submicroscopic deletions by FISH observed in increasing numbers

b. Norman–Roberts syndrome (Dobyns et al. 1984)
i. Probably an autosomal recessive disorder
ii. Brain abnormalities
a) Lissencephaly (type I)
b) Numerous heterotopias
c) Failure of opercularization
d) Slightly enlarged ventricles (probable colpocephaly)
e) Probable hypoplasia of the corpus callosum

iii. Neurologic abnormalities
a) Profound mental retardation
b) Decreased spontaneous activity
c) Poor feeding
d) Seizures

iv. Cranial abnormalities
a) Microcephaly
b) Bitemporal hollowing
c) Slightly prominent occiput
d) Low, sloping forehead

v. Facial features
a) Widely set eyes
b) Broad, prominent nasal bridge
c) Micrognathia
d) Absence of upturned nares
e) Normal eyes

vi. Other features
a) Clinodactyly
b) Chordee
c) Low birth weight

vii. Normal chromosomes

c. Walker–Warburg syndrome
i. Most commonly seen in the United Kingdom
ii. An autosomal recessive disorder
iii. Type II lissencephaly
iv. Hydrocephalus
v. Cerebellar malformation (vermian hypoplasia)
vi. Eye abnormalities
a) Retinal dysplasia
b) Microphthalmia
c) Colobomata
d) Cataracts
e) Glaucoma
f) Corneal clouding commonly due to a Peter anomaly
g) Congenital muscular dystrophy in all patients
h) Elevated CK
i) Abnormal EMG
j) Pathological changes on muscular histology

vii. Other abnormalities
a) Cleft lip/palate
b) Genital anomalies in males: cryptorchidism, small penis
c) Occasional contractures

d. Muscle-eye-brain disease
i. Mainly reported in Finnish population
ii. An autosomal recessive disorder
iii. Type II lissencephaly
iv. Hydrocephalus
v. Eye abnormalities
a) Primarily myopia
b) Occasional glaucoma, retinal dystrophy, and cataracts

vi. Congenital muscular dystrophy: a constant feature
vii. Elevated CK levels
viii. Hypotonia
ix. Feeding difficulties

x. Severe mental retardation
xi. Seizures common

e. Fukuyama congenital muscular dystrophy
i. Mainly reported in the Japanese population
ii. An autosomal recessive disorder
iii. Cobblestone lissencephaly (type II)
iv. Eye abnormalities
a) Myopia
b) Optic atrophy in some patients
v. Muscular dystrophy in all patients
vi. CK levels ranging from 10 to 50 times of normal
vii. Hypotonia
viii. Marked mental retardation

Diagnostic Investigations

1. Chromosome analysis to detect microdeletion at 17p13.3
   a. High-resolution analysis indicated for all patients with type I or atypical lissencephaly
   b. Molecular cytogenetic technology using FISH to detect a submicroscopic deletion when chromosome analysis is normal and Miller–Dieker syndrome is suspected based on clinical evaluation
   c. Parental studies in case of positive findings
2. MRI of the newborn brain
   a. Smooth brain
   b. Bilateral primitive Sylvian fissure giving rise to a "figure 8" appearance of the brain
   c. Persistent fetal configuration of the posterior horns of the ventricular system (colpocephaly)
3. DNA mutation analysis of *LIS1* available clinically (Dobyns and Das 2009)
   a. Direct sequencing
   b. Deletion/duplication analysis to identify deletions/duplications not detectable by sequence analysis
   c. Array comparative genomic hybridization (aCGH)
   d. Multiplex ligation-dependent probe amplification (MLPA) analysis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: based on the specific cytogenetic mechanism involved
      i. Very low recurrence risk in most patients (80% of individuals with MDS) whose abnormalities occur de novo
      ii. Very high recurrence risk in families (20% of individuals with MDS) where one parent is the carrier of a balanced chromosome rearrangement involving 17p13
      iii. Proband with an intragenic mutation in *LIS1*: The risk to sibs is negligible if neither parent has mosaicism for the mutation present in the proband.
   b. Patient's offspring: patients not surviving to reproductive age
   c. A high risk for abnormal phenotypes for an individual carrying a balanced translocation with a breakpoint in 17p13 ascertained because of a relative with Miller–Dieker syndrome or dup(17p)
      i. Approximately 26% risk in all recognized pregnancies
      ii. Thirty-three percent risk in pregnancies which remain viable in the second trimester or after
      iii. Frequency of spontaneous miscarriages and stillbirths not appearing to be unduly elevated in these families
2. Prenatal diagnosis
   a. Ultrasonography for pregnancy at risk (Sultzman 1991)
      i. Polyhydramnios
      ii. IUGR
      iii. Lissencephaly
      iv. Microcephaly
      v. Mild ventriculomegaly
      vi. Absence of corpus callosum
      vii. Cardiac and other malformations
   b. Prenatal diagnosis by amniocentesis or CVS
      i. Indications
         a) Carrier parents with balanced chromosome rearrangements involving 17p13
         b) Probably parents of all Miller–Dieker syndrome patients because of the small possibility of gonadal mosaicism in apparently de novo cases
         c) Normal relatives of unknown karyotype
      ii. Cytogenetic analysis
         a) High-resolution analysis of chromosome 17
         b) Molecular cytogenetic studies (FISH)
      iii. Analysis of fetal DNA if a *LIS1* variant is identified in the proband.

iv. Preimplantation genetic diagnosis: available for families in which the disease-causing mutation has been identified.

3. Management
   a. Supportive care
   b. Early infant intervention
   c. Anticonvulsants for seizures

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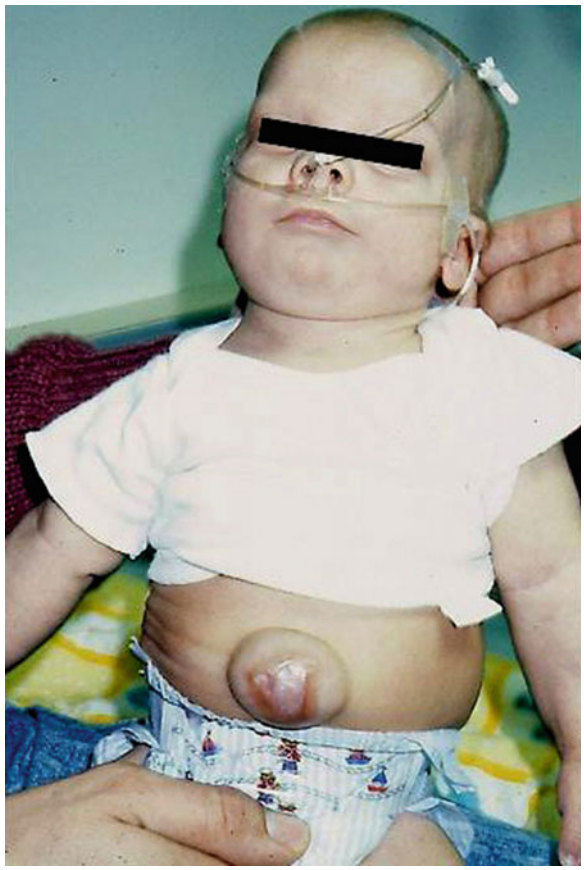

Fig. 1 A child with Miller–Dieker syndrome showing high forehead, frontal bossing, bilateral temporal narrowing, small nose with anteverted nares, prominent upper lip, micrognathia, and a surgically repaired omphalocele

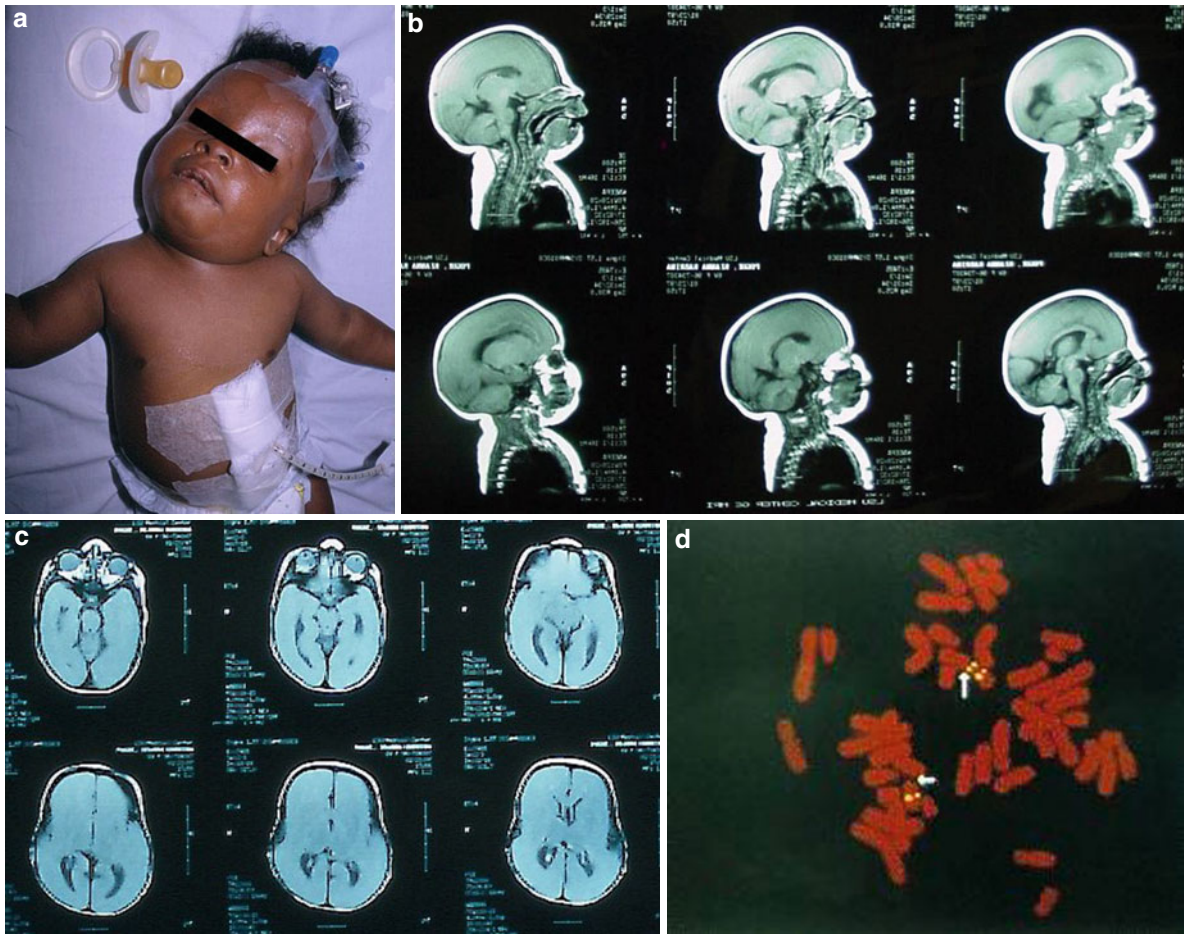

Fig. 2 (**a**–**d**) A child with Miller–Dieker syndrome showing characteristic facial traits like the previous child. The MRI of the brain showed diffuse and complete type I lissencephaly. FISH revealed one chromosome 17 lacked a signal at 17p13 indicating the presence of a deletion

Mitochondrial Leber Hereditary Optic Neuropathy

Mitochondrial disorders are a major cause of chronic human disease with an estimated prevalence of 1 in 10,000 in the United Kingdom, and 1 in 200 individuals are at-risk mutational carriers (Elliott et al. 2008; Schaefer et al. 2008). Ocular involvement, especially optic nerve dysfunction, is a prominent feature in this group of disorders, suggesting the underlying mitochondrial etiology. Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (DOA) (Kjer type optic atrophy) are the two most common inherited optic neuropathies, resulting from mitochondrial dysfunction.

In 1871, the German ophthalmologist Theodore Leber first described the distinctive clinical entity of LHON with a characteristic pattern of visual loss among members of four families, subsequently confirmed in pedigrees from different populations (Bell 1931; Imai and Moriwaki 1936; Lundsgaard 1944). These early studies highlighted the salient features of LHON, including the maternal transmission of the disease, the predilection of males to lose vision, and the almost exclusive involvement of the optic nerve.

Autosomal dominant optic atrophy is the most common primary hereditary optic neuropathy (Yoshida et al. 2006). It is characterized by optic nerve pallor and reduced visual acuity (Eliott et al. 1993; Votruba et al. 1998a, b). It was first described clinically by Batten (1896) and later by Kjer (1959) and typically presents in childhood with bilateral visual loss that is usually symmetrical, temporal optic nerve pallor, centrocaecal visual field scotoma, and color vision deficit (Caldwell et al. 1971; Smith 1972; Hoyt 1980; Jaeger 1988).

Synonyms and Related Disorders

Hereditary optic neuropathy; Leber optic atrophy; Leber optic neuropathy; LHON

Genetics/Basic Defects

1. LHON (Yu-Wai-Man et al. 2009)
   a. Caused by primary mitochondrial DNA (mtDNA) mutations affecting the respiratory chain complexes
      i. Over 95% of LHON pedigrees are now known to harbor one of three mitochondrial DNA (mtDNA) point mutations: m.3460G > A, m.11778G > A (a point mutation within the mitochondrial genome known to cause the first human disease, LHON) (Wallace et al. 1988), and m.14484T > C, which all involve genes encoding complex I subunits of the mitochondrial respiratory chain (Mackey et al. 1996).
   b. Mitochondrial genetic factors
      i. Homoplasmy: In most LHON pedigrees, the primary mutation is homoplasmic (every mtDNA molecule harbors the mutant allele, i.e., only one type of mtDNA exists within an individual).
      ii. Heteroplasmy (both mutant and wild-type mtDNA coexist within an individual)
         a) Cells can contain anywhere between 100 and 10,000 mitochondria depending on their metabolic demands. With 2–10 mtDNA molecules in each

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mitochondrion, this results in a very high copy number per cell.
b) Ten to fifteen percentage of LHON carriers are thought to be heteroplasmic (one mtDNA subpopulation carrying the wild-type allele) (Smith et al. 1993; Harding et al. 1995; Man et al. 2003).
c) Available data suggest that heteroplasmy contributes to incomplete penetrance, with the risk of blindness being minimal if the mutational load is <60% (Chinnery et al. 2001).

iii. MtDNA haplogroups
a) MtDNA accumulates mutations ~10 times faster than nuclear genome, resulting in a high degree of polymorphism (Brown et al. 1979).
b) Because human mtDNA is strictly maternally inherited and does not recombine, polymorphisms have accumulated sequentially along radiating female lineages as women migrated out of Africa into the different continents ~150,000 years ago (Wallace et al. 1999).
c) Reflecting its evolution, a number of stable polymorphic variants cluster together in specific combinations referred to as haplogroups, with individuals of European ancestry belonging to one of nine haplogroups: H, I, J, K, T, U, V, W, and X (Torroni et al. 1996; Hofmann et al. 1997).
d) A recent meta-analysis of 159 European LHON pedigrees indicated that the risk of visual loss for the three primary LHON mutations is influenced by the mtDNA background (Hudson et al. 2007).

c. Nuclear genetic factors
i. The predominance of affected males in LHON cannot be explained by mitochondrial inheritance, and segregation analysis suggests the existence of a recessive X-linked susceptibility gene acting in synergy with the mtDNA mutation to precipitate the optic neuropathy (Bu and Rotter 1991, 1992; Nakamura et al. 1993).
ii. Although the actual causative gene in this region of interest has not yet been identified, a high-risk haplotype (DXS8090-DXS1068) at Xp21 was defined which increased the risk of visual failure ~35-fold for the m.11778G > A and m.14484T > C mutations but not for m.3460G > A (Hudson et al. 2005).
iii. The possibility of other autosomal nuclear modifier genes in LHON has not been excluded, and the genetic etiology of LHON might prove even more complex, with epistatic interaction of these multiple nuclear susceptibility loci and genetic heterogeneity.

d. Environmental factors
i. Existence of discordant monozygotic twins strongly suggests that environmental factors also contribute to penetrance.
ii. Anecdotal reports of nutritional deprivation, exposure to industrial toxins, antiretroviral drugs, psychological stress, or acute illness precipitating the onset of blindness in LHON (Mackey et al. 2003; Sanchez et al. 2006; Carelli et al. 2007)
iii. The role of environmental triggers in LHON remains largely unanswered, and more robust epidemiological data are needed, which will necessitate a multicenter collaborative effort in order to collect sufficient number of subjects for analysis.

2. DOA: caused by mutations in the *OPA1* gene, a gene encoding for a dynamin-like mitochondrial GTPase, an inner mitochondrial membrane protein critical for mtDNA maintenance and oxidative phosphorylation, in the majority of DOA families
3. Pathology for both LHON and DOA: limited in the majority of cases to the retinal ganglion cells (RGCs), a highly specialized group of cells within the eye
4. Expanding phenotype associated with LHON and DOA: providing important insights into possible disease pathways leading to optic nerve degeneration and visual failure

Clinical Features

1. LHON (Yu-Wai-Man et al. 2009; Milea et al. 2010)
a. Presymptomatic phase
i. Fundal abnormalities such as telangiectatic vessels around the optic discs and variable degrees of retinal nerve fiber layer edema
a) Documented in some asymptomatic carriers
b) Can fluctuate with time

ii. Thickening of the temporal retinal nerve fiber layer found in a proportion of unaffected carriers by using optical coherence tomography imaging: provides further evidence that the papillomacular bundle is particularly vulnerable in this disorder (Savini et al. 2005; Quiros et al. 2006)
iii. Subtle impairment of optic nerve function in some individuals on detailed psychophysical testing (Sadun et al. 2006)
a) Loss of color vision affecting mostly the red–green system
b) Reduced contrast sensitivity
c) Subnormal visual electrophysiological parameters

b. Acute phase
i. Experiencing blurring or clouding of vision in one eye
ii. Subacute presentation in the vast majority of an early age of onset (<20 years) with slow progression of the visual deficits and large optic nerve head surface area (Nikoskelainen et al. 1996; Barboni et al. 2006)
iii. Devastating, with the majority of patients showing no functional improvement and remaining as legally blind

c. Associated features
i. Cardiac arrhythmias
ii. Neurological abnormalities: rarely clinically significant, but a small number of LHON pedigrees have severe neurological deficits such as spastic dystonia, ataxia, and juvenile onset encephalopathy in addition to the optic neuropathy ("LHON plus" syndromes) (Bower et al. 1992; Nikoskelainen et al. 1994; 1995; Meire et al. 1995; Mashima et al. 1996)
a) Postural tremor
b) Peripheral neuropathy
c) Nonspecific myopathy and movement disorders

2. DOA
a. Prevalence
i. A historical figure of 1 in 50,000 among Caucasians often quoted in the literature (Lyle 1990)
ii. Thought to be the most common inherited optic neuropathy in the Netherlands, with a population frequency of 1 in 12,000, a higher prevalence linked to a mutational founder event (Thiselton et al. 2001)

b. Insiduous onset of symptoms: 13–25% of patients with optic atrophy in premolecular case series were visually asymptomatic and were only identified through contact tracing via other affected family members (Kline and Glaser 1979; Hoyt 1980).

c. Pronounced inter-/intrafamilial variability in the severity of visual symptoms
i. Makes genetic counseling difficult
ii. Visual decline: classically starts in the first two decades of life
iii. Visual acuity: ranges from 6/6 to the detection of hand movement only
iv. Rate of progression of visual loss: not easy to predict, with 19–50% of patients experiencing further, albeit slow, deterioration on long-term follow-up. (Kjer 1959; Eliott et al. 1993; Votruba et al. 1998a, b; Puomila et al. 2005; Cohn et al. 2008)

d. Better overall visual prognosis compared to LHON (Kjer et al. 1996; Votruba et al. 1998a, b; Cohn et al. 2007)
i. A mean visual acuity of 6/24–6/36
ii. Results in significant visual impairment with about half of all affected individuals failing the driving standards and 13–46% registered as legally blind

e. Generalized dyschromatopsia: predominant color defect involving both the blue–yellow and red–green axes, with a minority of patients having pure tritanopia (<10%), which was once considered to be a pathognomonic feature of dominant optic atrophy (Berninger et al. 1991)

f. Central, centrocaecal, and paracentral scotomas are the most common field abnormalities with sparing of the periphery, findings consistent with the primary involvement of the papillomacular bundle in this condition

g. The optic disc pallor in DOA falls into two main categories (Kline and Glaser 1979; Hoyt 1980; Kjer 1959)
i. Diffuse pallor involving the entire neuroretinal rim in about half of all cases
ii. A temporal wedge in the remainder of cases

h. Other common optic disc findings (Votruba et al. 1998a, b, 2003; Fournier et al. 2001)
i. Saucerization (79%)

ii. Peripapillary atrophy (69%)
iii. A cup to disc ratio 0.5 (48%)
iv. A typical profile with bilateral symmetrical thinning around the optic disc, most pronounced in the temporal quadrant (circumpapillary retinal nerve fiber layer thickness using optical coherence tomography) (Ito et al. 2007; Kim and Hwang 2007)

i. Normal tension glaucoma: single nucleotide polymorphisms in intron 8 and exon 4 of the *OPA1* gene could increase the risk of normal (but not high) tension glaucoma in whites (Yu-Kai-Man et al. 2010).
j. Extraocular findings: *OPA1* gene may be responsible for a continuum of phenotypes, ranging from mild visual loss to very variable, sometimes severe, multisystemic involvement of the disease (Amati-Bonneau et al. 2008; Hudson et al. 2008).
k. Optic atrophy associated with multiple sclerosis–like disease in a patient carrying a new missense *OPA1* mutation (p.S646L) in the highly conserved dynamin domain (Vemy et al. 2008), suggesting a relationship between mitochondrial dysfunction and the central nervous system defect
l. Optic atrophy and deafness occurring in patients with a specific R445H mutation (Zeviani 2008) and other mutations
m. Multisystemic disorders associated with optic atrophy 1 mutations (autosomal dominant optic atrophy "plus") (ADOA "plus syndrome"): an optic atrophy associated with early onset in childhood, followed by chronic progressive external ophthalmoplegia, ataxia, sensorineural deafness, sensorimotor neuropathy, and myopathy in adult life

Diagnostic Investigations

1. LHON (Yu-Wai-Man et al. 2009)
   a. Tentative diagnosis of LHON usually be made on the following:
      i. Clinical grounds (especially if classical ophthalmological features are present)
      ii. A clear maternal history is elicited.
   b. Ophthalmoscopic findings (Huoponen 2001)
      i. Presymptomatic stage
         a) Peripapillary telangiectatica microangiopathy visible in the presymptomatic stage: the first sign of the disease (Nikoskelainen et al. 1982, 1983)
         b) Increased hyperemia, swelling of the optic disc, and arteriolar dilation at the end of the presymptomatic stage
      ii. Acute stage
         a) Visual loss
         b) Severe hyperemia, arteriolar dilation, disc swelling, telangiectatica angiopathy, and a glistening, whitish, opaque nerve fiber layer: hallmarks of this stage of the disease
         c) Decreased visual acuity and development of a relative centrocaecal scotomas can be minimal or even absent.
      iii. End stage
         a) Disappearance of microangiopathy
         b) Fading of retinal nerve fiber layer
         c) Large and absolute centrocaecal scotoma
   c. Molecular genetic testing on a blood DNA sample: remains the gold standard and will confirm that the patient harbors one of the three primary mtDNA LHON mutations, with implications for future genetic counseling
      i. Targeted mutation analysis
         a) Primary pathogenic LHON-causing mtDNA mutations
         b) Secondary LHON-causing mtDNA mutations
      ii. Sequence analysis and mutation scanning
   d. Biochemical findings associated with the primary mutations
      i. Variable Complex I defects: associated with all the primary mutations
      ii. A defect in respiratory chain function in LHON: first demonstrated in platelet mitochondria from a family that was subsequently shown to harbor the ND1/3460 mutations (Parker et al. 1989)
      iii. A marked reduction in the specific activity of Complex I associated with the ND1/3460 mutation: further detected in lymphoblasts (Majander et al. 1991; Brown et al. 2000),

leukocytes (Carelli et al. 1997), and fibroblasts (Cock et al. 1999)
   iv. ND4/11778 mutation: less severe reduction in Complex I function
   v. A reduction in respiration of NADH-linked substrates (Majander et al. 1991; Lodi et al. 2000)
   vi. Alteration in the affinity of Complex I for ubiquinone (Degli Esposti et al. 1994)
e. Electrophysiological studies, including pattern electroretinograms (PERGs) and visual evoked potentials (VEPs), if indicated, can be carried out to exclude retinal pathology and confirm optic nerve dysfunction (Sherman and Kleiner 1994).
f. An electrocardiogram is also recommended to exclude a preexcitation syndrome which has been documented in LHON, although such a finding is rare and does not require any intervention in the absence of cardiac symptoms (Nikoskelainen 1994; Riordan-Eva and Harding 1995).
g. Computed tomography (CT) and magnetic resonance imaging (MRI) scans are usually normal in LHON.

2. DOA (Votruba et al. 1998a, b; Delettre-Cribaillet et al. 2009)
   a. Clinical diagnosis: the majority of patients present in early to mid-childhood and the clinical diagnosis is generally reliable from 6 years of age and above, except in rare cases.
   b. Visual acuity
   c. Color vision
   d. Visual fields
   e. Assessment of extraocular muscles
   f. Hearing evaluation
   g. Electrophysiology
      i. Visual evoked potentials (VEPs): typically absent or delayed, indicating a conduction defect in the optic nerve
      ii. Pattern electoretinogram (PERG): an abnormal N95:P50 ratio with reduction in the amplitude of the N95 waveform (Holder et al. 1998), supporting a ganglion cell origin for the optic atrophy since the N95 component of the PERG, is thought to be specific for the retinal ganglion cell.
   h. Molecular genetic testing available clinically
      i. Sequence analysis of all exons of *OPA1*
      ii. Target mutation analysis for the Danish founder mutation
      iii. Sequence analysis of RNA RT-PCR amplification on *OPA1*
      iv. Deletion/duplication analysis

Genetic Counseling

1. Recurrence risk (Yu-Wai-Man and Chinnery 2008; Yu-Wai-Man et al. 2009)
   a. LHON
      i. Not possible to predict accurately whether or when LHON carriers will become affected
      ii. Two main predictive factors for visual failure:
         a) Gender: males: a 50% lifetime risk of blindness; females: only 10% lifetime risk of blindness
         b) Age: Most patients experience visual loss in their late teens and 20s. Probability of becoming affected decreases with age, being minimal once past the age of 50 years.
      iii. Once a primary LHON mutation has been identified in a proband, other maternally related family members can be offered molecular genetic testing to exclude the possibility of a de novo mutation, which is rare.
      iv. Since LHON shows strict maternal inheritance, male carriers can be reassured that none of their children will inherit the mtDNA mutation whereas female carriers will transmit the pathogenic mutation to all of their offspring.
      v. Since most mothers are homoplasmic, their children will only harbor the mutant species, but the situation is more complex for a heteroplasmic mother as she could transmit a higher or a lower level of the mutation to a particular offspring, which will impact on the latter's risk of visual failure.
      vi. Although the mutant level can be determined and there is evidence that a mutational threshold of ~60% in blood is necessary for disease expression, genetic counseling for these unaffected heteroplasmic carriers remains difficult.
      vii. For similar reasons, the prenatal genetic testing of heteroplasmic women with

amniocentesis or chorionic villus sampling (CVS) would be difficult to interpret.

viii. Patient's sib
  a) The recurrent risk depends on the genetic status of the mother.
  b) All sibs at risk of inheriting the mutation if the mother has the mtDNA mutation.

ix. Patient's offspring
  a) An affected or unaffected male with a primary LHON-causing mtDNA mutation cannot transmit the mutation to any of his offspring.
  b) An affected or unaffected female with a primary LHON-causing mtDNA mutation transmits the mutation to all of her offspring.
  c) An affected female with heteroplasmy may transmit a low level of mutant mtDNA to her offspring, confirming a low disease risk (Chinnery et al. 2001).

x. Other family members
  a) The recurrence risk depends on the genetic status of the proband's mother.
  b) If the proband's mother has an mtDNA mutation, her sibs and mother are also at risk.

b. DOA (Votruba et al. 1998a, b; Yoshida et al. 2006; Delettre-Cribaillet et al. 2009)

i. Despite DOA being an autosomal dominant Mendelian disorder with high penetrance (0.98) (Eiberg et al. 1994), genetic counseling for mutational carriers is difficult because of the pronounced inter- and intrafamilial heterogeneity and variability in the visual phenotype.

ii. A multidisciplinary approach to the diagnosis and management of these patients is helpful, involving both clinical ophthalmologists and geneticists, electrodiagnostic services, low vision specialists, and educational advisors.

iii. An apparently sporadic person who presents with nonprogressive optic atrophy and normal neuroimaging
  a) Important to examine all family members fully, as relatives may be only mildly affected
  b) Establish a disease pedigree and the mode of transmission.

iv. A person uncertain of his clinical status from a family known to be affected by dominant optic atrophy: needs to include color vision and electrophysiology in the full clinical assessment of the patient in order to be able to make a diagnosis

v. Patient with absence of a mutation: genetic counseling relies on conventional risk assessment.

vi. With the availability of molecular testing for *OPA1* becoming more accessible, an increasing number of individuals with pathogenic mutations are being identified who are otherwise visually unaffected.

vii. Patient with *OPA1* mutation
  a) Genetic counseling is difficult since clinical manifestation of the same mutation within a family can be remarkably variable.
  b) Dramatic psychological impact on the person involved with awareness of one's susceptibility to the disease without an actual possibility of intervention

viii. Patient's sib
  a) Risk depends on the genetic status of the parents.
  b) A 50% risk if a parent is affected
  c) Apparently low risk when the parents are found to be clinically unaffected on the basis of visual acuity study, color vision evaluation, fundus examination, VET, and PERG
  d) Possibilities of germline mosaicism in a parent or a de novo mutation in the proband exist if a disease-causing mutation cannot be detected in the DNA of either parent.

ix. Patient's offspring: a 50% risk of inheriting the mutation

2. Prenatal diagnosis

a. LHON

i. Prenatal diagnosis for pregnancies at increased risk: possible by amniocentesis or CVS

ii. MtDNA mutation in the mother must be identified before prenatal testing can be performed.

iii. Reasons for difficult accurate interpretation of a positive prenatal test:
   a) The mtDNA mutational load in amniocytes and chorionic villi is unlikely to correspond to that of other fetal or adult tissues because of mitotic segregation.
   b) The presence of the mtDNA mutation does not predict the occurrence, age of onset, severity, or rate of progression of this typically adult-onset disease.

b. DOA
   i. Prenatal diagnosis for pregnancies at an increased risk is possible by amniocentesis or CVS.
   ii. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

3. Management
   a. LHON
      i. Mainly supportive
         a) Provision of visual aids
         b) Registration with the relevant social services
      ii. ECG may reveal a preexcitation syndrome in both affected and unaffected LHON carriers.
   b. DOA
      i. Supportive
      ii. Treatment of decreased visual acuity

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Fig. 1 A 10-year-old boy was relatively healthy until last year when he suddenly started having trouble seeing and complained constant headache. He was noted to have painless visual failure, optic nerve atrophy in his left eye, and exophthalmos. He has also experienced minor tremors, muscle weakness, nausea, and movement disorder. Family history revealed similarly affected males in two generations on the maternal side of the family. Molecular genetic analysis detected an apparently homoplasmic m.11778G > A mutation. This mutation in *ND4* gene is commonly associated with Leber hereditary optic neuropathy (LHON). The result confirms the carrier/affected status of this boy for a mitochondrial DNA disorder

Möbius Syndrome

Möbius syndrome (MBS) is a rare congenital disorder characterized by complete or partial facial diplegia accompanied by other cranial nerve palsies and musculoskeletal anomalies.

Synonyms and Related Disorders

Mobius sequence

Genetics/Basic Defects

1. Multifactorial etiology
   a. The term "Möbius sequence" represents a pattern of multiple anomalies due to multiple etiologies, compared with the designation "syndrome" which implies a single cause.
   b. Usually a sporadic occurrence but familial descriptions have been rarely reported (Briegel 2006; Graziadio et al. 2010)
   c. Genetic heterogeneity
      i. Familial cases usually without associated anomalies
      ii. Low incidence of familial cases with associated anomalies such as limb defects and mental retardation
      iii. Autosomal dominant inheritance (Verzijl et al. 1999)
         a) Autosomal dominant Möbius syndrome has been linked to markers on 3q21-q22 in a large Dutch family (Kremer et al. 1996).
         b) A second gene for autosomal dominant Möbius syndrome is localized to chromosome 10q in a second large Dutch family.
      iv. Autosomal recessive inheritance
      v. X-linked recessive inheritance
   d. Four genetic loci for MBS have been described to date (Van Der Zwaag et al. 2002).
      i. MBS1 on chromosome 13q12.2-q13 (Ziter et al. 1977; Slee et al. 1991), based on the following observations:
         a) A reciprocal translocation of 13q12.2-q13 cosegregating with the disease in a three-generation MBS family
         b) An MBS patient with a deletion of chromosome 13q12.2
      ii. MBS2 on chromosome 3q21-q22 (Kremer et al. 1996)
      iii. MBS3 on chromosome 10q21.3-22.1 (Verzijl et al. 1999)
      iv. MBS4 on chromosome 1p22 (Donahue et al. 1993; Nishikawa et al. 1997), based on
         a) A t(1;11)(p22;p13) in a patient with Möbius syndrome
         b) A t(1;2)(p22.3;q21.1) in a patient with Möbius-like syndrome
   e. *HOXA1* mutations: not a common cause of sporadic Möbius syndrome in the general population (Rankin et al. 2010)
      i. The *HOXA1*-related syndromes result from autosomal recessive truncating mutations in the homeobox transcription factor, *HOXA1*.

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ii. Limited horizontal gaze and sensorineural deafness are the most common features.
iii. Affected individuals can also have facial weakness, mental retardation, autism, motor disabilities, central hypoventilation, and carotid artery and/or conotruncal heart defects.
iv. Möbius syndrome is also phenotypically heterogeneous, with minimal diagnostic criteria of nonprogressive facial weakness and impaired ocular abduction; mental retardation, autism, motor disabilities, additional eye movements restrictions, hearing loss, hypoventilation, and craniofacial, lingual, and limb abnormalities also occur.

f. Chromosome abnormalities (Verzijl et al. 1999)
g. Ischemia: vascular disruption in the subclavian artery territory
h. Teratogens
i. Thalidomide
ii. Alcohol
iii. Benzodiazepines
iv. Cocaine
v. Ergotamine
vi. Infections
vii. Hyperthermia
viii. Trauma
ix. Misoprostol (a synthetic prostaglandin analogue used in the therapy of upper gastrointestinal ulceration or self-administered by the mothers in Brazil as an abortifacient) (Strömland et al. 2002)

2. Pathogenesis (Van Der Zwaag et al. 2002; Graziadio et al. 2010)
a. A primary metameric defect in the brain stem nuclei in the region of the tegmentum
b. An ischemic process resulting from an interruption of the vascular supply of the brain stem and other structures during early fetal development
3. An etiopathologic classification (Pedraza et al. 2000)
a. Type I (central lesion in the brain stem nuclei due to congenital origin)
b. Type II (primary peripheral nerve involvement)
c. Type III (central lesion in the brain stem nuclei due to an anoxic-infectious cause)
d. Type IV (wasting of skeletal muscle tissue due to myopathic cause)

Clinical Features

1. Congenital onset
2. Complete or partial facial diplegia (essential for the diagnosis of Möbius syndrome), often accompanied by other cranial nerve palsies
a. Signs and symptoms
i. Incomplete eyelid closure during sleep
ii. Drooling
iii. Difficulty in sucking
iv. Inability to smile
v. Lack of facial movement when crying (masklike facies)
vi. Asymmetry of the angles of the mouth
vii. Indistinct speech secondary to the inability to close the lips leading to labial sounds
b. Involved cranial nerves (Kumar 1990)
i. Facial nerve (VII) palsy (all cases), resulting in masklike facies and flattened facial expression
ii. Abducens nerve (VI) palsy (75%), less commonly oculomotor (III) and trochlear (IV) nerve palsies, resulting in marked internal strabismus, lateral gaze paralysis, and ophthalmoplegia
iii. Hypoglossal nerve (XII) palsy (25%), leading to paralysis, hypoplasia, and atrophy of the tongue
iv. Paresis of cranial nerves V (trigeminal), IX (glossopharyngeal), and X (vagus), leading to bulbar weakness (swallowing and speech difficulties due to velopharyngeal insufficiency)
3. Involvement of cerebellum, hypothalamus, and pituitary gland
4. Oculofacial abnormalities (Strömland et al. 2002)
a. Masklike facial appearance: may create profound difficulties in social interactions with other people, especially strangers who are unfamiliar with the syndrome
b. Epicanthal folds
c. Ptosis
d. Strabismus
e. Nystagmus
f. Micrognathia
g. Tongue abnormalities
i. A common anomaly

   ii. A small asymmetric tongue with irregular atrophic areas: characteristic of Möbius syndrome
   iii. Impaired motility and fasciculations
  h. At risk for caries and periodontal disease
  i. Impaired speech
   i. A severe and disabling condition
   ii. Factors affecting speech development
    a) Cognitive and language skills
    b) Hearing
    c) Communication ability
    d) Orofacial anatomy
    e) Oral motor function
   iii. Dysarthria caused by cranial nerve dysfunction, worsened by orofacial anomalies, mental retardation, and autism
5. Frequent occurrence of limb malformations
  a. Reduction malformation of limbs
  b. Hypoplasia to aplasia of digits
  c. Brachydactyly
  d. Syndactyly
  e. Ectrodactyly
  f. Talipes deformities (club foot)
  g. Clinodactyly
  h. Polydactyly
  i. Joint contractures
6. Other musculoskeletal features
  a. Rib defects
  b. Klippel–Feil anomaly
  c. Aplasia of muscles
7. Mental retardation (10%)
8. Autistic behavior (30–40%)
9. Association with other anomalies or syndromes
  a. Poland syndrome
   i. Hypoplasia/aplasia of pectoralis major muscle
   ii. Generally unilateral
   iii. Associated with mammary hypoplasia of the same side
   iv. Poland syndrome, Möbius syndrome, and Möbius–Poland syndrome may be a spectrum of the same condition.
  b. Hyoglossia-hypodactyly
  c. Arthrogryposis multiplex congenita
  d. Dextrocardia
  e. Robin syndrome
  f. Corey–Fineman–Ziter syndrome (congenital nonprogressive myopathy with Möbius and Robin sequence)
  g. Kallmann syndrome (association with anosmia and hypogonadotropic hypogonadism)
10. Several similar syndromes (Strömland et al. 2002)
  a. Oromandibular-limb hypogenesis syndrome
   i. Characteristic features
    a) Micrognathia
    b) Cranial nerve palsies
    c) Limb anomalies
    d) Sometimes combined with aplasia of the pectoral muscle (Poland anomaly)
   ii. Entities included:
    a) Möbius syndrome
    b) Hanhart syndrome
    c) Hypoglossia-hypodactyly (aglossia/adactyly)
    d) Glossopalatinus ankylosis
  b. Terminal transverse defects with orofacial malformations
   i. Orofacial features
    a) Micrognathia
    b) Cleft palate
    c) Tongue anomalies
    d) Ear anomalies
    e) Dental anomalies
   ii. Limb malformations
    a) Syndactyly
    b) Clubfeet
    c) Toe deformities
    d) Symbrachydactyly
    e) Absent digits (ectrodactyly)
    f) Amputation-type defects of the limbs

Diagnostic Investigations

1. CT of the head: normal in most patients (Pedraza et al. 2000)
  a. Medial deviation of the eyes
  b. Hypoplastic or dysplastic brain stem
  c. Hypoplastic cerebellum consistent with Dandy–Walker variant malformation
  d. Bilateral calcifications adjacent to the fourth ventricle floor at the level of the VIth cranial nerve nuclei
2. Autopsies in patients with normal CT studies
  a. Focal necrosis and calcifications
  b. Hypoplasia to agenesis of the respective cranial nerve nuclei

3. MRI of the brain
   a. Calcification in the pons within the abducens nuclei
   b. Hypoplasia of the brain stem
   c. Hypoplasia of the cerebellum
4. Neurophysiological studies: may be helpful in locating the site of the lesion
   a. Abnormal nerve conduction studies
   b. Electromyography (EMG) of facial muscles (Jaradeh et al. 1996):
      i. Reveals multifocal chronic neurogenic changes
      ii. Indicates a brain stem process predominantly affecting the facial nuclei and their internuclear connections rather than a supranuclear or muscular site of involvement
   c. Abnormal brain stem evoked potential

Genetic Counseling

1. Recurrence risk
   a. Lower recurrence risk (2%) for Möbius syndrome with congenital sixth and seventh nerve paralysis with skeletal defects (MacDermot et al. 1991)
   b. Higher recurrence risk (25–30%) for Möbius syndrome with isolated facial palsy, deafness, ophthalmoplegia, and digital contractures without skeletal defects (MacDermot et al. 1991)
   c. Autosomal recessive inheritance
      i. Patient's sib: 25%
      ii. Patient's offspring: not increased unless the spouse is a carrier
   d. Autosomal dominant inheritance
      i. Patient's sib: 50% if a parent is affected; otherwise not increased
      ii. Patient's offspring: 50%
   e. X-linked recessive inheritance
      i. Patient's sib: 50% affected in the brothers if the mother is a carrier; otherwise not increased
      ii. Patient's offspring: 50% carrier risk in the daughters
2. Prenatal diagnosis possible in the Möbius–Poland spectrum
3. Management
   a. Supportive care
   b. Intervention programs
      i. Physical therapy useful for congenital orthopedic problems or postoperative orthopedic intervention
      ii. Occupational therapy to help activities of daily living, especially in patients with absent hands or digits
      iii. Speech therapy for patients affected by severe facial nerve paralysis or lower cranial nerve deficit
   c. Dental hygiene
   d. Treat corneal ulcerations or abrasions secondary to exposure keratitis and conjunctivitis secondary to incomplete eyelid closure
   e. Splints and prostheses for congenital limb anomalies
   f. Surgical care
      i. Clubfoot
      ii. Tracheotomy to support the airway and permit tracheobronchial clearing when airway functions are compromised
      iii. Feeding gastrostomy tube required in some cases
      iv. Ocular surgical procedures in some cases

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Fig. 1 (**a**, **b**) A child with Möbius syndrome showing masklike facies, epicanthal folds, strabismus, and facial palsy

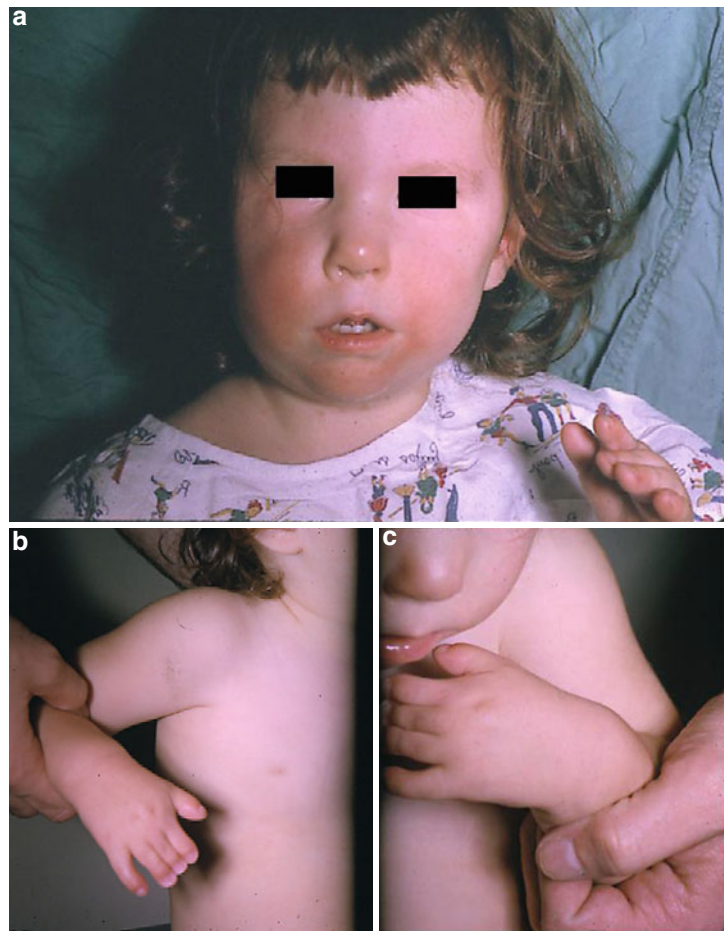

Fig. 2 (**a**–**c**) A child with Möbius syndrome showing masklike facies, epicanthal folds, strabismus, and limb defect

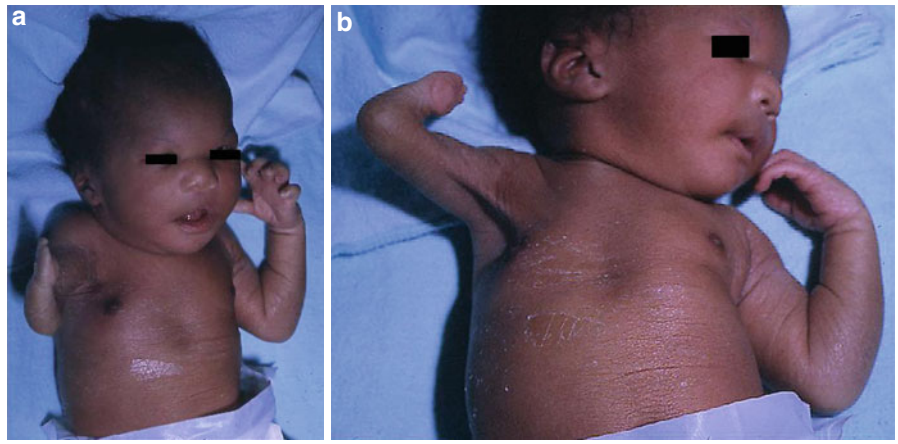

Fig. 3 (**a**, **b**) A child with Möbius–Poland syndrome showing masklike facies, strabismus, and ptosis, associated with right arm defect and absence of right pectoralis major muscle

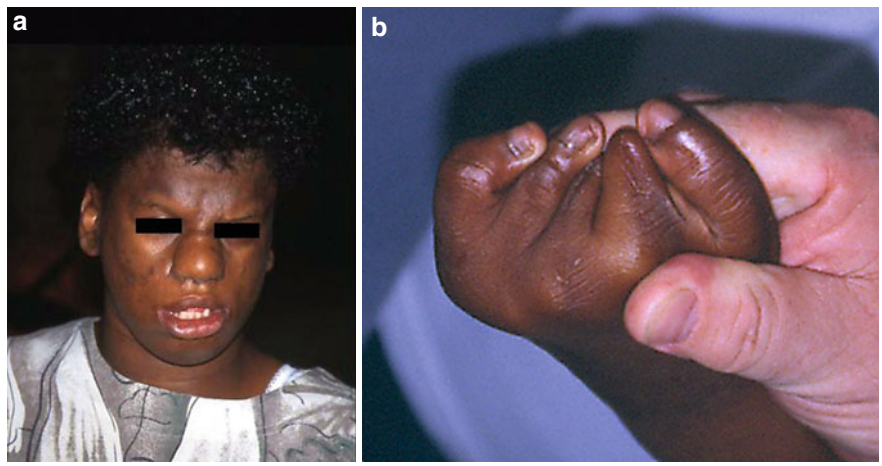

Fig. 4 (**a**, **b**) An adult with Möbius syndrome showing masklike facies, ptosis, strabismus, and digital anomaly

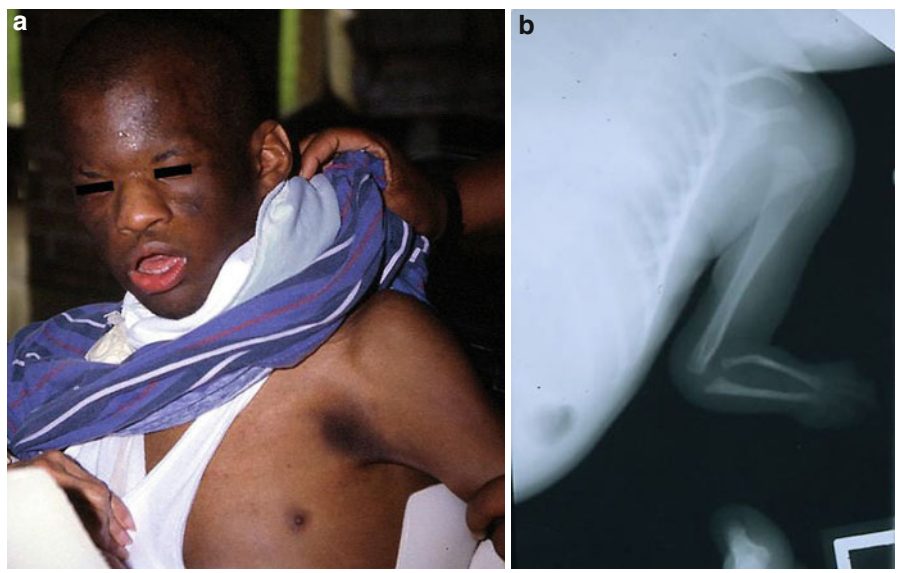

Fig. 5 (**a**, **b**) An adult with Möbius–Poland syndrome showing masklike facies, ptosis, absence of left pectoralis major muscle and limb defect, which were illustrated in the patient's earlier radiographs

Fig. 6 (**a**–**c**) Three children with Poland anomaly showing unilateral absence of pectoralis major muscle associated with ipsilateral limb defect

Mowat–Wilson Syndrome

In 1998, Mowat et al. described a new syndrome, now known as Mowat–Wilson syndrome (MWS), consisting of Hirschsprung disease or severe constipation, microcephaly, mental retardation, and characteristic facial features, including hypertelorism, medially flared and broad eyebrows, prominent columella, pointed chin, and uplifted earlobes.

The prevalence of MWS is currently unknown. However, it seems probable that the syndrome is underdiagnosed, particularly in patients without Hirschsprung disease. Approximately 171 patients with *ZEB2* mutations, deletions or cytogenetic abnormalities have been reported and over 100 mutations have been described.

Synonyms and Related Disorders

Hirschsprung disease-mental retardation syndrome; Microcephaly, mental retardation, and distinct facial features with or without Hirschsprung disease

Genetics/Basic Defects

1. Caused by heterozygous mutations and deletions in the gene ZEB2 on chromosome 2 (also known as ZFHX1B or SIP-1) in approximately 81% of cases
2. Typically resulting from a de novo dominant mutation
3. Cytogenetic deletions or translocations of the chromosome 2q21-q23 region were found in several patients

Clinical Features

1. Typical facial features
   a. Seen in all individuals with this combination of characteristics were found to have mutations or deletions in the *ZEB2* gene (Zweier et al. 2005)
      i. Ocular hypertelorism
      ii. Medially flared and broad eyebrows
      iii. Prominent columella
      iv. Prominent or pointed chin
      v. Open-mouthed expression
      vi. Uplifted earlobes with a central depression
         a) Earlobes described as resembling "orechietta pasta" or "red blood corpuscles."
         b) Ear configuration not changing significantly with age with the exception of the central depression, which is less obvious in adults.
   b. Additional suggestive facial features (Mowat et al. 2003; Adam et al. 2006)
      i. Telecanthus
      ii. Deep-set eyes
      iii. Broad nasal bridge with prominent and rounded nasal tip
      iv. Full or everted lower lip
      v. Posteriorly rotated ears
   c. Natural history of facial phenotype (Wilson et al. 2003; Horn et al. 2004)
      i. More pronounced facial phenotype with age, making diagnosis easier in older individuals
      ii. Lengthening of the nasal tip and becoming more depressed

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iii. More pronounced columella, leading to appearance of a short philtrum
iv. Elongation of the face
v. More prominent jaw
vi. Eyebrows becoming heavier with an increased medial flare

2. Spectrum of structural anomalies
   a. Gastrointestinal anomalies
      i. Hirschsprung disease
         a) A strong cross-reference marker when present
         b) Not a constant finding
         c) Present in approximately 57–63% of cases
      ii. Pyloric stenosis
   b. Genitourinary anomalies, particularly hypospadias in males
   c. Congenital heart defects, including abnormalities of the pulmonary arteries and/or valves
   d. Agenesis or hypogenesis of the corpus callosum
   e. Ophthalmologic anomalies, including microphthalmia and Axenfeld anomaly
   f. Teeth anomalies
      i. Widely spaced teeth
      ii. Dental crowding
      iii. "Malpositioned" teeth
      iv. Delayed tooth eruption
3. Other features
   a. Mental retardation, typically in the moderate to severe range, with severe speech impairment but relative preservation of receptive language
   b. Seizures
   c. Growth retardation (short stature) with microcephaly
   d. Chronic constipation in those without Hirschsprung disease

Diagnostic Investigations

1. Cytogenetic testing
   a. Chromosomal rearrangements that disrupt the *ZEB2* gene cause MWS in approximately 2% of cases
   b. FISH analysis. Large deletions encompassing all or part of the *ZEB2* gene detectable by FISH in approximately 15% of cases
2. Molecular genetic testing
   a. *ZEB2* mutation detection rate by sequencing/FISH/QPCR for individuals with the "typical MWS" facial phenotype approaches 100%
   b. No evidence of locus heterogeneity for MWS
3. Hirschsprung disease evaluation
4. MRI imaging of the brain for CNS anomalies
5. Echocardiograph for congenital heart disease
6. Ophthalmologic evaluation for eye anomalies
7. Renal ultrasound for renal anomalies
8. EEG for seizures

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. De novo mutation: low recurrence risk
      ii. Possibility of constitutional and/or germline mosaicism: low recurrence risk but greater than that of the general population (1–2%)
         a) Possibility of germline mosaicism suggested in two families with two and three affected sibs, respectively
         b) Low-level paternal mosaicism observed in a family with two affected sibs has been reported
   b. Patient's offspring: individuals with MWS and an unbalanced chromosome rearrangement unlikely to reproduce
2. Prenatal diagnosis
   a. Prenatal diagnosis of a pregnancy at theoretically increased risk because of constitutional and/or germline mosaicism in a clinically unaffected parent.
      i. Disease-causing allele of an affected family member being identified prior to prenatal diagnosis
      ii. Molecular genetic analysis on DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling
   b. Prenatal diagnosis of a pregnancy at increased risk because of parental balanced structural rearrangement: possible by chromosome analysis of fetal cells obtained by amniocentesis or chorionic villus sampling.
   c. Preimplantation genetic diagnosis: available for families at increased risk because of parental

mosaicism in which the disease-causing mutations have been identified.

3. Management
   a. Mostly supportive including seizure control and developmental intervention
   b. Specific management for structural anomalies, including Hirschsprung disease

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Fig. 1 (**a**–**d**) A three-and-a-half-year-old boy was noted to have Mowat–Wilson syndrome. Note the unusual facies (hypertelorism, telecanthus, strabismus, wide prominent nasal bridge, an unusual nose with a rounded tip and prominent columella, a prominent chin, and unusual ears with fleshy uplifted ear lobes), long tapering fingers, and an unusual stereotypic use of his hands in which he moves his fingers in front of his face and regards them. He is severely developmentally delayed and has hypotonia. Chromosome microarray analysis revealed a loss in copy number in the long arm of chromosome 2, detected with two clones, spanning at least 100 kb (including the ZFHX1B gene), and confirmed by FISH analysis. Deletions in this region have been associated with Mowat–Wilson syndrome

Mucopolysaccharidosis I (MPS I)

Mucopolysaccharidosis I consists of three clinical entities with varying degrees of clinical manifestations, all due to the same lysosomal enzyme deficiency, α-L-iduronidase. Hurler (MPS I-H) and Scheie (MPS I-S) syndromes represent phenotypes at the two ends of the clinical spectrum; the Hurler–Scheie syndrome (MPS I-H/S) represents a phenotype of intermediate clinical severity. In most instances, the subtype of MPS I can only be assigned on the basis of clinical criteria, including the rate of progression of symptoms. The incidences for MPS I-H, MPS I-H/S, and MPS I-S are estimated to be 1/76,000–1/144,000, 1/280,000, and 1/840,000–1/1,300,000 live births, respectively.

Synonyms and Related Disorders

α-L-Iduronidase deficiency; Hurler (MPS I-H); Hurler–Scheie (MPS I-H/S); Scheie (MPS I-S) Syndromes

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. The *IDUA* gene
   a. Localized to chromosome 4p16.3, close to the Huntington disease gene
   b. Spans 19 kb including 14 exons
3. Caused by mutations in the α-L-iduronidase (*IDUA*) gene
   a. Two major alleles (W402X and Q70X) and a minor allele (P533R) accounting for over half the MPS I alleles in the Caucasian population.
   b. No functional enzymes produced by above-mentioned alleles, giving rise to the severe form of α-L-iduronidase deficiency (MPS I-H).
   c. Limited mutations expected to cause the attenuated clinical phenotypes of MPS I-S or MPS I-H/S.
   d. One of a mutation resulting in Scheie syndrome is a base substitution in intron 7 that creates a new splice site and produces a frameshift. Since the old splice site is not obliterated, some normal enzymes still can be made to overcome the worst features of MPS I.
   e. Most other alleles that lead to MPS I-S or MPS I-H/S carry missense mutations.
   f. In the Japanese population studied, MPS I-H/S results from compound heterozygosity of two mutations (704ins5 and R89Q), which, in homozygous form, would give rise to MPS I-H and MPS I-S, respectively.
4. Genotype-phenotype correlations
   a. General principle
      i. Any combination of two severe alleles leads to severe MPS I. A severe allele is one that produces the severe phenotype in either the homozygous state or compound heterozygous state.
      ii. Intermediate and mild MPS I: usually associated with one severe allele and another allele that permits production of some residual enzyme activity.
   b. Alleles associated with severe phenotype
      i. Two common severe mutations (W402X and Q70X) always confer a severe phenotype whether present in a homozygous state or in a compound heterozygous state.

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ii. Additional mutations (474-2a-g, A327P, P533R, A75T, L218P).
c. Alleles associated with mild phenotype
i. 678-7a-g
ii. R89Q
5. Pathophysiology
a. Underlying molecular defect leads to a loss or marked reduction in α-L-iduronidase (*IDUA*), a lysosomal enzyme involved in the degradation of glycosaminoglycans heparan sulfate and dermatan sulfate.
b. Because of the enzyme deficiency, excessive accumulation of acid mucopolysaccharides (glycosaminoglycans) in the tissue occurs, leading to wide effect on various systems and remarkable changes in the morphogenesis.

Clinical Features

1. Hurler syndrome (MPS I-H)
a. General clinical characteristics
i. The prototype of MPS representing the severe end of clinical spectrum
ii. A progressive disorder with multiple organ and tissue involvement, leading to death in childhood
iii. Normal phenotype at birth and in early infancy but deteriorates progressively afterward
iv. Diagnosis usually made between 4 and 18 months of age
v. Short stature (linear growth stops at 2–3 years of age)
vi. Developmental delay by age 12–24 months, with a maximum functional age at the level of 2–4 years, followed by progressive mental deterioration
b. Coarse facial features (one of the earliest signs)
i. Ocular hypertelorism
ii. Prominent eyes
iii. Bushy eyebrows
iv. Depressed nasal bridge
v. Wide nostrils
vi. Large and thickened lips
vii. Large tongue
viii. Hypertrophy of the gum and the bony alveolar ridge
c. Other craniofacial features
i. A large scaphocephalic head with frontal bossing.
ii. Communicating hydrocephalus common after age 2–3 years. Shunting procedures may be beneficial for relieving increased intracranial pressure for some children.
iii. Noisy breathing with persistent nasal discharge (chronic rhinorrhea).
iv. Upper respiratory and ear infections.
d. Ophthalmologic features
i. Progressive clouding of the cornea (the hallmark of the syndrome) beginning at the first year of life, leading to impaired vision
ii. Open-angle glaucoma
iii. Retinal degeneration resulting in decreased peripheral vision
iv. Night blindness
e. Auditory features
i. Frequent sensorineural or mixed deafness
ii. Contributing factors:
a) Frequent middle ear infection from Eustachian tube dysfunction, caused by storage of glycosaminoglycans within the oropharynx
b) Dysostosis of the ossicles of the middle ear
c) Scarring of the tympanic membrane
d) Damage to the eighth nerve
f. Cardiovascular features
i. Cardiac valvular disease resulting from storage of mucopolysaccharide in the mitral, aortic, tricuspid, or pulmonary valves, leading to congestive heart failure.
ii. Thickened coronary artery valves, leading to angina pectoris and myocardial infarction.
iii. Possible fatal cardiomyopathy as a presenting feature for some MPS I infants less than 1 year old. Endocardial fibroelastosis has been noted postmortem in these patients.
iv. Aortic stenosis and uncontrolled hypertension (Taylor et al. 1991; Eakins and Kan 2010): Although uncommon, aortic stenosis should be included in the differential diagnoses in children with Hurler syndrome and poorly controlled hypertension.
g. Gastrointestinal features
i. Protuberant abdomen
ii. Progressive hepatosplenomegaly
h. Skeletal abnormalities: dysostosis multiplex
i. Short neck

ii. Characteristic kyphoscoliosis when on attempt to sit
iii. Ultimate frank gibbus deformity
iv. Stiff joints with limited mobility
v. Claw hands (flexed stubby fingers and broad hands)

i. Connective tissue abnormalities
i. Inguinal and umbilical hernias: common findings and usually present at birth
ii. Thick skin

j. Prognosis
i. Bedridden before the end of the juvenile period
ii. Early demise prior to 10 years of age
iii. Usual causes of death
a) Obstructive airway disease
b) Respiratory infection
c) Cardiac complications

2. Scheie syndrome (MPS I-S)
a. The mildest form of MPS I
b. Normal stature
c. Normal intelligence
d. Onset of significant signs usually after 5 years
e. Diagnosis commonly made between 10 and 20 years of age
f. Coarse facial features
g. Deafness in some patients
h. Joint stiffness
i. Claw hands
ii. Stiff painful foot
i. Carpal tunnel syndrome
j. Pes cavus
k. Genu valgum
l. Ocular manifestations
i. Corneal clouding
ii. Glaucoma
iii. Retinal degeneration
m. Aortic valvular disease (stenosis and regurgitation due to mucopolysaccharide deposits in the valves and chordae tendineae)
n. Obstructive airway disease with sleep apnea in some patients
o. Mild hepatosplenomegaly
p. Mild dysostosis multiplex
q. Less common pachymeningitis cervicalis (compression of the cervical cord by thickened dura) than MPS I-H/S
r. Potential normal life span

3. Hurler–Scheie compound (MPS I-H/S)
a. Clinical phenotype intermediate between Hurler and Scheie syndromes
b. Progressive somatic involvement, including dysostosis multiplex, with little or no intellectual dysfunction
c. Age of onset: usually between 3 and 8 years
d. Survival to adulthood: common
e. Deafness
f. Craniofacial features
i. Coarse facial features: less obvious
ii. Micrognathia in some patients
iii. Broad mouth
iv. Square jaw
v. Short neck
g. Ophthalmologic features
i. Corneal clouding in all patients
ii. Glaucoma
iii. Retinal degeneration
iv. Optic atrophy
h. Valvular heart disease (mitral valve insufficiency) developing by the early to mid-teens
i. Skeletal features
i. Short stature
ii. Small thorax
iii. Severe joint involvement (stiffness)
iv. Kyphoscoliosis
v. Back pain
vi. Characteristic claw hand deformity
vii. Carpal tunnel syndrome
j. Gastrointestinal features
i. Varying degrees of hepatomegaly
ii. Hernias
k. Pachymeningitis cervicalis (compression of the cervical cord due to mucopolysaccharide accumulation in the dura)
l. Communicating hydrocephalus uncommon in patients who have normal intelligence
m. Spondylolisthesis of the lower spine, leading to spinal cord compression
n. Causes of death (around teens and 20s)
i. Upper airway obstruction
ii. Cardiac involvement

Diagnostic Investigations

1. Developmental assessment
2. Ophthalmologic examination

3. ECG and echocardiography for cardiac status
4. Cranial ultrasound for hydrocephalus
5. Skeletal survey
   a. Dysostosis multiplex
   b. Skull
      i. Large, thickened calvarium
      ii. Premature closure of lambdoidal and sagittal sutures
      iii. Shallow orbits
      iv. Enlarged J-shaped sella
      v. Abnormally spaced teeth with dentigerous cysts
   c. Ribs
      i. Oar-shaped, narrowed at the vertebral ends
      ii. Flat/broad at the sternal ends
   d. Vertebra
      i. Beaked anteriorly (anterior hypoplasia) of lumbar vertebrae with kyphosis (an early sign)
      ii. Scalloped posteriorly
      iii. Thoracolumbar gibbus, resulting from anterior wedging of the vertebrae
      iv. Hypoplasia of the odontoid, leading to atlantoaxial subluxation
   e. Pelvis
      i. Poorly formed pelvis
      ii. Small femoral heads
      iii. Coxa valga
   f. Long bones
      i. Widened diaphysis of the long bones
      ii. Lack of normal modeling and tabulation
      iii. Irregular metaphysis
      iv. Poorly developed epiphyseal centers
      v. Distal ends of the radius and ulna angulate toward each other
      vi. Claw hands
      vii. Thickened and bullet-shaped phalanges
      viii. Coarsening of the trabeculae of the phalanges and metacarpals
      ix. Proximal narrowing of the metacarpals
      x. Marked irregularity and retarded ossification of the carpal bones
   g. Other bones
      i. Short, thickened, and irregular clavicles
      ii. Shortened and trapezoid-shaped phalanges with widened diaphyses
6. Biochemical/molecular studies for MPS I-H, MPS I-HS, and MPS I-S
   a. Excessive urinary excretion of glycosaminoglycans (dermatan and heparan sulfates): a useful preliminary test
   b. Metachromatic staining of fibroblasts and leukocyte inclusions (nonspecific lab findings)
   c. Enzyme assay: deficient α-L-iduronidase in WBC, serum, cultured fibroblast, and CSF
   d. Accumulation of glycosaminoglycans in cultured fibroblasts correctable by uptake of α-L-iduronidase
   e. Mutation analysis or sequence analysis of *IUDA* gene: possible to identify both *IDUA* mutations in 95% of patients with MPS I
   f. Characterization of gene mutation: worthwhile for phenotype prediction and genetic counseling
7. Carrier testing
   a. Measurement of α-L-iduronidase enzyme activity: not a reliable method, requiring testing of obligatory carriers within the family first to determine if their levels of IDUA enzyme activity can be distinguishable from the normal
   b. Molecular genetic testing of *IUDA* to identify carriers among at-risk family members when both mutation alleles have been identified in an affected family member

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25% chance of being affected
   b. Patient's offspring:
      i. MPS I-S: not increased unless the spouse is a carrier
      ii. MPS I-H and MPS I-H/S: not surviving to reproductive age
2. Prenatal diagnosis from samples of CVS, amniocentesis, and fetal blood
   a. Enzyme assays (deficient α-L-iduronidase) and increased level of ^{35}S-sulfate incorporation measured in cultured cells obtained from amniocentesis or CVS for pregnancy at risk
   b. Mutation analysis of the *IDUA* gene in fetal DNA extracted from cells obtained by CVS or amniocentesis if both mutant *IDUA* alleles have been identified in a previously affected sib or in the parents of the at-risk fetus
3. Preimplantation genetic diagnosis (PGD) for at-risk pregnancies: requires prior identification of both *IDUA* disease-causing mutations in the family

4. Management (Clarke and Heppner 2011)
   a. Supportive care
      i. Early infant stimulation programs
      ii. Eye care: corneal transplantation successful but donor grafts eventually becoming cloudy
      iii. Range of motion exercises to preserve joint function
      iv. Physical therapy
   b. Orthopedic surgery (Peters et al. 1998)
      i. Surgical decompression of the median nerve for carpal tunnel syndrome resulting in various restoration of motor hand activity
      ii. Trigger digits
      iii. Genu valgum
      iv. Kyphoscoliosis
      v. Acetabular dysplasia
      vi. Atlantooccipital stabilization
   c. Ventriculoperitoneal shunting for hydrocephalus
      i. Generally palliative
      ii. May improve quality of life
   d. Tracheotomy or high-pressure continuous positive airway pressure with supplemental oxygen
   e. Tonsillectomy and adenoidectomy to correct Eustachian tube dysfunction and to decrease upper airway obstruction
   f. Cardiovascular care
      i. Bacterial endocarditis prophylaxis
      ii. Valve replacement surgery
   g. Surgical repair of inguinal hernias
   h. Early surgical intervention to prevent severe complications from progressive compression of the spinal cord
   i. Major anesthetic risks exhibited by patients with MPS I
      i. Avoid hyperextension of the neck since dysostosis multiplex can lead to instability of the spine including the atlantoaxial joint
      ii. Difficulty in induction of anesthesia due to inability to maintain an adequate airway
      iii. Require fiberoptic laryngoscopy for intubation
      iv. Slow recovery from anesthesia
      v. Common postoperative airway obstruction
   j. Allogenic bone marrow transplantation from an unaffected, HLA-compatible donor
      i. Beneficial effect: replacement of deficient macrophages by marrow-derived donor macrophages to provide ongoing source of normal enzyme capable of gaining access to the various sites of storage.
      ii. Slows the course of cognitive decline if the therapy starts before the developmental delay is evident.
      iii. Improves survival, reducing facial coarseness, hepatosplenomegaly, hearing, and normal cardiac function.
      iv. Skeletal manifestations and corneal clouding continue to progress despite successful transplantation. Surgeries will be required for the persistent orthopedic problems.
      v. Significantly limited by the availability of donors. The immunosuppressive therapy for the prevention of rejection carries significant toxicity.
      vi. The procedure of the transplantation carries a high risk of morbidity and mortality. Failure to achieve stable engraftment and development of graft-versus-host disease are significant barriers to successful bone marrow transplantation for many children.
      vii. Hematopoietic stem cell transplantation: the treatment of choice for a child with Hurler syndrome who is younger than 2 years of age and has minimal or no central nervous system disease (Muenzer 2004).
   k. Cord blood transplantation (Staba et al. 2004)
      i. Use cord blood transplants from partially HLA-matched, unrelated donors
      ii. Donors readily available
      iii. An excellent source of stem cells for transplantation
      iv. Sustained engraftment can be achieved without total-body irradiation in young children.
      v. Low incidence for acute graft-versus-host disease (GVHD)
      vi. Absence of extensive chronic GVHD
      vii. As effective as bone marrow transplantation
   l. Enzyme replacement therapy (ERT)
      i. An etiology-specific treatment that seeks to address the underlying pathophysiology of MPS I by delivering sufficient IDUA activity to reverse and prevent glycosaminoglycans accumulation (Wraith et al. 2004)
      ii. Effectiveness depending on the ability of recombinant enzymes injected intravenously to enter cells and localize to the lysosome, the appropriate intracellular site

iii. Use of recombinant human α-L-iduronidase (laronidase: Aldurazyme)
   a) Aldurazyme®: currently licensed in the USA, Europe, and Canada for use in treating non-CNS manifestations of MPS I. The current dose regime involves premedication with an anti-inflammatory and antihistamine drugs and intravenous weekly infusion of 100 U/kg of Aldurazyme® over 4 h (Clarke and Heppner 2011).
   b) Significant reduction in liver size.
   c) Increase in height and weight.
   d) Decrease in joint restriction.
   e) Improvement in breathing (respiratory function) and sleep apnea.
   f) Decreased glycosaminoglycan storage.
   g) Improvements in cardiopulmonary function, airway obstruction and joint mobility in Hurler–Scheie syndrome (nonneuronopathic MPS I) (Bijarnia et al. 2009).
   h) Recommended for patients with milder or attenuated forms of MPS I. Infusions of recombinant enzyme are a safer alternative for treating the somatic disease and improving the quality of life of such patients. Intravenously administered enzyme is not expected to cross the blood–brain barrier and affect central nervous system disease (Muenzer 2004).

m. Hematopoietic stem cell transplantation (HSCT) (Bijarnia et al. 2009): Treatment of choice for children <2 years of age with MPS IH who have minimal or no central nervous disease

n. Combination of ERT followed by HSCT in neuronopathic Hurler syndrome
   i. Corrects the enzyme deficiency until endogenous enzyme production is established
   ii. Reverses airway obstruction and cardiovascular complications thus reducing mortality and morbidity at the time of transplant

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Fig. 1 (**a**, **b**) A child with Hurler syndrome showing a large head with frontal bossing, coarse facial features, ocular hypertelorism, cloudy (steamy) cornea, depressed nasal bridge, large tongue, short neck, protuberant abdomen, umbilical hernia, stiff joints, and claw hands

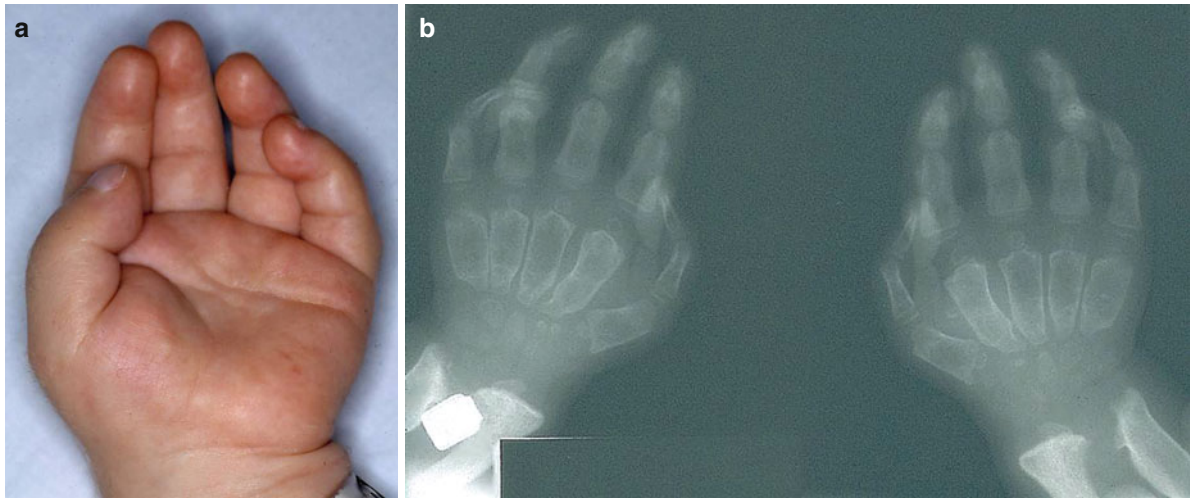

Fig. 2 (**a**, **b**) Claw hand. The radiographs show thick bullet-shaped phalanges, proximal narrowing of the metacarpals, poorly ossified carpal bones, and angulating toward each other of the distal ends of the radius and the ulnar

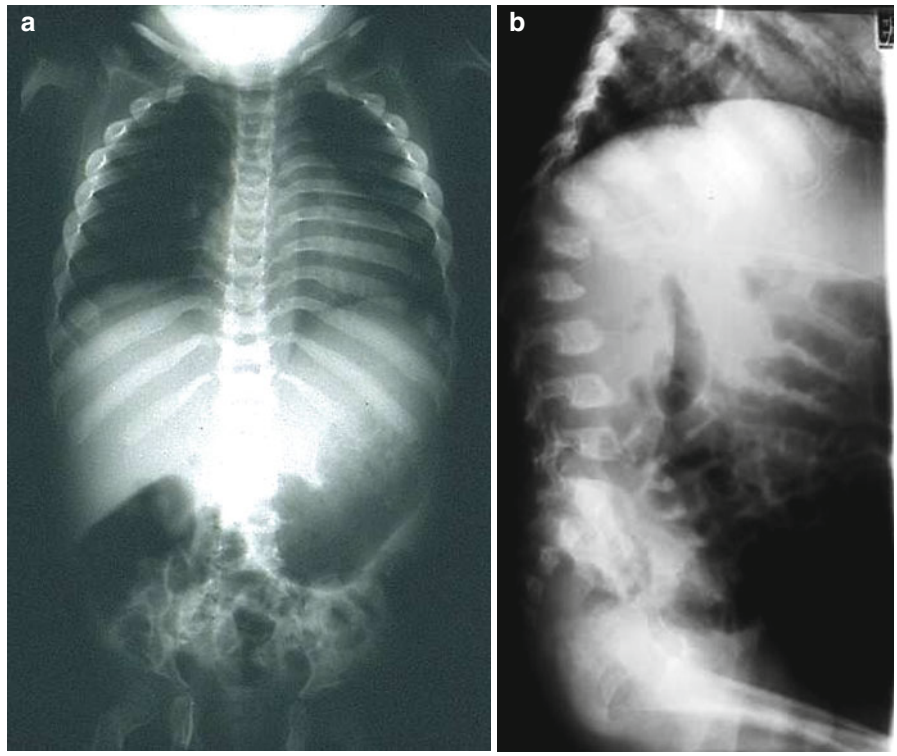

Fig. 3 (**a**, **b**) Radiographs showing oar-shaped ribs with relatively narrow proximal portion, narrow iliac bodies and flaring wings, shallow acetabula, coxa valga, anterior wedging of the lumbar vertebrae, decreased AP diameter of the vertebral bodies with posterior scalloping, and marked thoracolumbar gibbus

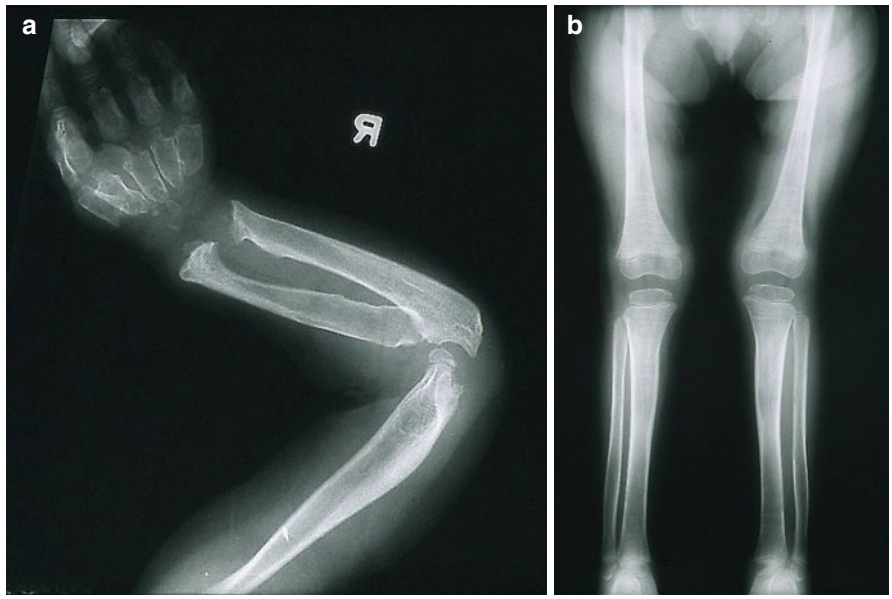

Fig. 4 (**a**, **b**) Radiograph of the upper extremities show the lack of normal modeling and tabulation of the diaphyses, leading to short tubular bones. The radial and ulnar articular surfaces are angulated toward each other. Marked irregularity and retarded ossification of the carpal bones are noted. The findings in the lower extremities are less marked

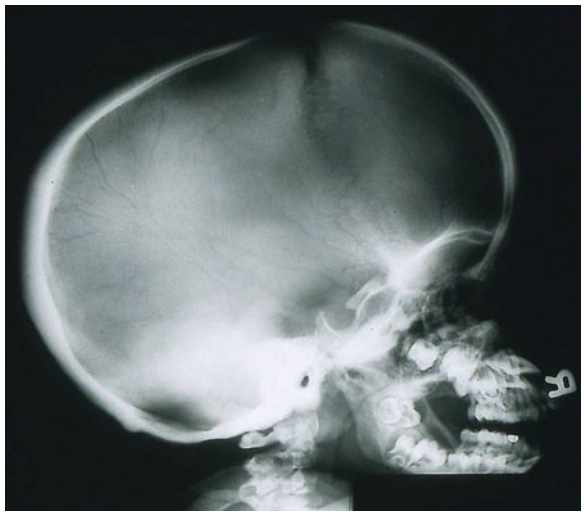

Fig. 5 Skull radiograph showing a large scaphocephalic calvarium with early appearance of the J-shaped sella turcica

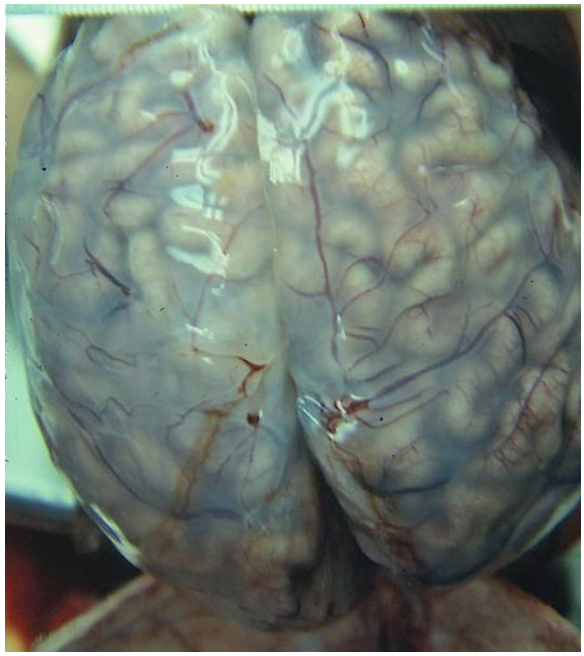

Fig. 6 Postmortem findings of the brain showing cloudy leptomeninges secondary to cloudy CSF

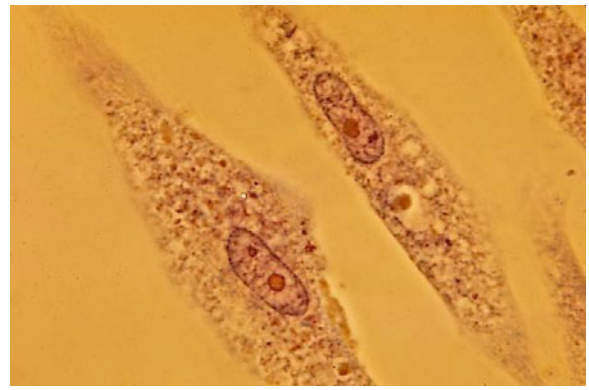

Fig. 7 Metachromasia of the cultured fibroblasts

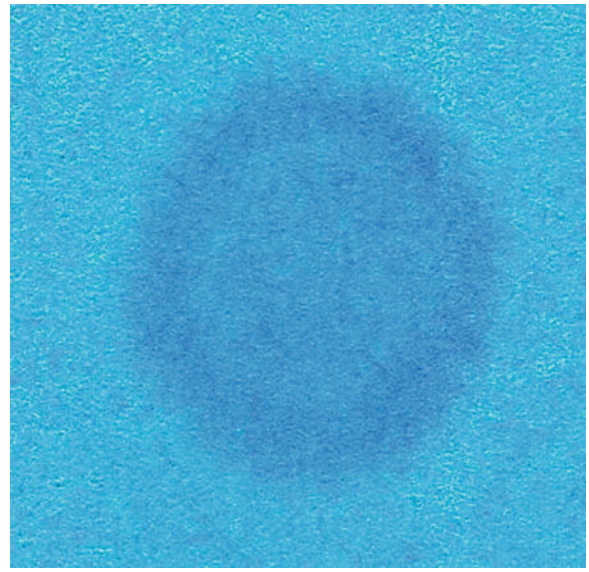

Fig. 8 Positive MPS spot test

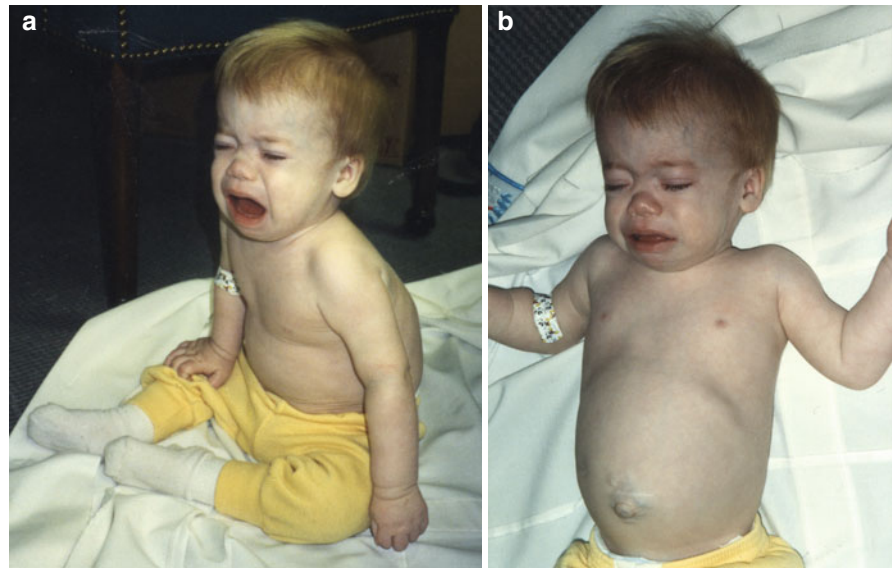

Fig. 9 (**a**, **b**) A 14-month-old boy with Hurler syndrome showing a large head, coarse facies, protuberant abdomen, umbilical hernia, a lumbar gibbus, and claw hands. The radiographs showed cardiomegaly, thickened ribs, and beaked vertebral body (L2). The α-L-iduronidase enzyme level was 0.0 (87.10–190.50 nmol/mg/h)

Fig. 10 A 14-year-old boy with Hurler–Scheie compound showing short stature, semi-crouching stance, joint stiffness (**a, b**), coarse facies (**c, d**), and claw hands (**e**). When he was 3½ year old, he started to complain difficulty in raising his arms above his head and difficulty in moving his hands and fingers because of bent fingers and joint contractures. He was noted to have dwarfism; coarse thickened skin; hirsutism; a big head with frontal bossing; coarse facies with hypertelorism; cloudy cornea; large lips and large tongue; short neck; short trunk with a mild kyphosis; hepatomegaly; claw hands; anteriorly converted shoulders; protuberant abdomen; flexion contractures of elbows, wrists, and knees; and crouching stance. The urine for mucopolysaccharide was positive, and the blood for metachromasia was positive. Skin fibroblasts was deficient in α-L-iduronidase

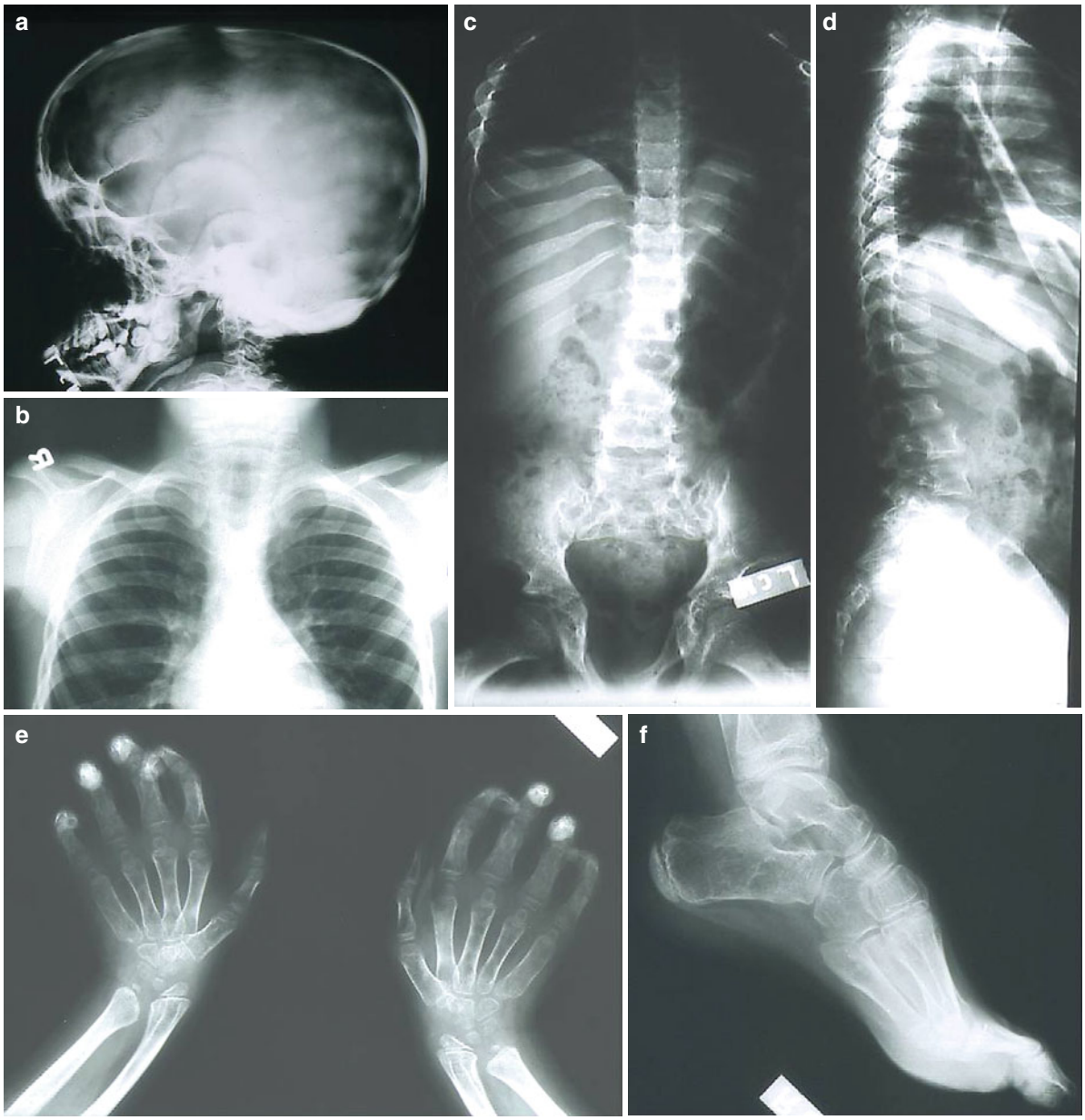

Fig. 11 Radiographs. Skull (**a**) shows macrocephaly, frontal bossing, small and airless mastoids, and anterior pocketing of the sella turcica ("shoe-shaped" or "J-shaped" sella). Clavicles (**b**) are short with widened medial aspects of both clavicles. Ribs are oar-shaped and wide in their lateral and anterior portions with moderate narrowing of the paravertebral portions of the lower ribs (**c, d**). Vertebral bodies have concaved anterior and posterior margins and decreased in sagittal diameters. The second lumbar vertebra was hypoplastic with anterior inferior beaking forming almost a hook-shaped deformity. Claw hands were present with tapering of both distal ends of radius and ulna to form "V-shaped" (**e**). Carpal bones were small, irregular, and crowded together. Metacarpals and phalanges were wide and short with proximal pointing of metacarpals. Bone age was retarded. Pes cavus was present (**f**)

Fig. 12 (**a**–**e**) A 7-year-old girl was diagnosed to have Hurler syndrome at the age of 2. She received a male, 4/6 HLA-matched unrelated umbilical cord blood transplant. She engrafted quickly with an absolute neutrophil count greater than 500 on day +28. Her transplant complications included a Klebsiella UTI prior to admission, mucositis, medicine-induced hypertension controlled with nifedipine, diarrhea treated with Flagyl empirically, and graft-versus-host disease. Presently, she has less coarse facial features, resolving cloudy cornea, improved cognitive capacity, but still has some claw hands and lumbar gibbus which is illustrated radiographically

Mucopolysaccharidosis II

In 1917, Hunter described the syndrome in two brothers. Hunter syndrome is an X-linked recessive form of the mucopolysaccharidosis. Severe and mild (attenuated) forms of the syndrome are caused by the same enzyme deficiency, iduronate-2-sulfatase with consequent increase of the urinary concentration of the glycosaminoglycan (CAG) dermatan sulfate and heparin sulfate. The estimated incidence is approximately 1 in 100,000 births.

Synonyms and Related Disorders

Hunter syndrome; Iduronate 2-sulfatase deficiency

Genetics/Basic Defects

1. Inheritance (Beighton 1993)
   a. X-linked recessive inheritance from pedigree data
   b. The gene for iduronate sulfatase mapped to Xq28
2. Primary biochemical defect and pathophysiology
   a. Deficient iduronate-2-sulfatase (*IDS*), the enzyme required for cleavage of sulfate from iduronic acid moieties of dermatan and heparan sulfates
   b. Excessive intracellular accumulation of acid mucopolysaccharides (dermatan sulfate and heparan sulfate) due to deficient iduronate sulfatase activity, leading to multiple organ system involvement, including the musculoskeletal, integumentary, cardiovascular, pulmonary, and ocular systems
3. Molecular defect
   a. Mutations of *IDS* gene.
      i. Missense and nonsense mutations
      ii. Mutations affecting splicing
      iii. Small insertions and deletions
      iv. Partial gene deletions
      v. Deletions or rearrangements of the whole *IDS* gene
   b. Major structural alterations and gross deletions of the *IDS* gene result in the most severe forms of Hunter syndrome.
   c. Single-base substitutions causing diminished but not obliterated enzyme activity is observed in mild disease.
4. Hunter syndrome in females: an exceedingly rare event possibly due to the following mechanisms:
   a. As the offspring of a carrier female and affected male or an unaffected male whose sperm carries a new mutation
   b. Uniparental disomy of the mutant X chromosome from a heterozygous female or an affected male
   c. Genetic rearrangement: e.g., translocation or deletion resulting in nonrandom lyonization toward expression of a mutant allele

Clinical Features

1. Clinical presentation showing a spectrum of mild to severe forms as a result of different mutations in the functional gene (Beighton 1993)
2. Severe Hunter syndrome (MPS IIA)
   a. Onset: usually between 2 and 4 years of age with progressive neurologic and somatic involvement

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b. More common than the mild form
c. Short stature not pronounced
d. Coarse facial features
    i. Frontal bossing
    ii. Depressed nasal bridge
    iii. Wide nostrils
    iv. Depressed nasal bridge
    v. Thick lips
    vi. Hypertrophic gums
    vii. A large tongue
e. Skeletal deformities
    i. Kyphosis
    ii. Digital contractures
    iii. Claw hands
    iv. Joint stiffness
    v. Absence of gibbus
f. CNS manifestations (Al Sawal et al. 2008)
    i. Mental retardation
    ii. Hydrocephalus
    iii. Seizures
    iv. Sleep apnea
    v. Cerebral infarction
    vi. Spinal cord compression/cervical myelopathy
    vii. Other CNS lesions
        a) Enlarged perivascular spaces
        b) Widening of subarachnoid spaces
        c) White-matter lesions
        d) Delayed myelination
g. Ocular manifestations
    i. Absence of corneal clouding
    ii. Thickened sclera
    iii. Optic atrophy
    iv. Papilledema
    v. Retinitis pigmentosa–like retinal fundus
    vi. Night blindness
    vii. Scotomas
h. Hearing loss
i. Respiratory difficulties
    i. Upper airway obstruction due to adenoid hypertrophy, nasal congestion, and thick rhinorrhea
    ii. Mouth breathing secondary to choanal stenosis
    iii. Sonorous breathing, frank obstructive sleep apnea, and even death secondary to adenoid hypertrophy, tongue enlargement, and supraglottic swelling
j. Cardiovascular disorders
    i. Cardiac valvular involvement leading to congestive heart failure, the leading cause of death in affected individuals
    ii. Mild thickening and shortening of the chordae tendineae contributing to the regurgitant valve dysfunction
k. Gastrointestinal problems
    i. Chronic diarrhea secondary to autonomic nervous system involvement and mucosal dysfunction
    ii. Hepatosplenomegaly
    iii. Umbilical and inguinal hernias
l. Thick skin often with nodular skin lesions over the scapular area or arms
m. Peripheral nervous system manifestations
    i. Carpal tunnel syndrome secondary to median nerve compression
    ii. Cubital tunnel syndrome
n. Additional features of most severely affected patients, caused by large deletions that include iduronate sulfate sulfatase and contiguous genes
    i. Hurler-like symptoms
    ii. Early onset of seizures
    iii. Ptosis
o. Prognosis: typically advancing to cachexia and death before 15 years

3. Mild Hunter syndrome (MPS IIB)
    a. Diagnosed slightly later than the severe form
    b. Much less frequent than the severe form
    c. Preservation of normal intelligence
    d. No central nervous system involvement
    e. Somatic involvement less progressive
    f. Hearing impairment
    g. Cardiovascular disorders
    h. Joint stiffness
    i. Cervical myopathy due to a narrowed spinal canal and cord compression
    j. Carpal tunnel syndrome more frequent and severe compared to the severe form
    k. Loss of hand function resulting from joint stiffness and carpal tunnel syndrome
    l. Prognosis
        i. Longer survival
        ii. Typically surviving to adulthood
        iii. Possible death in early adulthood or even in the late teens due to airway obstruction and cardiac failure

Diagnostic Investigations

1. Echocardiography
2. Electrocardiography
3. Radiographic features
   a. Kyphosis
   b. Claw hands
   c. Thick cortex of the bones progressively becoming thinner as the marrow cavities expand
   d. Large calvarium with shoe-shaped sella
   e. Broad and spatulate lower ribs
   f. Hypoplasia and beaking of the lumbar vertebrae
4. MRI of the brain (Al Sawaf et al. 2008)
   a. Most common findings: widely distributed white-matter lesions, predominantly found peri- and supraventricularly as well as in the basal ganglia and the corpus callosum. These changes were regarded as filling defects rather than immaturity of white matter and are suspected to progress with age.
   b. Even before the development of white-matter lesions, clearance of MPS deposits in white matter may result in demyelination. In addition, delay of myelination may also occur in Hunter disease.
   c. Common findings with questionable clinical relevance
      i. Enlargement of the perivascular spaces
      ii. Ventriculomegaly
      iii. Mega cisterna magna
      iv. Widening of the subarachnoid spaces
5. Biochemical/molecular studies
   a. Measurement of mucopolysaccharides in the urine: abnormal excretion of a large amount of dermatan sulfate and heparin sulfate in the urine
   b. Deficient iduronate sulfatase in leukocytes and fibroblasts
   c. Excessive intracellular accumulation of dermatan sulfate and heparin sulfate
   d. Peripheral lymphocytes, when stained with toluidine blue, exhibit metachromatic granules within vacuoles.
   e. The gold standard for diagnosis of MPS II in a male proband is assay of I2S enzyme activity in white cells or serum (Martin 2007).
   f. Molecular genetic testing of *IDS*, the only gene known to be associated with MPS II, is used to confirm the diagnosis in a male proband with an unusual phenotype or a phenotype that does not match the results of GAG testing (Martin 2007).
      i. Sequence analysis
      ii. Deletion testing for exonic and whole gene deletions
      iii. Southern blot analysis: used to detect complex rearrangements resulting from recombination with the pseudogene and accounting for 9% of all mutations (Froissart et al. 2007)
6. Heterozygote detection
   a. Carrier detection by enzyme analysis for MPS II is unreliable.
   b. Identification of *IDS* gene mutations

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Carrier mother: 50% of brothers affected, 50% of brothers normal, 50% of sisters carriers, 50% of sisters normal
      ii. Noncarrier mother (mother of a sporadic case): recurrence possible due to presence of gonadal mosaicism
   b. Patient's offspring
      i. Severe form: not surviving to reproduction
      ii. Mild form: none of the sons affected, all daughters carriers
2. Prenatal diagnosis
   a. Maternal serum analysis
      i. Consistent increase of iduronate sulfatase in the serum of pregnant women from prepregnancy levels toward the end of pregnancy
      ii. No change in the serum enzyme levels of heterozygous mothers until the affected fetuses are aborted
   b. Amniocentesis
      i. Reduced enzyme activity in the amniotic fluid
      ii. Low enzyme levels in cultured amniotic cells
      iii. Abnormal $^{35}SO_4$ incorporation into cultured amniotic fluid cells
      iv. Karyotyping for fetal sex

v. Direct detection of *IDS* gene mutation, provided the disease-causing mutation in the family has been identified previously

c. CVS
   i. Diminished enzyme activity in uncultured chorionic villi of affected male fetuses. This may be seen in female carrier fetuses.
   ii. Karyotyping for fetal sexing
   iii. Direct detection of *IDS* gene mutation, provided the disease-causing mutation in the family has been identified previously

d. Umbilical fetal blood sampling: severe deficiency of iduronate sulfate sulfatase in the plasma of affected male fetuses

e. Preimplantation diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.

3. Management (Beighton 1993)
   a. Tympanostomy, adenoidectomy, and provision of hearing aids for management of otologic complications
   b. Symptomatic management of airway obstruction (sleep apnea)
   c. Ventriculoperitoneal shunting for hydrocephalus, a relatively rare complication of Hunter syndrome
   d. Difficulties during anesthesia secondary to the following factors:
      i. Rigid thoracic cage
      ii. Abdominal distention
      iii. Macroglossia
      iv. Temporomandibular ankylosis
      v. Atlantoaxial instability
      vi. Short and wide neck
   e. Prophylactic antibiotics for at-risk procedures in patient with mucopolysaccharidosis
   f. Surgical repair of inguinal and umbilical hernias
   g. Surgical release to preserve apposition of the thumbs at the earliest sign of an electrophysical evidence of progressive median nerve compression
   h. Musculoskeletal complications
      i. Shoe orthotics and ankle braces well tolerated and useful in maintaining mobility
      ii. Achilles tendon release in some patients with advanced disease
      iii. Surgical stabilization of the spine rarely indicated for kyphoscoliosis which is only mildly progressive and not usually resulting in spinal cord compression
   i. Bone marrow transplantation
      i. Possible reduction in hepatosplenomegaly, improvement in airway disease, and reduction in urinary glycosaminoglycan excretion
      ii. Long-term prognosis for longevity, cardiac complications, and neurologic outcome after marrow transplantation still remained to be determined.
   j. Hematopoietic stem cell transplantation (HSCT) has been performed in numerous individuals with varying degrees of severity of MPS II, but limited success and significant risk; therefore, HSCT is not currently recommended for individuals with MPS II (Martin et al. 2008).
   k. Enzyme replacement therapy (ERT) (Burrow and Leslie 2008; da Silva et al. 2010)
      i. Recently, recombinant iduronate-2-sulfatase (idursulfase, Elaprase®; Shire Human Genetic Therapies, Inc., Cambridge, MA), a recombinant human I2S produced in a human cell line, was approved in the United States and the European Union as a safe and effective treatment for individuals with MPS II.
      ii. The rationale for therapy is that exogenous I2S would replace the iduronate-2-sulfatase that is deficient in patients and either stop or reverse disease progression.
      iii. Recent clinical trials have shown promise in the treatment of MPS II, with potential to help many patients, providing that it is started early in the course of the disease (Wraith et al. 2008).
      iv. ERT involves the intravenous administration of a recombinant human enzyme into individuals in whom the enzyme is missing or defective.
      v. The recombinant enzyme undergoes receptor-mediated cell uptake and subsequent intracellular trafficking into the lysosomes, where it carries out its specific function.
      vi. Elaprase® does not cross the blood–brain barrier; thus, no effect on CNS disease is anticipated. Thus, CNS disease remains a major challenge, and an innovative approach to treatment will be needed if this is to be addressed fully (Wraith et al. 2008).

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Fig. 1 (**a**, **b**) A boy with MPS II showing mild short stature, coarse facial features, large abdomen, and claw hands

Mucopolysaccharidosis III

In 1962 and 1963, Sanfilippo et al. described eight children with mental retardation and heparan sulfate mucopolysaccharidosis and delineated the syndrome which now bears his name. Earlier in 1961, Harris reported a 6-year-old girl with hepatosplenomegaly, a normal skeletal survey, and excretion of large amounts of heparan sulfate in the urine. Sanfilippo syndrome is one of the most common mucopolysaccharidoses (MPS) (1/24,000–1/200,000).

Sanfilippo syndrome is comprised of four biochemically heterogeneous types (MPS IIIA, IIIB, IIIC, and IIID), which are clinically indistinguishable. Because the deficiency of these four various lysosomal enzymes involved the same breakdown of heparan sulfate, their clinical phenotype is similar. Type A is the most common type of MPS III in Northwest Europe, while type B is thec most frequent type in Southeast Europe (Meikle et al. 1999; Poorthuis et al. 1999; Baehner et al. 2005). Types C and D appear to be much rarer (Valstar et al. 2008).

Synonyms and Related Disorders

Sanfilippo Syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Failure to degrade heparan sulfate may result from deficiency of one of the following four lysosomal enzymes:
   a. MPS IIIA caused by deficient heparan N-sulfatase (sulfamidase)
   b. MPS IIIB caused by deficient α-N-acetylglucosaminidase
   c. MPS IIIC caused by deficient acetyl-CoA:α-glucosaminide-N-acetyltransferase
   d. MPS IIID caused by deficient N-acetyl-α-glucosamine-6-sulfatase
3. Four subtypes of MPS III
   a. Clinically indistinguishable
   b. Each characterized by deficiency of a different enzyme
   c. MPS IIIA mapped to 17q25.3
   d. MPS IIIB mapped to 17q21
   e. MPS IIIC mapped to 8p11.1
   f. MPS IIID mapped to 12q14

Clinical Features

1. Severe CNS involvement
   a. Developmental milestones near normal prior to age 3–4 years
   b. Developmental delay, especially in speech (first stage usually starts between 1 and 4 years of age)
   c. Behavioral problems (second stage usually starts around 3–4 years)
      i. Aggressiveness
      ii. Hyperactivity
      iii. Attention deficit
      iv. Temper tantrums
      v. Destructive behavior
      vi. Physical aggression
      vii. Sleep disturbance
         a) Setting difficulties
         b) Night walking

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c) Sometimes awake all night
d) Crying out
e) Wandering around house
f) Entering parents' bed
g) Talking in sleep
h) Body rocking
i) Chewing bedclothes

viii. Poor attention span
ix. Marked mood swings
x. Self-injury

d. Progressive motor difficulties due to spasticity and joint stiffness and slowly disappearing behavioral problems, starting about 10 years of age (marking the third and final stage)
e. Severe hearing loss common in the moderate to severely affected patient
f. Severe neurologic degeneration occurring in most patients by 6–10 years of age, accompanied by rapid deterioration of social and adaptive skills (mental deterioration)
g. Progressive dementia resulting in withdrawal and losing contact with the environment
h. Seizures: uncommon
i. Patients usually die at the end of the second or beginning of the third decade of life, although survival into the fourth decade has been reported.

2. Mild somatic disease
   a. Coarse hair (hirsutism): hypertrichosis often present, especially on the back
   b. Macrocephaly
   c. Copious nasal discharge
   d. Repeated upper respiratory tract infections
   e. Cardiac signs and symptoms much lesser degree compared to other types of mucopolysaccharidosis
   f. Mild hepatosplenomegaly
   g. Joint stiffness
   h. Recurrent and sometimes severe diarrhea, usually improves in later childhood
   i. Early onset of puberty
3. Prognosis
   a. Type A
      i. The most severe type
      ii. Earlier onset
      iii. More rapid progression of symptoms
      iv. Shorter survival: death usually by late teens
   b. Type B: known to remain functional into the third or even fourth decades
   c. Type C: clinically heterogeneous
   d. Type D
      i. Least common type
      ii. Clinically heterogeneous

Diagnostic Investigations

1. Increased urinary excretion of heparan sulfate
2. Imaging features
   a. Radiography: mild degree of dysostosis multiplex
   b. Echocardiography for rare cardiac abnormalities
   c. CT
      i. Mild to moderate cortical atrophy at onset
      ii. Severe cortical atrophy at late stage
   d. MRI (Barone et al. 1999)
      i. Cortical atrophy
      ii. Corpus callosum atrophy
      iii. Abnormal or delayed myelination
      iv. MRI findings may precede the onset of overt neurological symptoms.
3. Biochemical analysis (Defendi and Varma 2009)
   a. Biochemical differentiation of the different forms within MPS II is possible, and diagnosis is confirmed by specific enzymatic assay.
      i. Deficient heparan N-sulfatase (type A)
      ii. Deficient N-acetylglucosaminidase (type B)
      iii. Deficient α-glucosamine-N-acetyltransferase (type C)
      iv. Deficient N-acetyl-α-glucosamine-6-sulfatase (type D)
   b. Enzymatic activity for all types of MPS III may be assayed in cultured skin fibroblasts and in peripheral blood leukocytes.
4. Mutation studies are available clinically by sequence analysis and deletion/duplication analysis.
   a. MPS IIIA
      i. Missense mutations (most common)
      ii. Premature termination mutations
      iii. Small deletion mutations
   b. MPS IIIB
      i. Great molecular heterogeneity
      ii. Most mutations: private mutations
   c. MPS IIIC: no mutation analysis available currently
   d. MPS IIID: frameshift and premature termination mutation

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not reproducing due to mental retardation
2. Prenatal diagnosis (Di Natale et al. 1999)
   a. Fetuses at risk for MPS IIIA
      i. Measuring sulfamidase activity using radioactive assay in CVS and amniocytes
      ii. Using fluorimetric sulfamidase assay in CVS and amniocytes
      iii. Molecular diagnosis in characterized families
   b. Fetuses at risk for MPS IIIB
      i. Assay of α-N-acetylglucosaminidase activity in cultured amniocytes and CVS
      ii. Increased level of heparan sulfate in amniotic fluid by two-dimensional electrophoresis of glycosaminoglycans: used as an adjunctive method in prenatal diagnosis
      iii. Molecular diagnosis in characterized families
   c. Fetuses at risk for MPS IIIC
      i. Assay of Acetyl-CoA:α-glucosamine-N-acetyltransferase in amniocytes and CVS
      ii. Molecular diagnosis in characterized families
   d. Fetuses at risk for MPS IIID
      i. Spectrophotometric assay for the N-acetyl-α-glucosamine-6-sulfatase activity
      ii. Molecular diagnosis in characterized families
3. Management (Cleary and Wraith 1993)
   a. Supportive treatments
      i. Antibiotics for otitis media and respiratory tract infections
      ii. Anticonvulsants for seizure activities
   b. Muscle relaxants for painful spasms
   c. Gastrostomy to maintain adequate nutrition
   d. Special education program
   e. Behavioral management to allow the family to function as near normal as possible
      i. Alteration to the physical environment within home
      ii. Drug treatment to control hyperactivity and aggression
   f. Physical therapy to maintain joint mobility
   g. Wheelchair for transportation
   h. Respite care: availability of suitable respite accommodation
   i. Identify professional and community resources.
   j. Risperidone treatment of behavioral disorder in children with MPS IIIA: appeared to be safe and effective (Ucar et al. 2010)
   k. Bone marrow transplantation
      i. Biochemical correction readily achievable
      ii. Disappointing intellectual outcome

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Fig. 1 (**a**–**c**) A child with MPS IIIA at 8 months and 3 years

Fig. 2 A 32-year-old male with Sanfilippo syndrome type A showing mental retardation and severe behavioral problems. Molecular genetic analysis revealed heparan sulfamidase (SGSH) gene mutations. A C > T substitution was detected at nucleotide 892 resulting in a serine being replaced by a proline at amino acid 298 (S298P). The second nucleotide change resulted in insertion of a cystine at nucleotide 1,028 which creates a frameshift and premature truncation of protein (1028insC). The detection of two mutations in the heparan sulfamidase gene is associated with Sanfilippo A syndrome

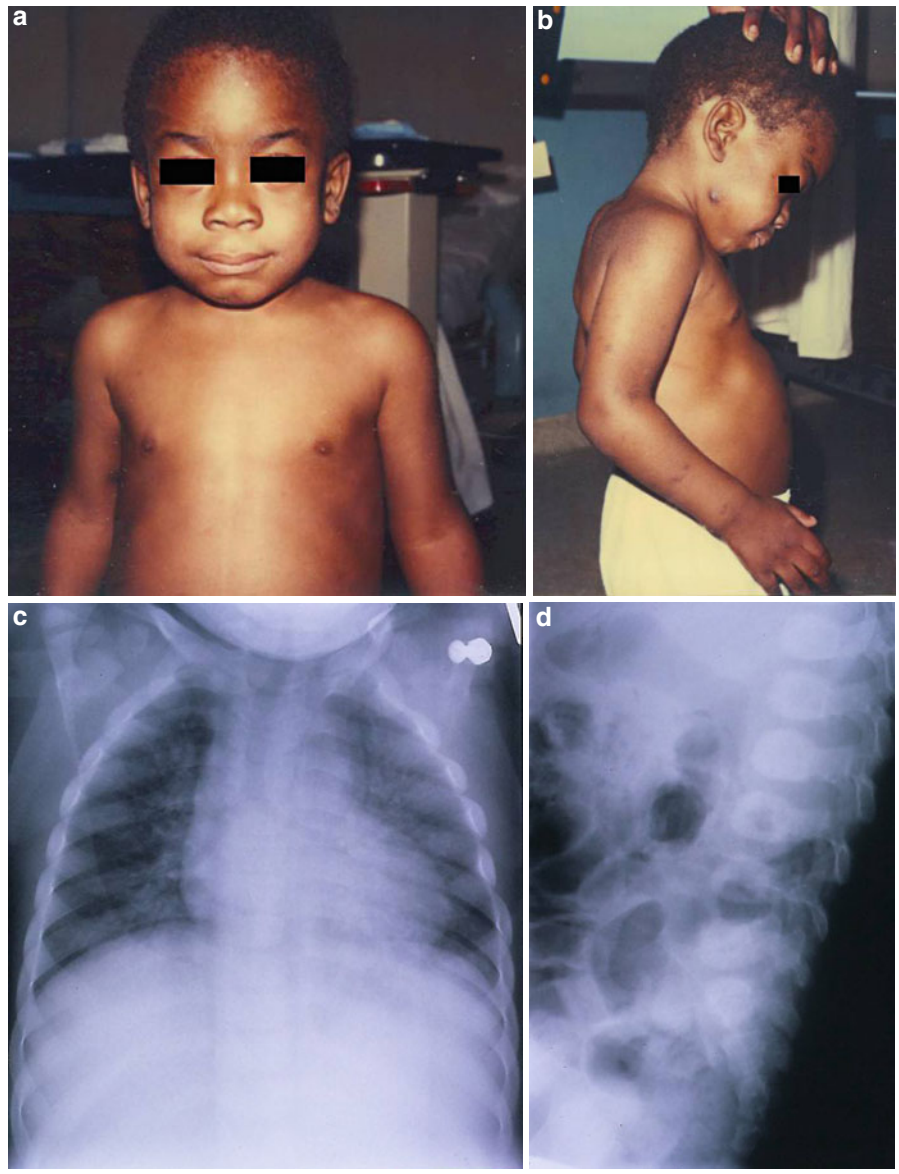

Fig. 3 (**a**–**d**) A child with MPS IIIB at 3 years of age. The radiographs show mild degree of dysostosis multiplex

Mucopolysaccharidosis IV

In 1929, Morquio and Brailsford independently described cases of what is now believed to be Morquio syndrome. The exact incidence is unknown but is estimated to be 1 in 75,000–1 in 200,000.

Synonyms and Related Disorders

Galactosamine-6-sulfatase deficiency; Morquio disease; Morquio syndrome

Genetics/Basic Defects

1. Genetic inheritance: autosomal recessive
2. Two forms of MPS IV
   a. MPS IVA
      i. Deficient *N*-acetyl-galactosamine-6-sulfate sulfatase (*GALNS*) gene, which is mapped to 16q24.3
      ii. Wide spectrum of clinical manifestations
   b. MPS IVB
      i. Deficient β-galactosidase (*GLB1*) gene
      ii. Wide spectrum of clinical manifestations
3. Pathogenesis (Braverman and Hoover-Fong 2003)
   a. Defective degradation of keratan sulfate secondary to deficiency of either *N*-acetyl-galactosamine-6-sulfate sulfatase (*GALNS* gene) in MPS IVA or β-galactosidase (*GLB1* gene) in MPS IVB
   b. Cartilage and cornea: The major organs affected in Morquio syndrome since keratan sulfate is predominantly found in these tissues.

Clinical Features

1. MPS IVA
   a. Classic form
      i. The most common form
      ii. Appears normal at birth
      iii. Skeletal symptoms occurring between 1 and 3 years of age
      iv. Clinical diagnosis usually not made until 3–15 years of age
      v. Skeletal manifestations
         a) Marked dwarfism
         b) Waddling gait with tendency to fall
         c) Short neck
         d) Hypoplasia or absence of the odontoid process of the axis with risk of resulting in life-threatening atlantoaxial subluxation
         e) Cervical myelopathy
         f) Gibbus
         g) Restrictive chest wall movement
         h) Pectus carinatum
         i) Kyphoscoliosis
         j) Genu valgum
         k) Semicrouching stance
         l) Progressive skeletal deformities frequently resulting in neurologic compromise
      vi. Joint manifestations
         a) Hypermobile due to ligamentous laxity
         b) Decreased mobility in large joints (e.g., hips, knees, elbows)
      vii. Unusual facial appearance
         a) Coarse facies
         b) Prognathism
         c) Broad mouth

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viii. Eye manifestations
  a) Mild corneal clouding
  b) Glaucoma
  c) Cataract
ix. Dental features (Rølling et al. 1999)
  a) Abnormally thin enamel
  b) Spade-shaped incisors
  c) Pointed cusps
  d) Pitted buccal surfaces
  e) Frequent caries formation
x. Cardiac manifestations
  a) Aortic valve insufficiency or stenosis
  b) Mitral valve thickening and stenosis
  c) Cardiac failure
xi. Progressive deafness
xii. Hepatomegaly
xiii. Upper airway obstruction
  a) Obstructive sleep apnea
  b) Nocturnal dyspnea
xiv. Intelligence usually normal, rarely with progressive mental regression

b. Mild form
  i. Almost normal stature
  ii. Mild skeletal abnormalities
    a) Odontoid dysplasia but without atlantoaxial instability
    b) Pectus carinatum deformity
    c) Dysplastic hips
    d) Waddling gait
    e) Kyphoscoliosis
    f) Deformity of femoral heads
    g) Platyspondyly
    h) Limitation of joint movement
    i) Deformities of metacarpals
  iii. Enamel hypoplasia
  iv. Mild corneal clouding
  v. Absent keratosulfaturia

2. MPS IVB
  a. Severe form: clinical manifestations as severe as MPS IVA
  b. Mild form
    i. Less severe progression of skeletal dysplasia
    ii. Less severe short stature
3. Prognosis
  a. Atlantoaxial instability and subsequent cervical myelopathy
    i. Cord transection and subsequent quadriparesis or death secondary to a minor fall or extension of the neck
    ii. Bowel and bladder dysfunction and apnea secondary to cervical myelopathy
    iii. Prolonged periods of hypoxia, pulmonary hypertension, and even death from obstructive sleep apnea
    iv. Airway obstruction secondary to thickening of tissue in the upper airway from mucopolysaccharide deposition
  b. Predisposition to pulmonary infection because of progressive truncal deformity and immobility
  c. Early-onset coronary heart disease and valve thickening (aortic and mitral) with resultant cardiac dysfunction
  d. Visual disturbance and photophobia secondary to corneal clouding
  e. Predisposition to dental caries secondary to enamel abnormalities

Diagnostic Investigations

1. Urine MPS spot tests: associated with false-positive and false-negative results
2. Excessive urinary excretion of keratin sulfate: determination by spectrophotometric assays with dimethylmethylene blue
3. Metachromatic granules in cultured fibroblasts
4. Diagnosis confirmed by direct enzymatic assay in leukocytes or fibroblasts
  a. N-acetylgalactosamine-6-sulfatase deficiency (classic form)
  b. β-galactosidase deficiency (mild form)
5. Radiographic features
  a. Short trunk dwarfism
  b. Dysostosis multiplex
  c. Spondyloepiphyseal dysplasia (the hallmark of the syndrome)
  d. Odontoid hypoplasia
  e. Sternal protrusion
  f. Platyspondylia
  g. Kyphosis
  h. Hyperlordosis
  i. Scoliosis
  j. Ovoid deformities of the thoracic vertebrae
  k. Hook-shaped lumbar bodies
  l. Long pelvic configuration
  m. Coxa valga
  n. Genu valgum
  o. Ulnar deviation of the wrist

p. Valgus deformity of the elbow
q. Inclinations of distal ends of radius and ulna toward each other
r. Metacarpal deformities
s. Short phalanges
t. Epiphyseal deformities of the tubular bones
u. Wide metaphysis
v. Osteoporosis

6. CT and MRI of the brain and cervical spine for evaluation of odontoid hypoplasia and cord compression
7. Echocardiography for cardiac involvement
   a. Aortic valve insufficiency or stenosis
   b. Mitral valve thickening and stenosis
   c. Ventricular hypertrophy
8. Slit-lamp examination for corneal clouding
9. Molecular genetic diagnosis
   a. Sequence analysis
   b. Deletion/duplication analysis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is a carrier in which case there will be 50% of offspring affected
2. Prenatal diagnosis (von Figura et al. 1982; Mossman and Patrick 1982; Zhao et al. 1990; Beck et al. 1992; Kleijer et al. 2000)
   a. Demonstration of GalNac-6S or Gal-6S sulphatase deficiency in cultured amniotic fluid cells or chorionic villi
   b. Abnormal glycosaminoglycans electrophoretic pattern in amniotic fluid
   c. Mutation analysis in amniocytes or chorionic villi, provided the disease-causing mutation has been identified in the family member
3. Preimplantation genetic diagnosis of Morquio syndrome: accomplished by mutation analysis from the embryos following whole genome amplification of single blastomeres using multiple displacement amplification (Qubbaj et al. 2008)
4. Management (Mikles and Stanton 1997)
   a. Orthopedic management
      i. Surgery to stabilize the upper cervical spine, usually by spinal fusion, can be lifesaving for spinal cord compression
      ii. Bilateral osteotomies to correct the knock-knee deformity (severe coxa valgum)
   b. Anesthetic difficulties
      i. Difficult endotracheal intubation due to odontoid hypoplasia and atlanto-axial instability
      ii. Compression of the cord during hyperextension of the neck
      iii. Reduction in vital capacity, functional residual capacity, and total lung capacity due to chest cage dysfunction (kyphoscoliosis and pectus carinatum)
   c. Infection control
   d. Medications for glaucoma
   e. Cornea transplant not very helpful
   f. Hearing aids helpful
   g. Hernia repairs
   h. Cardiac management
      i. Aortic regurgitation
      ii. Endocarditis prophylaxis
      iii. Cardiac valve replacement historically not considered for these patients
   i. Potential strategies for treatment including enzyme replacement, gene therapy, and allogenic bone marrow transplantation in which engrafted cells provide the normal enzyme

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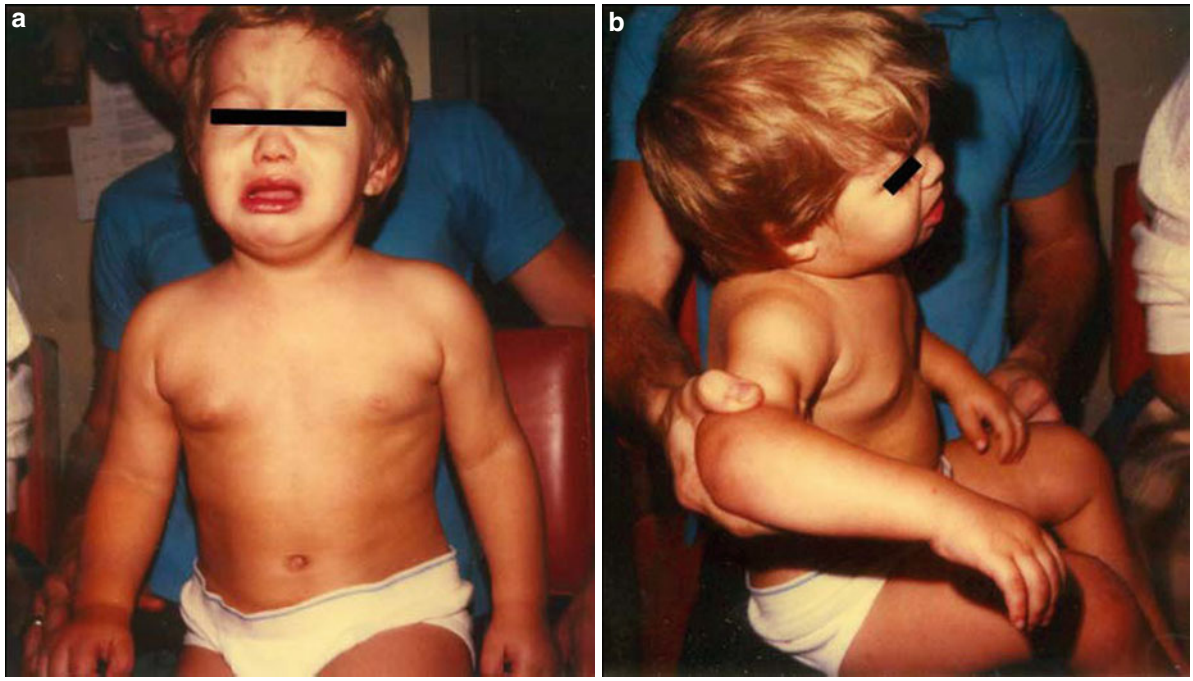

Fig. 1 (**a**, **b**) A boy with MPS IVB showing coarse facial appearance and short trunk

Fig. 2 Lateral view of the spine showing platyspondyly, anterior beaking of vertebral bodies, and lumbar gibbus similar to those seen in Hurler syndrome

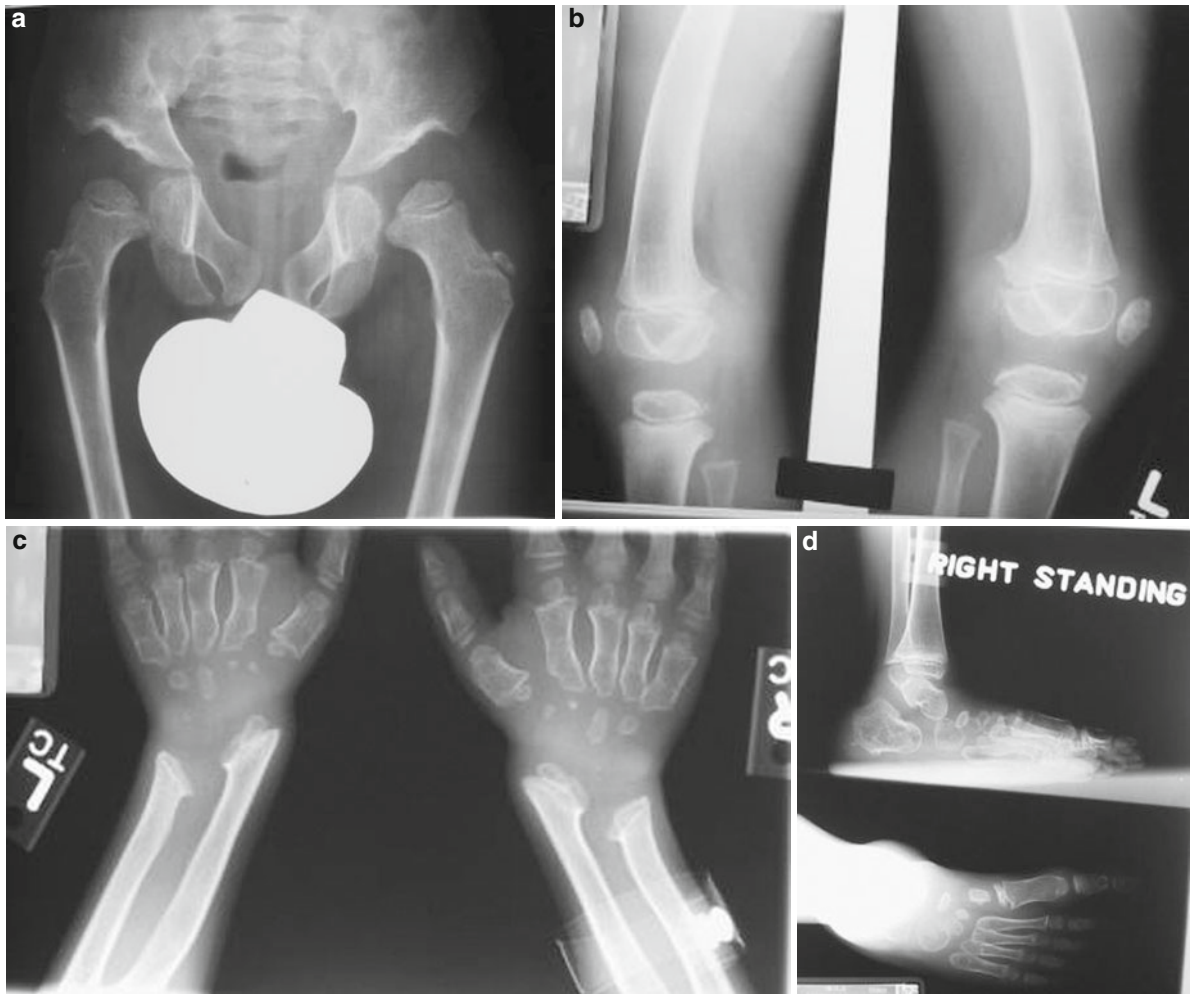

Fig. 3 (**a**–**d**) Radiographic studies showing dysostosis multiplex with proximal conical metacarpals and angling of the ulna toward the radius with dysplastic ulnar and radial growth plates

Mucopolysaccharidosis VI

Mucopolysaccharidosis VI was first recognized by Maroteaux and coworkers in 1963 as a Hurler-like syndrome but with preservation of intelligence and excretion of dermatan sulfate unaccompanied by heparan sulfate. Milder forms of MPS VI have been recognized since the initial description of the disorder. The estimated birth incidence of MPS VI ranges from 1 in 100,000 to 1 in 1,300,000 in various populations (Harmatz et al. 2004).

Synonyms and Related Disorders

Arylsulfatase B deficiency; Maroteaux–Lamy syndrome

Genetics/Basic Defects

1. Genetic inheritance: autosomal recessive
2. Cause
   a. Deficiency of *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B) which:
      i. Is deficient in both mild and severe forms
      ii. Is Involved in the degradation of dermatan sulfate and chondroitin 4-sulfate
      iii. Causes intralysosomal storage and urinary excretion of the glycosaminoglycan, dermatan sulfate
   b. The gene encoding *N*-acetylgalactosamine-4-sulfatase (*ARSB*) mapped to chromosome 5q13-q14
   c. Mutations: The vast majority of MPS VI mutant alleles are either unique to a patient or are present in a small number of patients.
      i. Null mutations
         a) Frameshift mutations
         b) Nonsense mutations
      ii. Missense mutation giving rise to:
         a) Severe disease
         b) Intermediate disease
         c) Mild disease
   d. Genotype/phenotype correlation for missense mutations in MPS VI: not reliable enough for prognosis or counseling

Clinical Features

1. Variable clinical phenotype (mild to severe) causing considerable difficulty in recognition and diagnosis of the syndrome
2. The severe form (MPS IVA)
   a. Somatic involvement similar to that in Hurler syndrome
   b. Growth
      i. Normal growth for the first few years of life
      ii. Growth retardation (short stature) first noted at the age of 2–3 years
      iii. Ultimate height of 110–140 cm in severely affected patients
   c. Other skeletal involvement
      i. An enlarged head at birth
      ii. Deformed chest at birth
      iii. Joint stiffness (knee, hip, and elbow) developing in the first years of life
      iv. Progressively restricted articular movements
      v. Crouching stance

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vi. Shortened limbs
vii. Claw hand deformities secondary to flexion contractures of the fingers
viii. Carpal tunnel syndrome contributing to the hand abnormality
ix. Shortened trunk
x. Anterior sternal protrusion
xi. Lumbar gibbus
xii. Prominent lumbar lordosis/kyphosis
xiii. Genu valgum

d. Mental development usually normal
e. The facies
   i. Mild coarseness of facies in some patients
   ii. Coarse facies characteristic of Hurler syndrome in other patients
f. Ocular findings
   i. Corneal opacities (clouding) developing early, resulting in significant visual impairment
   ii. Glaucoma
   iii. Pigmented retinopathy
g. Dentigerous cysts
h. Upper airway obstruction
i. Cardiovascular involvement
   i. Thickened atrioventricular valves of the heart
   ii. Endomyocardial fibroelastosis
   iii. Dilated cardiomyopathy
j. Associated neurologic complications
   i. Not typically associated with progressive impairment of mental status, although physical limitations may impact learning and development
   ii. Hydrocephalus
   iii. Spinal cord compression secondary to:
      a) Atlantoaxial subluxation associated with craniovertebral canal stenosis
      b) Hypertrophy of the posterior longitudinal ligament
      c) Dural thickening secondary to the deposition of glycosaminoglycans
   iv. Spastic paraplegia resulting from compressive myelopathy
   v. Arachnoid cysts
   vi. Pachymeningitis
   vii. Nerve entrapment syndromes, particularly of the carpal tunnel
   viii. Occasional hearing loss due to recurrent otitis media
k. Abdomen and visceral involvement
   i. Hepatomegaly always present after the age of 6 years
   ii. Splenomegaly in 50% of patients
   iii. Prominent abdomen
   iv. Inguinal/umbilical hernias common
l. Skin
   i. Tightness
   ii. Hirsutism
m. Most reported patients with the severe form died from heart failure in the second to third decades

3. The mild to intermediate form (MPS IVB)
   a. Clinical recognition often delayed till 5 years of age
   b. Mildly affected
   c. Minimal dysostosis multiplex
   d. Aortic and mitral valvular dysfunction
      i. Primarily due to calcified thickened and stenotic valves
      ii. The most prominent cardiac involvement in the milder phenotypes
   e. Spinal cord compression from thickening of the dura in the upper cervical spinal canal with resultant myelopathy: a frequent occurrence in patients with the milder forms
   f. Compression myelopathy associated with a kyphoscoliotic deformity of thoracolumbar spine

Diagnostic Investigations

1. Increased urinary excretion of glycosaminoglycans (Valayannopoulos et al. 2010)
   a. Dermatan sulfate accumulation
   b. Absence of chondroitin 4-sulfate, heparan sulfate, keratan sulfate, or hyaluronate using thin layer chromatography (TLC) or high-resolution electrophoresis fractionation
2. Biochemical diagnosis (Valayannopoulos et al. 2010)
   a. Demonstration of deficient N-acetylgalactosamine-4-sulfatase (arylsulfatase B) in cultured skin fibroblasts or leukocytes (generally less than 10% of the lower limit of normal ASB activity)
   b. Identification of normal enzyme activity of a different sulfatase to exclude the diagnosis of multiple sulfatase deficiency

3. Demonstration by an accredited laboratory of intermediate levels of leukocyte ASB enzyme activity in both parents to support diagnosis of carriers
4. Slit-lamp examination for corneal opacities
5. Radiographic features
   a. Skeletal changes similar to radiographic findings of Hurler syndrome in the severe form
   b. Striking examples of dysostosis multiplex, particularly severe pelvic changes
      i. Acetabulum hypoplasia
      ii. Small flared iliac wings
   c. Macrocephaly with a large sella
   d. Vertebrae
      i. Ovoid deformity of vertebral bodies
      ii. A hood-shaped deformity or blunt anterior hypoplasia of vertebral bodies of L1 or L2
      iii. Epiphyseal dysplasia of the proximal femur
      iv. An elongated femoral neck in a valgus position
      v. Irregular diaphyseal distension of tubular bones
      vi. Vertebral subluxation, especially atlantoaxial joint
6. Confirmation by mutational analysis of the *ARSB* gene (Karageorgos et al. 2007) should be considered if the diagnosis is in question, and is important in carrier testing or prenatal diagnosis.
   a. Sequence analysis
   b. Duplication/deletion analysis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is a carrier
2. Prenatal diagnosis
   a. Demonstration of deficient N-acetylgalactosamine-4-sulfatase (arylsulfatase B) in amniotic-fluid cells from the pregnancy at risk (Kleijer et al. 1976)
   b. Mutation analysis of amniocytes and CVS in characterized families
3. Management
   a. Supportive care
      i. Optimizing general health with nutrition counseling
      ii. Occupational and physical therapy
      iii. Management of individual symptom complications
         a) Respiratory insufficiency requiring oxygen and/or positive airway pressure during sleep, tonsillectomy, adenoidectomy, or tracheostomy
         b) Cardiac failure requiring medications
   b. Keratoplasty for progressive opacification of the cornea
   c. Surgery to improve common nerve entrapment syndromes, particularly of the carpal tunnel
   d. Successful single and double (aortic and mitral) valve replacements have been reported in MPS.
   e. Substantial improvement following laminectomy and excision of the markedly thickened dura in myelopathy due to spinal canal stenosis
   f. Bone marrow transplantation or hematopoietic stem cell transplantation in patients with the severe form of MPS VI
      i. Efficacy
         a) Arylsulfatase B activity increased to normal levels in peripheral lymphocytes and granulocytes
         b) Decreased urinary excretion of acid mucopolysaccharide
         c) Decreased inclusions in the liver
         d) Improved cardiopulmonary function
         e) Improved visual acuity and joint mobility
         f) May provide better life quality (improved motor function, exertional dyspnea, severe snoring, and vertigo) (Wang et al. 2008)
      ii. Not universally performed due to lack of a suitable donor and is associated with significant morbidity and mortality
   g. Allogeneic CD34 selected peripheral stem cell transplant with rapid hemopoietic and biochemical reconstitution
   h. Enzyme replacement therapy
      i. Clinical trials of enzyme replacement therapy with human recombinant N-acetylgalactosamine-4-sulfatase (rhASB) (Harmatz et al. 2006, 2004)
         a) Well tolerated
         b) Reduces lysosomal storage as evidenced by a dose-dependent reduction in urinary glycosaminoglycan
         c) An increase in distance walked

d) Stair-climbing ability
e) Shoulder range of motion
f) Decrease in pain and arthritis

ii. The largest gains occurred in patients with advanced disease receiving high-dose rhASB

iii. Currently, a recombinant formulation (galsulfase) (Naglazyme®) is available as an enzyme replacement therapy: Therapeutic response may be influenced by disease stage, and early intervention may lead to better outcomes (El Dib and Pastores 2009).

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Fig. 1 (**a**–**d**) A boy with MPS VI showing dwarfism, short trunk with protruding sternum, and crouching stance

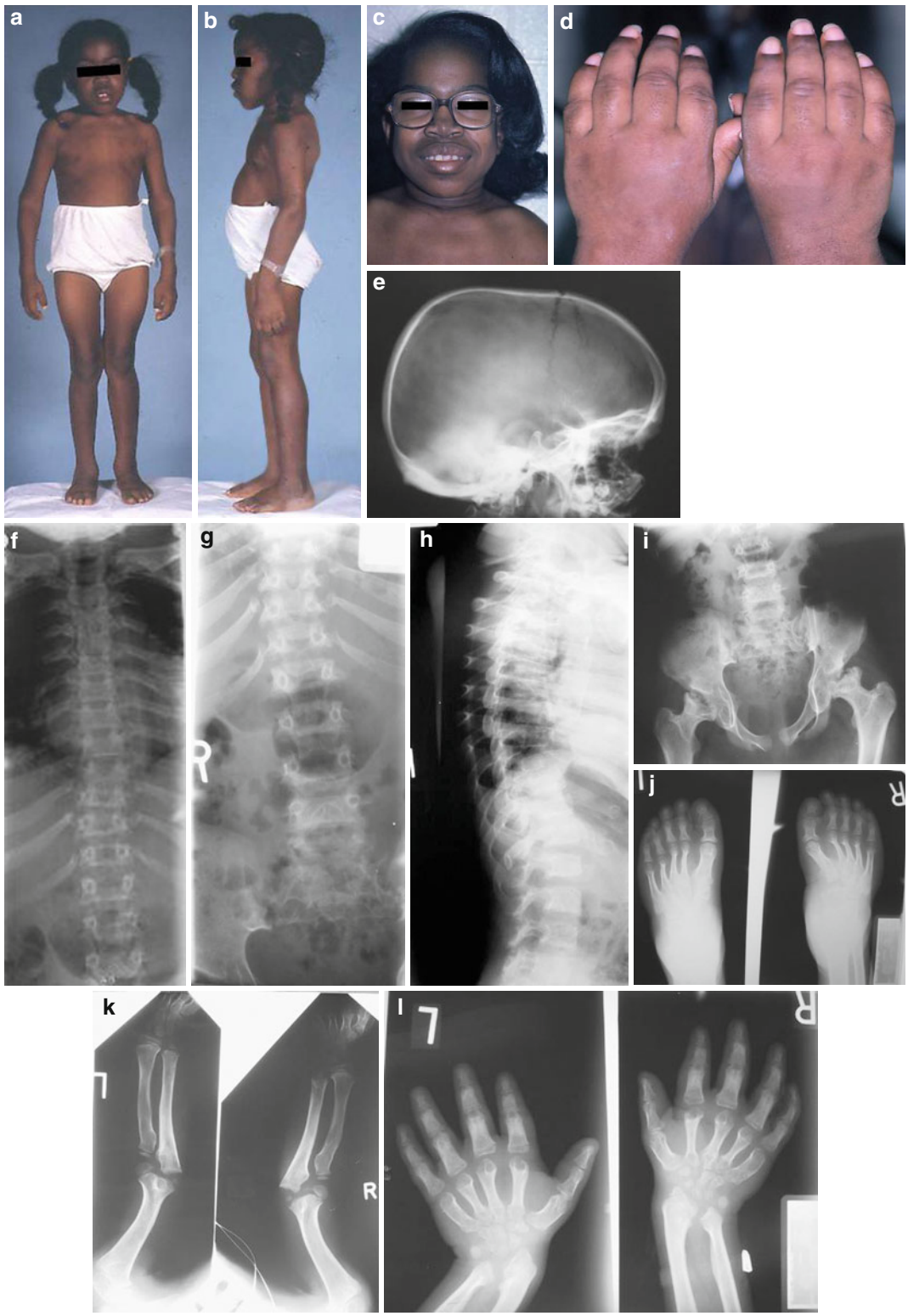

Fig. 2 A girl with MPS VI showing dwarfism, short trunk with sternal protrusion, and craw hands (**a**-**d**). The patient's radiographs demonstrate dysostosis multiplex (**e**-**l**)

Mucolipidosis II

Mucolipidosis II (ML II), or I-cell disease, is a rare autosomal recessively inherited storage disorder of lysosomal enzyme hydrolase trafficking due to deficient activity of the multimeric enzyme UDP-*N*-acetylglucosamine-1-phosphotransferase. The term "I-cell disease" is derived from the observation that fibroblasts from affected individuals show dense inclusions filled with storage material.

Synonyms and Related Disorders

I-cell disease

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Uridine diphosphate (UDP)-*N*-acetylglucosamine-1-phosphotransferase (GlcNAc-PT) (Beck et al. 1995)
   a. An enzyme that transfers phosphate groups onto oligosaccharide units of lysosomal enzyme precursors
   b. Deficient in mucolipidosis II (also in mucolipidosis III) (Bargal et al. 2006)
   c. Consequences of the enzyme deficiency
      i. Not generating common phosphomannosyl recognition marker of acid hydrolases
      ii. The enzymes not targeting to the lysosomes
      iii. Secretion of the enzymes into the extracellular space (high activities found in the serum of the patients)
      iv. Considerable reduction of the enzyme levels inside the cells (fibroblasts)
   d. GlcNAc-PT is made up of three subunits, α, β, and γ.
      i. The α/β subunits are encoded by the *GNPTA* gene (Tiede et al. 2005) and have a catalytic function (Reitman and Kornfeld 1981, Reitmman et al. 1981).
      ii. The γ subunit which is encoded by the *GNPTAG* gene (Raas-Rothschild et al. 2000) has a recognition and regulation function (Reitman et al. 1981a, 1981b).
   e. Mutations in *GNPTAB*, which encodes the α/β subunit, cause ML II and ML III α/β (Tiede et al. 2005). The γ subunit is encoded by *GNPTG*, and mutations in this gene lead to the clinically milder condition known as ML III γ (Raas-Rothschild et al. 2000).
3. Genotype-phenotype correlations (Leroy et al. 2009)
   a. *GNPTAB* gene sequencings have confirmed that homozygous and compound heterozygous genotypes that predict enzyme inactivation (caused by premature translation termination and/or frameshift effects) result in the ML II phenotype.
   b. The combination of less "morbid" mutations, such as missense and most of the splice-site mutations that may decrease but not abolish enzyme activity, often yields the more slowly evolving ML III phenotype alpha/beta with later clinical onset (Paik et al. 2005; Tiede et al. 2005; Bargal et al. 2006; Kudo et al. 2006).

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c. Some children have clinically intermediate phenotypes between the delineated ML II and ML III alpha/beta.
d. Correlating these phenotypes with the specific mutant genotypes requires more detailed and extensive clinical research efforts that are ongoing (Cathey et al. 2008).

Clinical Features

1. Symptoms and signs of ML II are similar to those encountered in patients with mucopolysaccharidoses and to a lesser extent gangliosidoses: characterized by coarse facial features, short stature, hyperplastic gums, organomegaly, and retarded psychomotor development (Maroteaux and Lamy 1966; Okada et al. 1985; Leroy and Opitz 1969).
2. A wide range of inter- and intrafamilial variability
   a. Age of onset: present at birth or appear in the first few months of life
   b. Organ manifestation
   c. Radiological findings
   d. Unusual findings in some patients
      i. Pericardial effusion
      ii. Profound brain atrophy
3. Features evident in affected newborn
   a. Coarse facial (gargoyle-like) features (Lee and O'Donnell 2003)
      i. Puffy eyelids with slight exophthalmia
      ii. Excessive prominence of the epicanthal folds
      iii. Depressed nasal bridge
      iv. Full cheeks exhibiting multiple fine telangiectasia
      v. Gingival hyperplasia and alveolar enlargement with buried teeth
      vi. Thick tongue
   b. Restricted joint mobility
   c. A tight, thickened skin
4. Early clinical features
   a. Low birth weight
   b. Congenital hip dislocation
   c. Pes equinovarus
   d. Joint contractures
   e. Inguinal hernias
   f. Generalized hypotonia
   g. Ocular abnormalities (Libert et al. 1977)
      i. Corneal clouding
      ii. Glaucoma
      iii. Megalocornea
5. Older patients
   a. Predominant features
      i. Skeletal deformities (dysostosis multiplex)
      ii. Progressive failure to thrive
      iii. Developmental delay with variable mental retardation
   b. Other features
      i. Short stature
      ii. Craniosynostosis
      iii. Progressive stiffness of all joints, first apparent in the shoulders
      iv. Variable hepatosplenomegaly
      v. Congestive heart failure
      vi. Recurrent pulmonary infections
6. Natural history (Leroy and Martin 1975)
   a. Slowly progressive course
   b. Fatal outcome usually before 4 years of age
7. ML III (see next Chapter Mucolipidosis III)
   a. Genetically heterogeneous
   b. A milder disorder with attenuated characteristics and survival to adult life (Kelly et al. 1975)
8. Differential diagnosis with other lysosomal storage disease (Leroy et al. 2009)
   a. Mucopolysaccharidosis type 1 H (see the Chapter Mucopolysaccharidosis I)
   b. GM1 gangliosidosis type 1
      i. More severe hepatomegaly
      ii. Dysostosis multiplex indistinguishable
      iii. Beta-D-galactosidase deficiency in leukocytes and plasma
   c. Infantile galactosialidosis
      i. Storage phenomena less pronounce than in GM1 gangliosidosis but more than in ML II
      ii. Absence of acid sialidase and of beta-D-galactosidase activity in leukocytes in addition to cathepsin A deficient in leukocytes and cultured fibrocytes
      iii. May present as congenital nonimmune hydrops fetalis
   d. Infantile sialidosis (formerly sialidosis type 2)
      i. May present as congenital nonimmune hydrops fetalis
      ii. More chronic disorder with moderate organomegaly, dysostosis multiplex that is milder than that of ML II
      iii. Mild limitation of joint mobility

iv. Growth and cognitive development considerably better than in children with ML II

e. Infantile free sialic acid storage disease
   i. Excessive amounts of free sialic acid in the urine
   ii. Deficient acid sialidase only
   iii. Less facial dysmorphism and much less dysostosis multiplex than ML II

Diagnostic Investigations

1. Elevated activities of multiple lysosomal enzymes in serum or plasma, including the following enzymes: Activity of nearly all lysosomal hydrolases is 5- to 20-fold higher in plasma and other body fluids than in normal controls because of improper targeting of lysosomal acid hydrolases to lysosomes in ML II.
   a. Arylsulfatase A
   b. α-Mannosidase
   c. β-Glucuronidase
   d. β-Hexosaminidase
2. Deficient enzyme activities in cultured fibroblasts, including the following enzymes:
   a. β-Galactosidase
   b. Arylsulfatase A
   c. β-Hexosaminidase
   d. β-Glucuronidase
   e. α-L-iduronidase
3. Primary biochemical defect: decreased or absent N-acetylglucosamine-1-phosphotransferase in cultured fibroblasts and leukocytes
4. Excessive urinary excretion of oligosaccharides
5. Normal excretion of urinary mucopolysaccharide
6. Radiography
   a. Fetal radiography
      i. Diffuse decrease in bone mineralization
      ii. A coarse, lacy, trabecular pattern
      iii. Overall shortening and undermodelling of the long bones
      iv. Subperiosteal bone deficiency in the diaphysis giving the appearance of periosteal new bone (cloaking)
      v. Retarded ossification of the vertebral bodies
      vi. Hypoplasia of the anterior superior aspect of the upper lumbar vertebral bodies
      vii. Broad ribs
      viii. Abnormal pelvis with squared iliac wings and flattened acetabular roofs
      ix. Brachyphalangy
      x. Mild tapering of the proximal ends of the metacarpals
      xi. A small irregular calcaneal "ossification center"
   b. Radiographic findings in early infancy
      i. Diffuse demineralization
      ii. Metaphyseal cupping and fraying
      iii. Excessive periosteal new bone formation
      iv. Diaphyseal expansion of the long tubular bones
      v. Irregular trabeculation without differentiation between the cortical and medullary zones
      vi. Mild anteriosuperior hypoplasia of the upper lumbar bodies
      vii. Pelvic dysplasia
      viii. Occasional punctate calcifications and bone defects following intrauterine calcific deposits
      ix. Skeletal changes in the neonatal I-cell disease resembling those of rickets, osteomyelitis, and hyperparathyroidism (David-Vizcarra et al. 2010)
   c. Dysostosis multiplex
      i. Neurocranium
         a) Long and thick
         b) Thickened and sclerotic cranial base
      ii. Widened ribs
      iii. Kyphoscoliosis
      iv. Anterior beaking and wedging of the vertebral bodies
      v. Lumbar gibbus deformity
      vi. Cloaking appearance of the long tubular bones
      vii. Proximal pointing of the metacarpals
      viii. Bullet-shaped phalanges
      ix. Claw hand deformities
7. Slit lamp examination to demonstrate corneal clouding
8. Echocardiography for valve thickening and valve insufficiency
9. MRI or CT scan: mild brain atrophy in most cases
10. Light microscopy and electron microscopy
    a. Inclusion bodies in peripheral lymphocytes in blood smear

b. An increased number of empty, large vacuoles that may fill the cytoplasm of cultured skin fibroblast cells
c. Presence of numerous intracytoplasmic inclusions in cells of mesenchymal origin
   i. Membrane-bound vacuoles filled with fibrillogranular material
   ii. Appear to contain a variety of lipids, mucopolysaccharides, and oligosaccharides
d. Cytoplasmic inclusions also observed in various types of cells in fetal I-cell disease
e. Molecular genetic diagnosis (Leroy et al. 2009)
   i. Sequence analysis: Bidirectional sequencing of the entire *GNPTAB* coding region detects two disease-causing mutations in more than 95% of persons with ML II.
   ii. Deletion/duplication analysis is also clinically available.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not surviving to reproductive age
2. Prenatal diagnosis (Carey et al. 1999)
   a. Ultrasonography
      i. Intrauterine growth retardation
      ii. Short tubular bones
   b. Measuring the levels of lysosomal enzymes (elevated activity of several lysosomal hydrolases) in cell-free amniotic fluid or cultured amniocytes
   c. Assay of the transferase activity (deficient) in cultured CVS cells and amniocytes
   d. Electron microscopy of chorionic villus biopsy tissue for detection of inclusion bodies
   e. Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutations in the family (Leroy et al. 2009).
3. Management
   a. Supportive care
      i. Low-impact therapies to avoid joint and tendon strain, including aqua therapy
      ii. Cognitive stimulation through interactive programs
      iii. Gingivectomy as needed for oral health
      iv. Myringotomy tube placement as needed for recurrent ear infections
   b. Prevention of secondary complications
   c. Bone marrow transplant from an HLA-identical carrier sibling (Grewal et al. 2003)
      i. Neurodevelopmental gains
      ii. Prevention of cardiopulmonary complications
      iii. No alteration to the course of musculoskeletal disease

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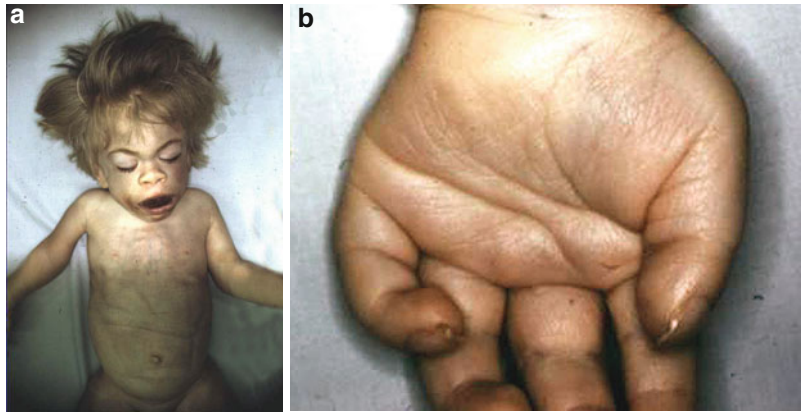

Fig. 1 (**a**, **b**) An 8-year-old girl with I-cell disease. She had severe growth retardation (67 cm), coarse facial features, claw hands, severe skeletal dysplasia, marked gingival hypertrophy, cardiomegaly with marked thickening and deformity of mitral and tricuspid valves, and bilateral duplication of ureters. Histological investigations showed foam cell infiltration in renal glomeruli, splenic corpuscles, atrioventricular valves, and thymus

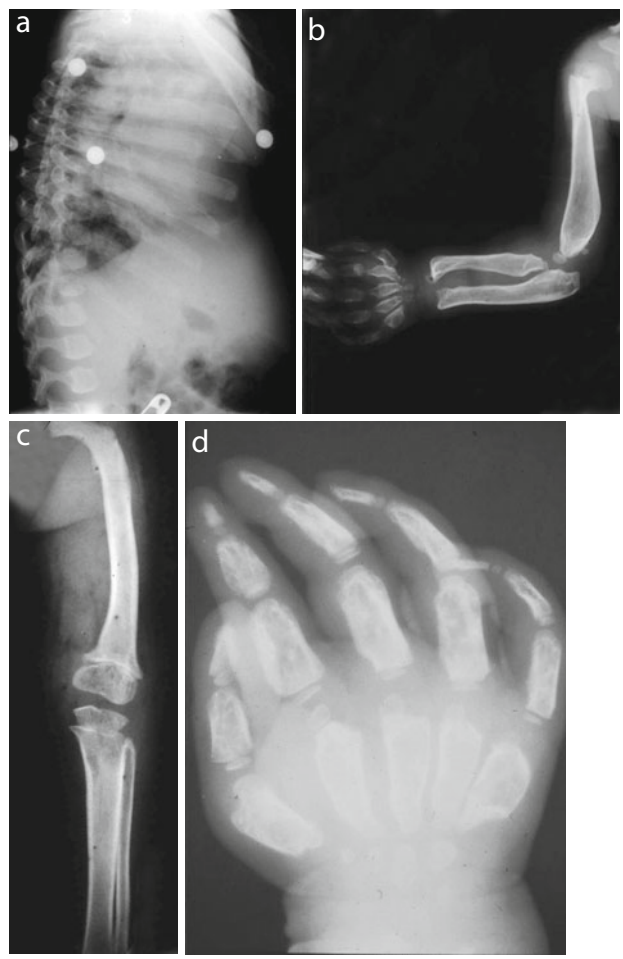

Fig. 2 Radiographs showed generalized dysplastic changes in the chest and upper and lower extremities. The ribs were extremely wide (**a**). Some vertebral bodies were slightly hook-shaped. The pedicles were long and there was slight gibbus. Midshafts of the humerus, radius, and ulna were wide and the neck of the humerus in varus position (**b**). Widening of the midshafts of the lower extremities was less marked than in the upper extremities (**c**). Metacarpals and phalanges were wide, but distal phalanges were short and thin (**d**). Metacarpal bones pointed proximally. Carpal bones were hypoplastic

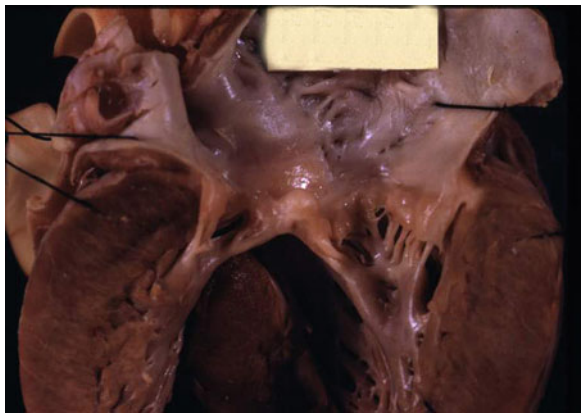

Fig. 3 Mitral valve was thickened and deformed

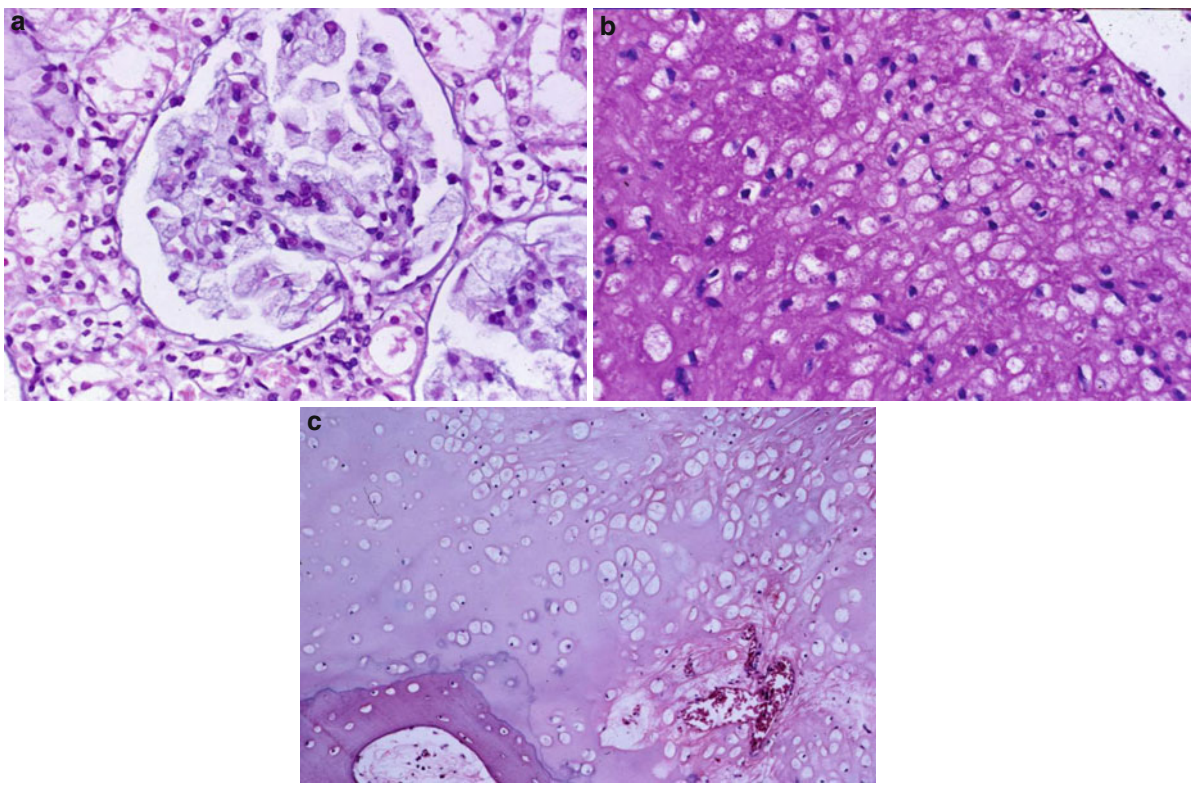

Fig. 4 (**a**–**c**) Foam cells were present in the renal glomeruli, mitral valve, and chondrocytes of cartilage

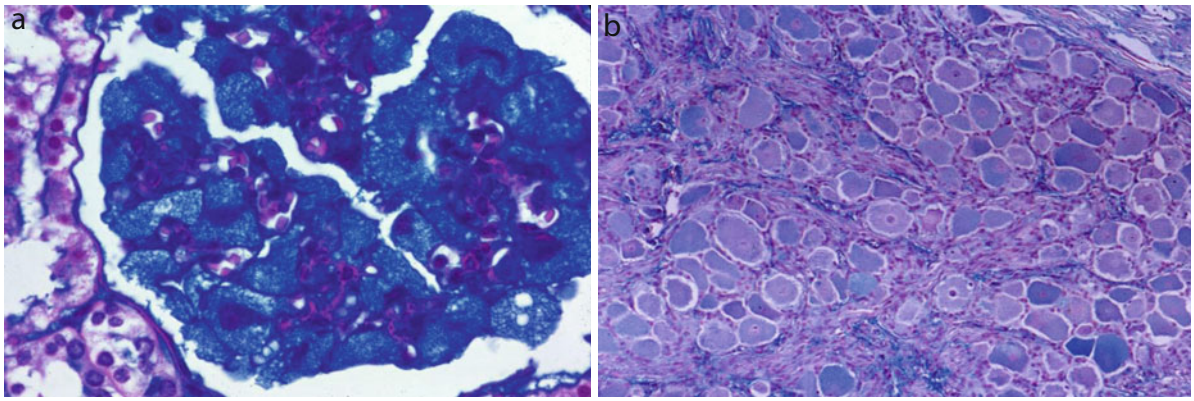

Fig. 5 (**a**, **b**) The foamy material was reactive with colloidal iron stain (renal glomeruli) and sympathetic ganglion (Alcian blue stain), indicating the presence of mucopolysaccharide

Mucolipidosis III

In 1966, Maroteaux and Lamy first described four girls with pseudo-Hurler polydystrophy, a condition milder in severity than the Hurler syndrome and similar to the Scheie syndrome but without hepatosplenomegaly, cloudy cornea or mucopolysaccharidiuria. In 1970, Spranger and Wiedemann designated pseudo-Hurler polydystrophy as mucolipidosis III because of Hurler-like features and vacuolated bone marrow cells (Kelly et al. 1975b).

Synonyms and Related Disorders

Pseudo-Hurler Polydystrophy

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Basic defect
   a. Resulting from deficiency of the enzyme UDP-*N*-acetylglucosamine: lysosomal protein precursor *N*-acetyl glucosamine 1-phosphate transferase (G1cNAcPT) (Mucolipidosis II also caused by deficiency of the same enzyme)
   b. Genetic complementation analysis of cultured fibroblasts derived from patients with mucolipidosis III identified complementation groups A, B, and C.
   c. Inability to form the correct recognition marker on lysosomal enzymes resulting in a marked intracellular deficiency of most lysosomal enzymes in various tissues, impairment of many lysosomal catabolic processes, and concomitant increase in lysosomal enzymes in plasma
3. Recent finding of molecular basis for mucolipidosis IIIC (variant pseudo-Hurler polydystrophy): a mutation, in C at codon 167, in the γ subunit of the G1cNAcPT in mucolipidosis IIIC (Raas-Rothschild et al. 2000). Mutations in *GNPTAB*, which encodes the α/β subunit, cause ML II and ML III α/β (Tiede et al. 2005).

Clinical Features

1. Onset of disease
   a. Usually appear at 2–4 years of age
   b. Progress slowly
   c. First sign: stiffness in the hands and shoulders
2. Short stature
3. Mild Hurler-like facial dysmorphism, usually apparent after age 6 years
4. Ophthalmologic abnormalities
   a. Constant ocular features
      i. Corneal opacities consisting of fine, peripheral infiltrates
      ii. Hyperopic astigmatism
   b. Optic nerve head swelling
   c. Surface wrinkling maculopathy
   d. Retinal vascular tortuosity
5. Mild mental retardation
6. Valvular heart disease
7. Orthopedic problems
   a. Stiffness of the hands progressing to claw hand deformities by 6 years of age in all patients
   b. Slow progression of the skeletal dysplasia during school years, the resulting physical disability most apparent in the hands, hips, elbows, and shoulders

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c. Generalized joint stiffness (limited joint mobility)
d. Spine abnormalities
   i. Kyphosis
   ii. Lordosis
   iii. Gibbus
e. Hip pain
f. Hip dysplasia
g. Less common clinical features (Smuts et al. 2009)
   i. Claw hand deformities
   ii. Carpal tunnel syndrome further complicates the claw hand deformities.
   iii. Recurrent, intermittent trigger fingers
   iv. Claw toes

8. Mucolipidosis III gamma (also known as variant ML III)
   a. Clinical features similar to but milder than those observed in individuals with mucolipidosis III alpha/beta (ML III alpha/beta)
   b. Affected individuals are mostly of Middle Eastern descent (Raas-Rothschild et al. 2000, 2004; Cathey et al. 2007).
9. Natural course of the illness: survive into beyond the fifth to sixth decade
10. Differential diagnosis (Leroy et al. 2009)
    a. Lysosomal storage diseases
       i. Attenuated MPS I (formerly called Hurler-Scheie syndrome or Scheie syndrome)
       ii. Attenuated MPS II (Hunter syndrome)
       iii. Morquio disease type B (MPS IV B)
       iv. Maroteaux-Lamy disease type B (MPS VI B)
       v. Sly disease type B (MPS VII B)
    b. Disorders clinically allied to the oligosaccharidoses
       i. Late infantile sialic acid storage disorder or Salla disease (free sialic acid storage disorders) and mucosulfatidosis: In both disorders, the neurodegenerative aspects are much more prominent.
       ii. In free sialic acid storage disorders, dysostosis multiplex is absent or minimal, and urinary excretion of free sialic acid is excessive.
       iii. In mucosulfatidosis, urinary acid mucopolysaccharides and sulfatides are excessive.
    c. Osteochondrodysplasias

Diagnostic Investigations

1. Radiography showing dysostosis multiplex (Melhem et al. 1973; Freisinger et al. 1992)
   a. Pelvis
      i. Flaring of the iliac wings
      ii. Constriction of the iliac bodies
      iii. Oblique acetabular roofs
   b. Vertebral bodies
      i. Moderately flattened
      ii. Presenting as a roughly ovoid contour
      iii. Underdevelopment of posterior parts in the dorsal spine
      iv. Hypoplasia of anterior third in the lumbar spine
      v. Irregular endplates
      vi. Scoliosis secondary to vertebral abnormalities
   c. Tubular bones
      i. Shortened and wide
      ii. The most striking changes observed in the proximal femur
         a) A small, flattened and irregular epiphysis
         b) Coxa valga deformity of the neck
         c) Subluxation
      iii. Hands
         a) Short first metacarpals
         b) Mild proximal pointing of the metacarpals
         c) Mild to moderate claw-hand deformities
         d) Relatively wide diaphysis of some phalanges
      iv. Retarded bone age
   d. Skull: normal despite the presence of craniostenosis in some patients
2. Nerve conduction test and electromyography to confirm the carpal tunnel syndrome
3. Slit-lamp examination for cornea opacification
4. Normal urinary excretion of acid mucopolysaccharides
5. Presence of cytoplasmic inclusions within cultured fibroblasts as demonstrated by phase-contrast or dark-field microscopy
6. Bone marrow: large, vacuolated plasmocytes
7. ML III alpha/beta (Leroy et al. 2009)
   a. Activity of nearly all lysosomal hydrolases: up to tenfold higher in plasma and other body fluids than in normal controls because of inadequate targeting to lysosomes (also in ML III gamma)

   b. Urinary excretion of oligosaccharides, a nonspecific finding, can be excessive but is not always present
   c. Significant deficiency (1–10% of normal) of the activity of the enzyme UDP-*N*-acetylglucosamine: Lysosomal hydrolase *N*-acetylglucosamine-1-phosphotransferase (GNPTA), encoded by *GNPTAB*, confirms the diagnosis.
8. Molecular genetic testing
   a. ML III alpha/beta (Leroy et al. 2009).
      i. Bidirectional sequencing of the entire *GNPTAB* coding region detects two disease-causing mutations in more than 95% of individuals with ML III alpha/beta. Such testing is clinically available.
      ii. Duplication/deletion analysis is also available.
   b. In ML III gamma: Molecular testing of *GNPTG* detects two disease-causing mutations in more than 95% of individuals with ML III gamma (Raas-Rothschild and Spiegel 2010).

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is a carrier
2. Prenatal diagnosis (Falik-Zaccai et al. 2003)
   a. Diagnosis confirmed by markedly reduced lysosomal enzyme activities in cultured chorionic villi
   b. Identification of the disease-causing mutation in fetal DNA in a newly recognized large Bedouin-Moslem kindred, allowing prenatal diagnosis, carrier detection, and identification of couples at risk
   c. Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutations in the family.
3. Management (Hetherington et al. 1999)
   a. Physiotherapy for joint stiffness and contractures
   b. Padded insoles for clawing of toes
   c. Carpal tunnel decompression for the median nerve entrapment
   d. Pelvic osteotomy for severe hip dysplasia

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Fig. 1 (**a**, **b**) Patient 1 (9-year-old boy) with mucolipidosis III showing short stature, mild coarse facial features, flexion contractures of knees, hips, elbows, wrists, and fingers. Fibroblast lysosomal acid hydrolase study revealed β-galactosidase 0.06 (control: 0.36 μmoles/h/mg protein), β-glucuronidase 0.05 (0.21), β-glucosaminidase 0.03 (3.9), α-L-iduronidase 0.12 (0.87), and aryl-sulfatase A 0.10 (0.67)

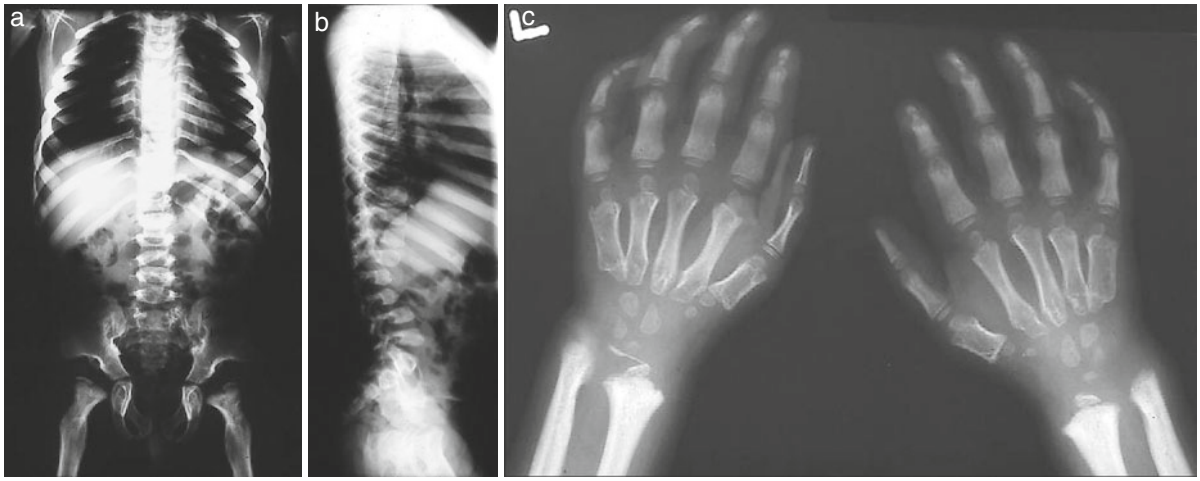

Fig. 2 (**a**–**c**) Radiographs of patient 1. Lateral lumbar spines showed severe hypoplasia with characteristic "beaked" configuration along their inferior aspects. Iliac bones were narrow and the basilar portions were hypoplastic with slanting acetabular roofs. Coxa valga deformity was present. Mild claw hand deformities with retarded bone age were evident

Fig. 3 (**a**, **b**) Patient 2 (sister of the patient 1) at age 7 years and 6 months showing similar clinical findings

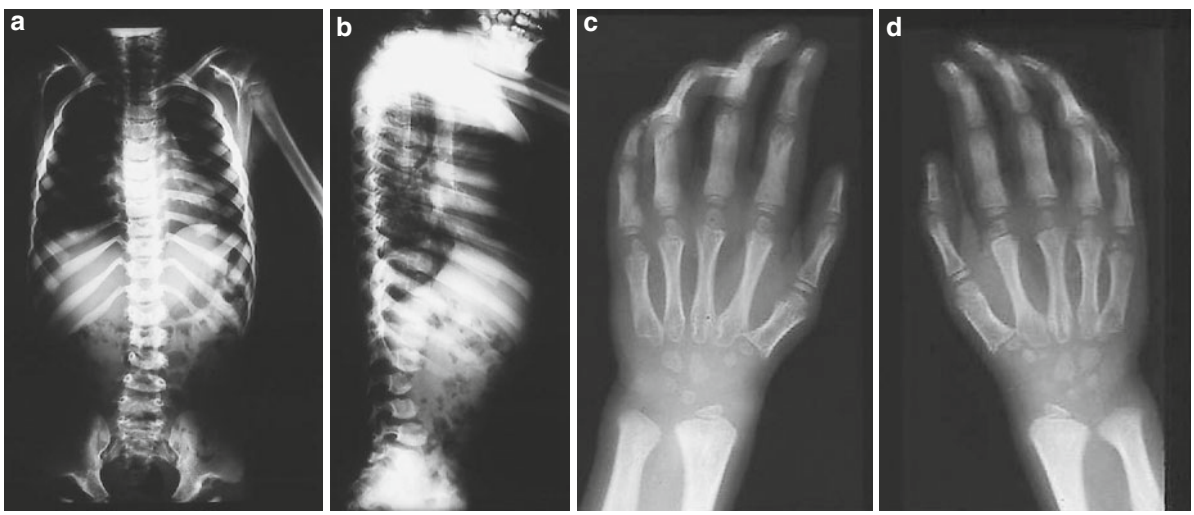

Fig. 4 (**a**–**d**) Radiographs of patient 2 showing similar radiographic findings

Fig. 5 (**a**, **b**) Two sisters (ages 10 years and 9 years) with mucolipidosis III showing developing delay, coarse facial features, claw hands, and more severe joint contractures. Radiographs (not shown) revealed bullet-shaped proximal phalanges, small carpal bones, and misshapen femoral heads

Multiple Endocrine Neoplasia Syndromes

The multiple endocrine neoplasia (MEN) syndromes are rare autosomal dominant conditions predisposing affected individuals to benign and malignant tumors of the pituitary, thyroid, parathyroids, and adrenals, endocrine pancreas, paraganglia, or nonendocrine organs. The classic MEN syndromes include MEN type 1 (MEN1) and MEN type 2 (MEN2). The prevalence of MEN1 is estimated to be 1 in 20,000–40,000 individuals and that of MEN2 is estimated to be 1 in 35,000 individuals (DeLellis et al. 2004).

MEN1 is a rare endocrine disorder presenting with various combinations of parathyroid, gastroenteropancreatic, and anterior pituitary tumors, but it can also include various combinations of more than 20 endocrine and nonendocrine tumors such as foregut, bronchial, and thymic carcinoids, lipomas and skin tumors (Gagel and Marx 2007). Generally, tumors in MEN1 are benign, although gastrinomas and foregut carcinoids may exhibit a malignant course (Falchetti et al. 2008).

MEN2 is a rare hereditary syndrome characterized by medullary thyroid carcinoma (MTC), unilateral or bilateral pheochromocytoma, and other hyperplasia and/or neoplasia of different endocrine tissues (Falchetti et al. 2008). If not diagnosed precociously, MTC can be fatal. MEN2 includes three clinical subtypes: MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC).

Synonyms and Related Disorders

Familial medullary thyroid carcinoma; MENI (multiple endocrine adenomatosis, Wermer syndrome); MENIIA (pheochromocytoma and amyloid-producing medullary thyroid carcinoma, Sipple syndrome); MENIIB (mucosal neuroma syndrome)

Genetics/Basic Defects

1. MEN1
   a. Caused by a germ-line mutation in the *MEN1* gene, which encodes the tumor suppressor protein menin
   b. Mutated gene: *MEN1* (inactivating mutations of the MEN1 gene)
      i. Mapped on chromosome 11q13
      ii. Menin: consists of ten exons with noncoding first exon and produces a 610-amino acid protein.
      iii. Two independent somatic mutations must occur within a single cell for tumor formation.
      iv. A single mutation is required in an individual with *MEN1*, since the first mutation is already present in all of the patient's cells (Pack et al. 1998; Vortmeyer et al. 1999).
      v. This accounts for the multiple tumors and the tumors occurring at an earlier age.
      vi. Approximately 700 different somatic and germline mutations have been identified (Thakker 2001).
   c. No genotype-phenotype correlations observed
2. MEN2
   a. Caused by germ line–activating missense mutations of the *RET* (*RE*arranged during *T*ransfection) proto-oncogene which:
      i. Mapped on chromosome 10q11.2

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ii. Encodes a receptor tyrosine kinase that functions as a signal transducer upon interaction with the glial-derived neurotrophic factor family of ligands (Santoro et al. 2004)
iii. MEN2-associated mutations: almost always located in exons 10, 11, or 13 through 16, although mutations in exons 5 and 8 have been reported on rare occasions (Dvorakova et al. 2005; Da Silva et al. 2003)

b. Strong genotype-phenotype correlations exist with respect to:
i. Clinical subtype
ii. Age at onset
iii. Aggressiveness of MTC in MEN2

c. MEN2A: at least 95% of individuals with MEN2A have an identifiable *RET* mutation (Schuffenecker et al. 1994; Mulligan et al. 1994)

d. MEN2B
i. An identifiable *RET* mutation in at least 98% of patients.
ii. The mutation is almost invariably M918T.
iii. Some individuals with mutation A883F (Mulligan et al. 1995; Gimm et al. 1997).

e. FMTC: mutated gene (*RET proto-oncogene*)

Clinical Features

1. MEN1 (Marini et al. 2006a, b; Callender et al. 2008; Falchetti et al. 2008)
   a. Presence of intrafamilial and interfamilial variation: highly variable in terms of the number of organ systems involved and the age of onset of tumors and symptoms
   b. MEN1 should be considered in patients with the following diagnoses:
      i. Primary hyperparathyroidism under age of 30 years
      ii. Primary hyperparathyroidism resulting from multigland involvement
      iii. Familial primary hyperparathyroidism
      iv. Zollinger–Ellison syndrome
      v. Multifocal pancreatic endocrine tumors or two or more MEN1-related tumors.
   c. Clinical diagnosis of MEN1 should be considered in:
      i. Patients with tumors in two of the three most commonly affected endocrine organs (parathyroid, pituitary, and pancreatic/duodenal endocrine tumors)
      ii. Patients with one such tumor and a family history of MEN1
   d. Clinical signs and symptoms: in order of decreasing frequency (Doherty 2005)
      i. Hypercalcemia
      ii. Nephrolithiasis
      iii. Peptic ulcer disease
      iv. Hypoglycemia
      v. Visual field loss
      vi. Hypopituitarism
      vii. Acromegaly
      viii. Galactorrhea–amenorrhea syndrome
      ix. Rarely Cushing's syndrome
   e. Characteristic endocrine tumors (Schussheim et al. 2001)
      i. Pituitary
         a) Prolactinoma (20%)
         b) GH and GH plus prolactin (10%)
         c) NF1 (5%)
         d) ACTH (2%)
         e) TSH and others (rare)
      ii. Parathyroid: adenoma (90%)
      iii. Foregut carcinoid
         a) Nonfunctioning gastric enterochromaffin-like cell tumor (10%)
         b) Bronchial carcinoid (2%)
         c) Thymic carcinoid (2%)
      iv. Entero-pancreatic
         a) Gastrinoma (40%)
         b) Insulinoma (10%)
         c) Nonfunctioning including pancreatic polypeptide (20%)
         d) Other (glucagonoma, VIPoma and somatostatinoma) (2%)
   f. Prognosis
      i. Decreased life expectancy, with a 50% probability of death by age of 50, and one half of MEN-1 patients die as a result of a malignant tumoral process or sequela of the disease (Wilkinson et al. 1993; Doherty et al. 1998; Dean et al. 2000)

ii. Pancreatic neuroendocrine tumors are responsible for significant morbidity and mortality in MEN1 kindreds

2. MEN2
   a. Following characteristics in a single patient
      i. Hallmark of MEN2: an extremely high lifetime risk of developing medullary thyroid carcinoma (MTC) (>95% in untreated patients)
      ii. Unilateral or bilateral pheochromocytoma
      iii. Other hyperplasia and/or neoplasia of different endocrine tissues
   b. Signs and symptoms (Richards 2010)
      i. Hypertension if a pheochromocytoma presents
      ii. Chronic constipation: constant finding in MEN2B patients resulting from hyperplasia of the intrinsic autonomic ganglia in the intestinal wall
      iii. A neck mass or dominant thyroid nodule with nontender anterior neck lymph nodes arising insidiously with progressive enlargement: may signify regional metastasis
      iv. MEN2B patients
         a) Marfanoid habitus (high-arched palate, pectus excavatum, bilateral pes cavus, and scoliosis)
         b) Neuromas on the eyelids, conjunctiva, nasal and laryngeal mucosa, tongue, and lips
         c) Prominent hypertrophied lips leading to a characteristic facies.
   c. Presence of three clinical subtypes
      i. MEN2A
      ii. MEN2B
      iii. Familial MTC (FMTC)
3. MEN2A
   a. The most common subtype.
   b. Associated with MTC.
   c. Risk of developing pheochromocytoma (approximately 50%).
   d. Risk of developing primary hyperparathyroidism (30–40%).
   e. Typical age at onset of biochemical evidence of MTC in untreated patients with MEN2A: 15–20 years. However, MTC is frequent in children ages 10 years and younger (Lips et al. 1994; Machens et al. 2003; O'Riordain et al. 1994).
   f. Rare variants of MEN2A can be associated with paraneoplastic syndromes.
      i. Cutaneous lichen amyloidosis
      ii. Excessive production of corticotrophin
      iii. Hirschsprung disease
4. MEN2B
   a. The rarest and most aggressive subtype
      i. Associated with the earliest onset (usually 10 years earlier than that for MEN2A) and most aggressive type of MTC
      ii. Pheochromocytomas (40–50% of patients)
      iii. Multiple neuromas and/or diffuse ganglioneuromatosis of the gastro-enteric mucosa (approximately 40% of patients)
   b. Characteristic facial appearance: resulting from mucosal neuromas in the tongue, lips, and eyelids (Schimke et al. 1968)
      i. Enlarged lips
      ii. A "bumpy" tongue
      iii. Eversion of the eyelids
   c. Often with a thin and lanky (Marfanoid) habitus with increased joint mobility, and with decreased subcutaneous fat
   d. Frequently with thickening of the corneal nerves or ganglioneuromatosis of the gastrointestinal tract, which can result in abdominal distention, megacolon, constipation, or diarrhea
   e. The physical traits: usually evident in early childhood
   f. Without prophylactic thyroidectomy at a young age (before 1 year of age), most patients with MEN2B develop metastatic MTC in childhood or adolescence (O'Riordain et al. 1994)
   g. Patients with MEN2B do not develop primary hyperparathyroidism
5. Familial medullary thyroid carcinoma (FMTC)
   a. MTC is the only clinical feature
   b. Refers to occurrence of medullary thyroid cancer in at least four affected members within the same family with documented absence of other endocrinopathies
   c. Clinical course of MTC
      i. More benign than that of MEN2A and MEN2B
      ii. Prognosis: relatively good in most cases

6. Differential diagnosis of other category of MEN (Callender et al. 2008)
   a. Von Hippel–Lindau syndrome (VHL)
      i. Mutated gene: *VHL*
      ii. Manifestations
         a) Pheochromocytoma
         b) Retinal and central nervous system hemangioblastoma
         c) Renal cysts and clear cell carcinoma
         d) Pancreatic cysts and islet cell tumors
         e) Endolymphatic sac tumors
         f) Papillary cystadenomas of the epididymis and broad ligament
   b. Familial pheochromocytoma/paraganglioma syndrome
      i. Mutated gene: *SDHB, SDHC, SDHD*
      ii. Manifestations: multiple paragangliomas and pheochromocytoma
   c. Cowden syndrome
      i. Mutated gene: *PTEN*
      ii. Manifestations
         a) Nonmedullary thyroid cancer (usually follicular rather than papillary)
         b) Benign and malignant tumors of skin, oral mucosa, breast, and uterus
   d. Carney complex
      i. Mutated gene: *PRKAR1A*
      ii. Manifestations
         a) Endocrine tumors (including thyroid, pituitary, and primary pigmented nodular adrenocortical diseases)
         b) Characteristic skin pigmentation
         c) Myxomas
         d) Melanotic schwannomas
   e. Familial isolated hyperparathyroidism
      i. Mutated gene: *MEN1, HRPT2, CASR*, others
      ii. Manifestations: nonsyndromic primary hyperparathyroidism
   f. Hyperparathyroidism-jaw tumor syndrome
      i. Mutated gene: *HRPT2*
      ii. Manifestations
         a) Primary hyperparathyroidism (usually single adenoma)
         b) Ossifying fibromas of maxilla or mandible
         c) Renal cysts and hamartomas
         d) Fifteen percent risk of parathyroid carcinoma
   g. Familial hypocalciuric hypercalcemia
      i. Mutated gene: *CASR*
      ii. Manifestations
         a) Benign hypercalcemia.
         b) Hypocalciuria.
         c) Low to normal parathyroid hormone levels.
         d) Renal calcium-to-creatinine clearance ratio <0.01.
         e) Parathyroidectomy does not cure hypercalcemia.
   h. Neurofibromatosis type I
      i. Mutated gene: *NF1*
      ii. Manifestations
         a) Pheochromocytoma
         b) Characteristic physical features (e.g., café-au-lait spots, neurofibromas, axillary and inguinal freckling)
   i. Familial adenomatous polyposis
      i. Mutated gene: *APC*
      ii. Manifestations
         a) Hundreds of adenomatous colon polyps
         b) Colon cancer
         c) Cribriform morular variant of papillary thyroid cancer
   j. Familial nonmedullary thyroid cancer
      i. Mutated gene: unknown
      ii. Manifestations: nonsyndromic nonmedullary thyroid cancer

Diagnostic Investigations

1. Diagnosis of component tumors in MEN1 (Callender et al. 2008)
   a. Hyperparathyroidism
      i. An elevated or high-normal serum calcium level in concordance with an inappropriately elevated serum parathyroid hormone level
      ii. A 24-h urine collection documenting no evidence of hypocalciuria (urinary calcium excretion <100 mg/24 h) should be performed to exclude the possibility of familial hypocalciuric hypercalcemia
   b. MEN1-related pituitary adenomas
      i. Most common functioning tumors produce prolactin (prolactinomas), growth hormone (somatotropinomas), or corticotropin
      ii. Approximately 15% of tumors are nonfunctioning with no hormone production (DeLellis et al. 2004)

c. Pancreatic and duodenal tumors
   i. Gastrinomas
      a) Gastrin level usually >1,000 pg/mL
      b) A rise in the gastrin level of >200 pg/mL by a secretin stimulation test confirms the diagnosis
      c) Tumors localized by a combination of octreotide scan, CT, and endoscopic ultrasonography
   ii. Insulinomas presents as "Whipple's triad":
      a) Fasting or exercise-induced hypoglycemia
      b) Plasma glucose level <50 mg/dL
      c) Reversal of symptoms with administration of glucose
      d) Localized by CT and endoscopic ultrasonography
   iii. Glucagonomas
      a) A serum glucagons level >1,000 pg/mL
      b) A secretin stimulation test may be useful
      c) Localized with an octreotide scan, CT, and endoscopic ultrasonography
   iv. Vasoactive intestinal peptide tumors (VIPomas)
      a) Fasting plasma vasoactive intestinal peptide (VIP) levels >200 pg/mL
      b) VIPomas: usually located in the body and tail of the pancreas and are localized by an octreotide scan, CT, and endoscopic ultrasonography
   v. Somatostatinoma
      a) A fasting somatostatin level of >100 pg/mL
      b) Localized with an octreotide scan, CT, and endoscopic ultrasonography
   vi. Nonfunctioning MEN1-associated pancreatic endocrine tumors: localized by an octreotide scan, CT, and endoscopic ultrasonography
d. Other tumor types: not part of the diagnostic criteria for MEN1, but their presence helps to support a diagnosis of MEN1
   i. Foregut (thymic, bronchial, or gastric) carcinoid tumors
   ii. Adrenal cortex tumors (adenomas, pheochromocytoma, adrenocortical carcinomas)
   iii. Thyroid tumors (follicular adenomas, goiters, nonmedullary thyroid carcinoma)
   iv. Benign facial angiomas
   v. Collagenomas of the neck, upper limbs and chest
   vi. Subcutaneous or visceral lipomas
   vii. Uterine or esophageal leiomyomas
   viii. Meningiomas
   ix. Spinal ependymomas

2. Diagnosis of component tumors in MEN2 (Falchetti et al. 2008).
   a. Medullary thyroid carcinoma
      i. Pentagastrin or calcium stimulation to evaluate calcitonin secretion: earlier detection of MTC
      ii. Ultrasonography, CT, or MRI: localize tumor extension and possible distant metastases
   b. Pheochromocytoma
      i. 24-h measurement of urinary excretion of catecholamines and their metabolites to assess adrenal gland function: recommended on an annual basis
      ii. CT and MRI to localize the tumor
   c. Primary hyperparathyroidism: diagnosis made by elevated serum PTH and calcium concentrations
3. Routine surveillance of presymptomatic patients and treated patients who are currently without evidence of disease (Brandi et al. 2001).
   a. Annual biochemical testing for all tumor types
      i. Parathyroid: serum calcium, parathyroid hormone (starts to screen at age of 8 years)
      ii. Gastrinoma: serum gastrin (starting at age of 20 years)
      iii. Insulinoma: fasting serum glucose, insulin (starting at age of 5 years)
      iv. Other enteropancreatic: chromogranin A, glucagons, proinsulin (starting at age of 20 years)
      v. Anterior pituitary: prolactin, insulin-like growth factor 1 (starting at age of 5 years)
   b. Imaging studies (CT or MRI) every 3 years
      i. Other enteropancreatic: octreotide scan, CT, or MRI (starting at age of 20 years)
      ii. Anterior pituitary: MRI of the brain (starting at age of 5 years)
      iii. Foregut carcinoid: CT (starting at age 30 years)
4. Molecular genetic testing for MEN1
   a. Should be offered to patients in whom a diagnosis of MEN1 is being considered.
   b. The benefit of offering genetic testing: a diagnosis of MEN1 at an early age allows

patients to be monitored for the development of subsequent MEN1-related tumors
   c. Sensitivity of genetic testing: varies, depending on the combination of affected organs and whether the patient is an index or familial case
   d. Mutations can be identified in only 75–90% of patients with a clinical diagnosis of MEN1.
      i. A negative test result cannot definitively rule out the risk for further MEN1-related tumors
      ii. Follow-up screening recommendations in such cases are controversial and require careful consideration of the index of suspicion of MEN1 based on the patient's personal and family history.
5. Molecular genetic testing for MEN2 (Moline and Eng 2010)
   a. MEN2A
      i. Approximately 95% of families with MEN 2A have a *RET* mutation in exon 10 or 11.
      ii. Other rare mutations, including codon 804 alterations, have been reported in a few cases
   b. MEN2B
      i. Approximately 95% of individuals with the MEN2B phenotype have a single point mutation in the tyrosine kinase domain of the *RET* gene at codon 918 in exon 16 (M918T).
      ii. Other rare mutations include second mutation at codon 883 in exon 15 (A883F) and two mutations (V804M and Y806C) in cis configuration
6. Molecular genetic testing for FMTC (Moline and Eng 2010): approximately 88% of families with FMTC have an identifiable *RET* mutation.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: a 50% risk if a parent is affected or has a disease-causing mutation
   b. Patient's offspring: a 50% risk of inheriting the mutation
2. Prenatal diagnosis: possible for pregnancies at increased risk by analysis of DNA extracted from fetal cells by amniocentesis or CVS, provided the disease-causing allele of an affected family member must be identified or linkage established in the family
3. Management
   a. MEN1 (Callender et al. 2008)
      i. Parathyroidectomy for parathyroid tumors
      ii. Transcervical thymectomy because there is an increased risk of supernumerary parathyroid glands and developing carcinoid tumors in the thymus
      iii. Pituitary tumors
         a) Surgery (usually from a minimally invasive transsphenoidal approach)
         b) Medication for patients with prolactin- or growth hormone–producing tumors with dopamine agonists, such as bromocriptine or cabergoline, and a GH receptor antagonist, respectively
         c) Radiation
      iv. Gastrinomas
         a) Proton pump inhibitors for medical control of acid hypersecretion
         b) Surgical approaches: no consensus
      v. Insulinomas
         a) Manage surgically
         b) Treat unresectable tumors with diazoxide (Proglycem)
      vi. VIPoma
         a) Manage surgically
         b) Octreotide (Sandostatin) for diarrhea control
   b. MEN2 (Falchetti et al. 2008)
      i. Medullary thyroid carcinoma
         a) Total thyroidectomy with lymph node dissection of at least the central compartment.
         b) An elevated serum calcitonin level after surgery can be a sign of persistent, recurrent or generalized MTC.
         c) Total thyroidectomy within the first month of life should be performed in patients with the highest risk mutations (MEN2B, codons 883 and 918) (Lewis and Yeh 2008).
      ii. Pheochromocytoma
         a) Surgical laparoscopy excision.
         b) Recommend lifelong follow-up after surgery.
         c) Long-term drug treatment with α and β adrenergic blockers should only be considered in those patients in whom the tumor is unresectable.

iii. Primary hyperparathyroidism
   a) Subtotal parathyroidectomy or total parathyroidectomy with autotransplantation of normal fresh or cryopreserved tissue in the forearm.
   b) All individuals who have undergone partial or total parathyroidectomy with autotransplantation need to be monitored for possible recurrences.

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Fig. 1 (**a**–**c**) The patient, a 13-year-old Caucasian female, was seen initially because of a history of weight loss of approximately 17 lb over a period of 4–6 weeks and a mass in her neck. The biopsy of the neck mass revealed a medullary thyroid carcinoma. She has a long history of developmental delay and an unusual appearance with a thin body habitus, long face, and full kips. *MEN2* mutation screening revealed a sequence change in exon 16 of 2,753T > C (ATG > ACG) with an amino acid change of M918T (Met918Thr). The presence of this mutation in codon 918 of the RET proto-oncogene is consistent with a clinical diagnosis of MEN2B

Multiple Epiphyseal Dysplasia

In 1945, Fairbank first described multiple epiphyseal dysplasia (MED). MED is a type of short-limbed dwarfism characterized by impaired endochondral ossification affecting multiple epiphyses and premature degenerative joint disease.

Synonyms and Related Disorders

Autosomal dominant multiple epiphyseal dysplasia (Fairbank type, Ribbling type); Autosomal recessive multiple epiphyseal dysplasia (with bilayered patellae, with clubfoot)

Genetics/Basic Defects

1. Inheritance: genetically heterogeneous
   a. Autosomal dominant (Briggs et al. 2011)
      i. Multiple epiphyseal dysplasia type I (EDM1)
      ii. Multiple epiphyseal dysplasia type II (EDM2)
      iii. Multiple epiphyseal dysplasia type III (EDM3)
      iv. Multiple epiphyseal dysplasia type V (EDM5)
      v. Multiple epiphyseal dysplasia type VI (EDM6)
   b. Autosomal recessive: multiple epiphyseal dysplasia type IV (EDM4)
2. Causes
   a. EDM1: mutations in the gene (*COMP*) encoding cartilage oligomeric matrix protein (COMP) on the centromeric region of 19p (19p13.1-p12), same locus as (allelic to) pseudoachondroplasia (the disease that shares some clinical features with multiple epiphyseal dysplasia)
   b. EDM2: mutations in the type IX collagen, alpha-1 polypeptide gene (*COL9A1*) on 6q13
   c. EDM3: mutations in the type IX collagen, alpha-2 polypeptide gene (*COL9A2*) on 1p33-p32.2
   d. EDM4
      i. Mutations in the diastrophic dysplasia sulfate transporter gene (*DTDST*) on 5q32-q33.1
      ii. Recessive mutations in the *DTDST* gene also cause a spectrum of osteochondrodysplasias, including achondrogenesis type IB, atelosteogenesis type II, and diastrophic dysplasia
   e. EDM5: mutations in the gene (*MATN3*) encoding matrilin-3 on 2p24-p23
   f. EDM6: mutations in the type IX collagen, alpha-3 polypeptide gene (*COL9A3*) on 20q13.3
3. Mutations in extracellular matrix proteins, COMP, types II and IX collagens, and matrilin-3
   a. Produce a spectrum of mild to severe chondrodysplasias characterized by epiphyseal and vertebral abnormalities
   b. Disrupt protein processing and excessive accumulation of some of these proteins in the rER that appears to compromise cellular function
4. Genotype-phenotype correlations (Briggs et al. 2011)
   a. Patients with *COMP* mutations
      i. Significant involvement at the capital femoral epiphyses
      ii. Irregular acetabuli
   b. Patients with type IX collagen defects
      i. More severe involvement of the knees
      ii. Relative sparing of the hips
   c. Patients with *MATN3* mutations
      i. Abnormalities similar to those in patients with *COL9A2* mutations: more severe hip abnormalities
      ii. More intrafamilial/interfamilial variability

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Clinical Features

1. Broad historical classification: has not proved useful
   a. Ribbing: milder form with flat epiphyses and minimal involvement of the hands and feet
   b. Fairbank: more severe form with late appearing epiphyses and greater involvement of the hands and feet
2. Onset usually in childhood: as a rule, not recognizable at birth or during the first 1–2 years of life
   a. Joint pain after exercise initially: a common presenting sign
   b. Limp, pain, and stiffness in hip, knee, and ankle joints
   c. Waddling gait
   d. Easy fatigue
3. Mild to moderate short stature with normal body proportion
4. Mild short-limbed dwarfism
5. Stubby hands and feet
6. Osteoarthritis: severe osteoarthritis of the hip develops in early childhood.
7. Limited joint motions
8. Proximal muscle weakness with mild variability in muscle fiber size in EDM3
9. Association with diabetes mellitus in early infancy (Wolcott-Rallison syndrome)
10. Consider MED (Unger et al. 2008) in:
    a. Any child with bilateral Perthes disease
    b. Any child with noninflammatory joint pain, especially involving the knees
    c. Family history of early joint replacement
11. Prognosis
    a. Normal life expectancy
    b. Joint deformities resulting from abnormal epiphyseal ossification frequently leading to early degenerative arthroses
12. Distinctive features of the different forms of MED (Unger et al. 2008)
    a. EDM1 (COMP-MED)
       i. Distinctive clinical features
          a) Muscular hypotonia
          b) Pseudomyopathy
          c) Joint laxity
          d) Mild genu vara
       ii. Distinctive radiographic features
          a) Hand: carpal bones more delayed than phalangeal epiphyses; ragged carpal bones, small, rounded phalangeal epiphyses
          b) Proximal femoral epiphyses: round and small
          c) Knee: small epiphyses with lateral thinning, additional ossification centers with "glacier crevice" sign before puberty
    b. EDM4 (rMED)
       i. Homozygous and compound heterozygous mutations in the *DTDST* gene lead to a relatively mild phenotype that seems to be clinically dominated by a tendency to recurrent dislocation of a bilateral multilayered patella and by early-onset osteoarthritis of the hip joints (Miyake et al. 2008; Cho et al. 2010; Hinrichs et al. 2010).
       ii. Distinctive clinical features
          a) Club feet at birth
          b) Genu valga rather than genu vara
          c) Joint contractures
          d) Mild to moderate brachydactyly
       iii. Distinctive radiographic features
          a) Hand: phalangeal epiphyses delayed, but maturation of carpal bones normal or advanced; flat epiphyses or phalanges and radius; "snow cap" sign of metacarpals
          b) Proximal femoral epiphyses: small and flat
          c) Knee: double-layered patella
    c. EDM5 (MATN3-MED)
       i. Distinctive clinical features: not specific
       ii. Distinctive radiographic features
          a) Hand: unspecific changes at the hands
          b) Proximal femoral epiphyses: small but not as rounded as in COMP-MED
          c) Knee: small epiphyses with "harlequin hat" appearance; metaphyseal striations
    d. EDM2 (*COL9A2*)
       i. Rare but may be under reported
       ii. Knee epiphyses: more affected than proximal femoral epiphyses
    e. EDM3 (*COL9A3*)
       i. Rare but may be under reported
       ii. Knee epiphyses: more affected than proximal femoral epiphyses
    f. EDM6 (*COL9A1*): Very rare (only single family reported)

Diagnostic Investigations

1. Radiography
   a. Radiographic abnormalities may be present before the onset of physical symptoms.
   b. Predominantly epiphyseal involvement
      i. Initial stage: delayed appearance of epiphyseal ossification
      ii. Later stage in the appearance of epiphysis
         a) Usually small ossification centers
         b) Sometimes fragmented ossification centers with irregular contours
         c) Adjacent metaphyseal borders may be slightly abnormal.
      iii. Adulthood
         a) Flattened and dysplastic articular surfaces
         b) Presence of early features of osteoarthrosis
      iv. Characteristic epiphyseal involvement
         a) Epiphyses of the hips and knees: most affected
         b) Ivory epiphyses in the hands
         c) Schmorl nodes in the spine
         d) Double-layered patella
   c. Vertebrae
      i. Ovoid vertebral bodies
      ii. Mildly irregular vertebral endplates
   d. Limbs
      i. Late ossifying epiphyses
      ii. Small, irregular, fragmented, and in some cases flattened epiphyses
      iii. Osteoarthritis
      iv. Short femoral neck
      v. Markedly dysplastic capital femoral epiphyses
      vi. Often initially diagnosed as Legg-Perthes disease (avascular necrosis of femoral head)
      vii. Genu varum or valgum
      viii. Short metacarpals and phalanges with irregular epiphyses
      ix. Small, irregular carpal and tarsal bones
      x. Normal metaphyses
   e. Irregular acetabuli
   f. Patella
      i. Doubled-layered
      ii. Dislocation or subluxation
   g. Absence of severe spinal involvement and minimal metaphyseal defects allows differentiating multiple epiphyseal dysplasia from other disorders with similar clinical features such as spondyloepimetaphyseal dysplasia and spondyloepiphyseal dysplasia.
2. Histology: chondrocytic inclusion (ultrastructurally, a dilated rER containing accumulated material)
3. Molecular genetic diagnosis is important for accurate prognosis and genetic counseling: mutation analyses are available on clinical basis
   a. Mutations in the *COMP* gene
   b. Mutations in the *COL9A1* gene
   c. Mutations in the *COL9A2* gene
   d. Mutations in the *COL9A3* gene
   e. Mutations in the *MATN3* gene
   f. Mutations in the *DTDST* gene

Genetic Counseling

1. Recurrence risk
   a. Autosomal dominant inheritance
      i. Patient's sib
         a) 50% if one of the parent is affected
         b) Not increased if parents are normal
      ii. Patient's offspring: 50%
   b. Autosomal recessive inheritance
      i. Patient's sib: 25%
      ii. Patient's offspring: not increased unless the spouse is also carrying the gene
2. Prenatal diagnosis for pregnancies at risk for *COMP* and other mutations is possible if the disease-causing allele of an affected family member has been identified.
   a. Amniocentesis
   b. CVS
3. Management (Briggs et al. 2011)
   a. Initial aims of management
      i. Control pain
         a) Can be difficult
         b) Combination of analgesics and physiotherapy including hydrotherapy
      ii. Limit joint destruction and the development of osteoarthritis
   b. Weight control
   c. Avoid exercise that causes repetitive strain on affected joints

d. Realignment osteotomy and/or acetabular osteotomy to slow the progression of symptoms
e. Total joint arthroplasty in some cases
f. Psychosocial support to address issues of short stature, disability, and employment

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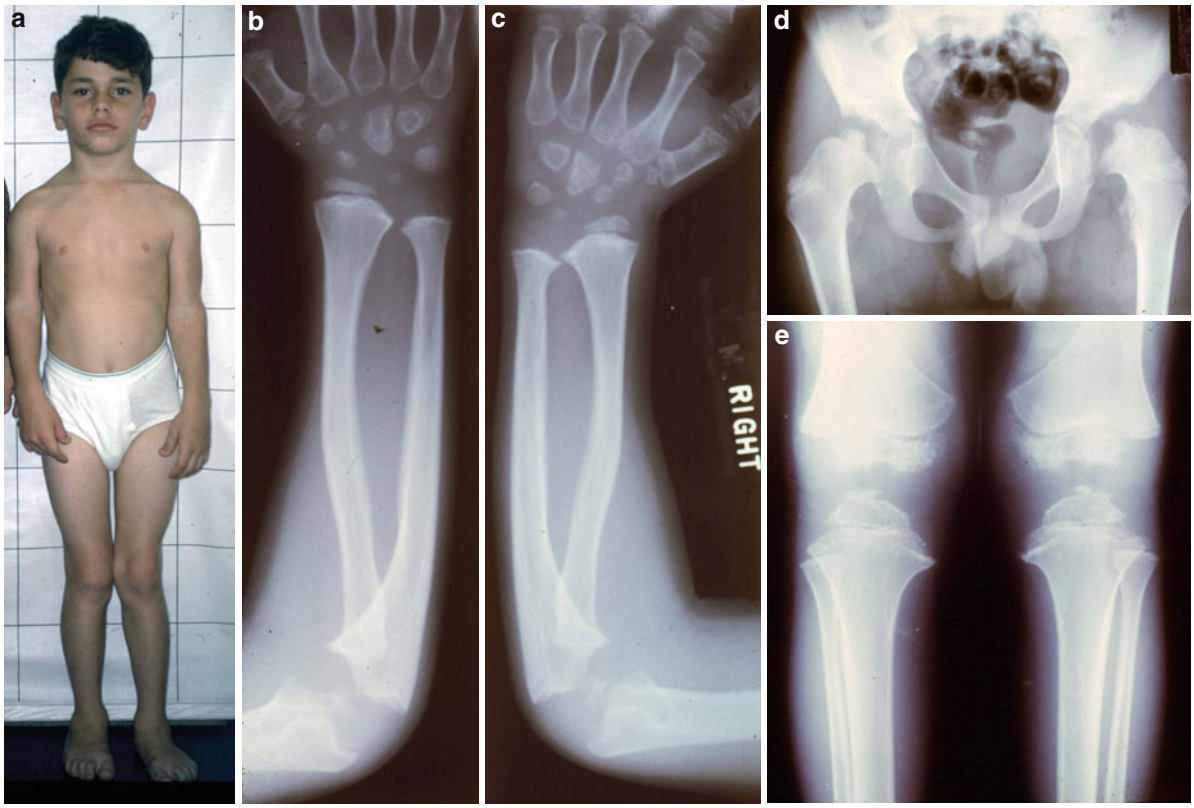

Fig. 1 (**a**–**e**) A boy with multiple epiphyseal dysplasia showing short stature and epiphyseal dysplasia in the wrists, hips, and knee joints

Fig. 2 (**a**, **b**) A girl and an adult female with multiple epiphyseal dysplasia showing mild short stature with normal body proportion

Fig. 3 Radiograph of the pelvis of a 12-year-old boy with multiple epiphyseal dysplasia showing poorly developed acetabular fossae and flat, fragmented femoral heads

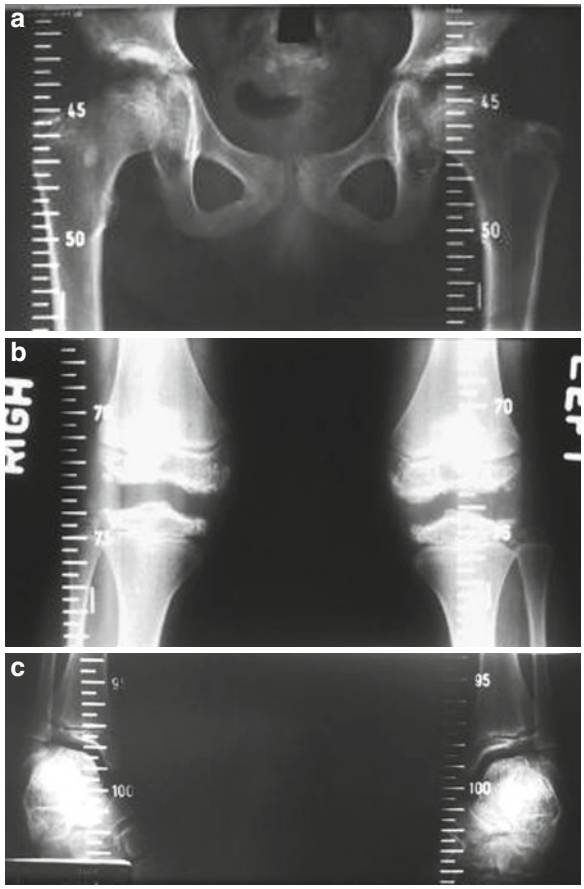

Fig. 4 (**a**–**c**) Radiographs of another patient with multiple epiphyseal dysplasia showing poorly formed acetabular fossae, poorly ossified femoral heads, and flattened epiphyses of the knees and ankles

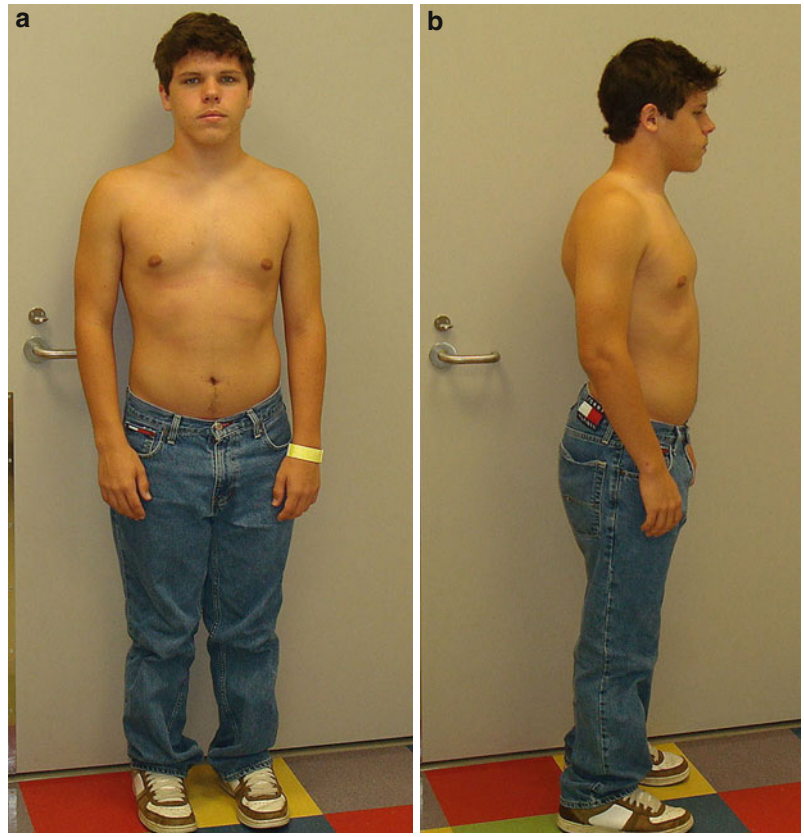

Fig. 5 (**a**, **b**) A 13 year old boy with multiple epiphyseal dysplasia has been complaining pain in knees, legs, and feet since 4 years of age. He was also noted to have limp, joint stiffness, and worsening waddling gait. Mutation analysis showed a heterozygous G > A nucleotide substitution in exon 16, resulting in the replacement of an aspartic acid codon (GAC) with an asparagine codon (AAC) at amino acid position 605 (c.1813G > A or p.Asp605Asn (D605N)). The D605N missense mutation in the COMP gene has been reported previously in association with multiple epiphyseal dysplasia and is consistent with the diagnosis of this patient

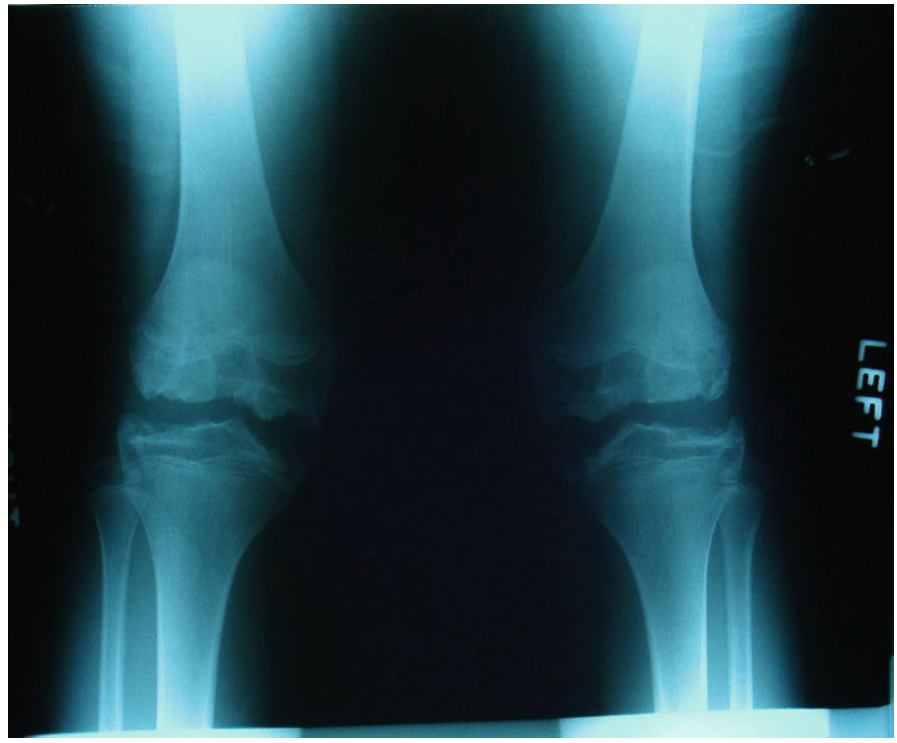

Fig. 6 Radiographs of the same patient showing epiphyseal dysplasias at the distal femoral epiphyses and the proximal tibial epiphyses causing weakness and pains at the knees

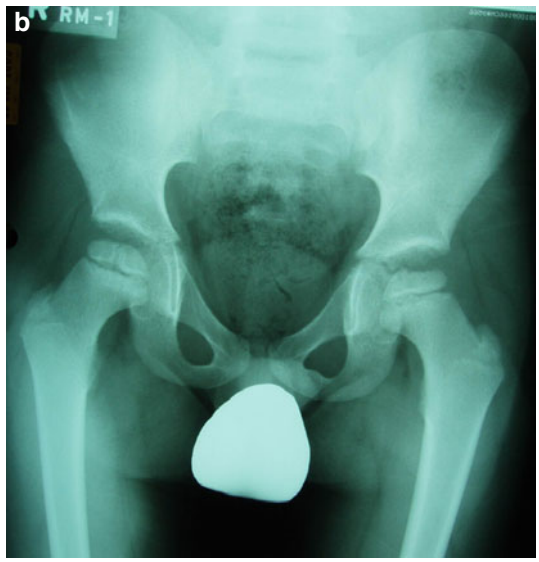

Fig. 7 (**a**, **b**) A 12-year-old boy with multiple epiphyseal dysplasia. Radiograph of the pelvis at 8 years of age showed poorly developed acetabular fossae and flat femoral heads

Fig. 8 A 10-year old girl was seen because of short stature. The radiographs were consistent with multiple epiphyseal dysplasia. DNA sequencing revealed a c.1445A > G transition in exon 13 of the *COMP* gene. This change converts a codon for aspartic acid (GAC) to a codon for glycine (GGC). The patient is heterozygous for the mutation. The mutation confirms the diagnosis of multiple epiphyseal dysplasia. She was also diagnosed to have growth hormone deficiency and was receiving daily Humatrope injection

Fig. 9 Note the short upper arms with short fingers

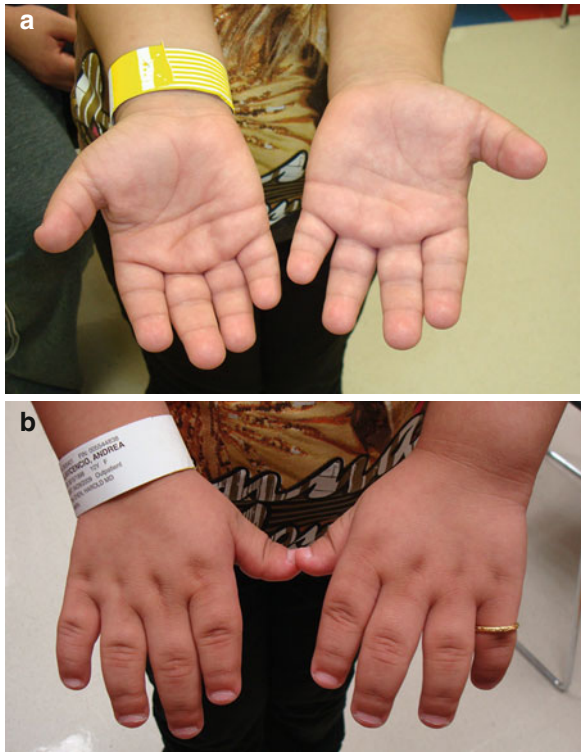

Fig. 10 (**a**, **b**) Note the short and stubby fingers

Fig. 11 Note short and stubby toes

Fig. 12 Hip radiograph 6 months earlier shows poorly developed acetabular fossae and flat fragmented femoral heads

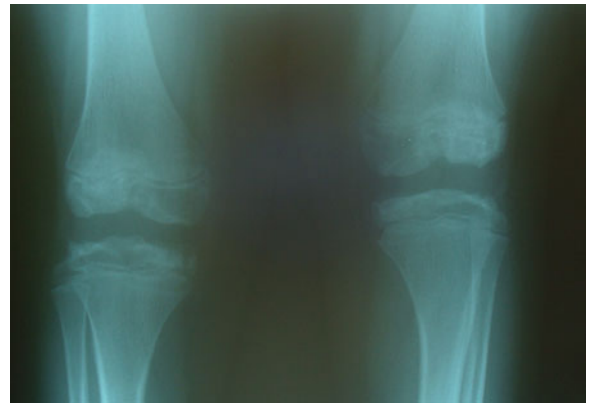

Fig. 13 Knee radiograph shows flattened epiphyses of the knees

Fig. 14 Hand radiograph shows short and broad phalanges

Fig. 16 Radiograph of feet shows short and stubby phalanges

Fig. 15 Radiograph of left upper extremity shows relatively short tubular bones with small proximal epiphysis of the left humerus

Multiple Pterygium Syndrome

Multiple pterygium syndrome is a distinct syndrome consisting of a constellation of congenital anomalies characterized by pterygia of the neck, antecubital, popliteal and intercrural areas, numerous flexion contractures of the joints, growth retardation, ptosis, antimongoloid slant with or without epicanthal folds, cleft palate, scoliosis, vertebral anomalies, rocker-bottom deformity of the feet, and genital anomalies.

Synonyms and Related Disorders

Escobar syndrome

Genetics/Basic Defects

1. Inheritance: genetic heterogeneity (Chen 2009)
   a. Autosomal recessive inheritance in most cases
      i. Recessive forms of MPS: clinically and genetically heterogeneous.
         a) May result from early-onset fetal akinesia
         b) Traditionally classified into prenatally lethal MPS and nonlethal Escobar variant-MPS
      ii. Escobar syndrome: Mutations in *CHRNG* gene, which encodes the acetylcholine receptor γ-subunit cause the autosomal recessive Escobar syndrome, one of the most common types of MPS, although other genes may be involved (Hoffmann et al. 2006; Morgan et al. 2006; Prontera et al. 2007).
      iii. Escobar syndrome has been recently described as a prenatal form of myasthenia associated with recessive mutations in genes of the neuromuscular junction (*CHRNG*, *CHRNA1*, *CHRNB1*, *CHRND*, and *RAPSN*) (Hoffmann et al. 2006; Morgan et al. 2006; Michalk et al. 2008; Vogt et al. 2008). This observation expands the cause of Escobar variant-MPS to a component of the contractile apparatus.
      iv. The first report of the clinical expression of the complete absence of TPM2 in human indicated that TPM2 expression at the early period of prenatal life plays a major role for normal fetal movements (Monnier et al. 2009).
      v. Clinical features.
         a) Multiple joint contractures with marked pterygia
         b) Dysmorphic facies (flat, sad, motionless facial appearance)
         c) Cervical vertebral anomalies
   b. Autosomal dominant inheritance in some cases (Mckeown and Harris 1988)
      i. Great variation in severity between affected individuals
      ii. Characterized by multiple pterygia with or without mental retardation
   c. X-linked inheritance (MacArthur and Pereira 1996)
   d. Sporadic occurrence (Ramer et al. 1988; Spranger et al. 1995; Aslani et al. 2002)
2. Phenotypic analysis
   a. Multiple congenital pterygia, joint contractures, and severe foot defects: deformation sequence secondary to reduced frequency of fetal movement
   b. Micrognathia: resulting from reduced use and represents "disuse hypotrophy"

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   c. Cleft palate: a mechanical disruption due to presumed interposition of tongue between palatine shelves
   d. Neck pterygia
      i. Able to exert a downward pull on facial structures
      ii. Responsible for the following effects:
         a) Down-turned angles of the mouth
         b) Long philtrum
         c) Antimongoloid slant of palpebral fissures
         d) Low posterior hairline
         e) Anteversion and apparently low-set position of auricles
         f) Often with strikingly abnormal directional hair patterning in posterior and posterior-lateral areas of scalp
      iii. Short neck due to:
         a) Lateral cervical pterygia
         b) Secondary fusion of upper vertebrae
   e. Congenital scoliosis: secondary to abnormal prenatal position, movement, and/or muscle pull
   f. Genital anomalies
      i. Small scrotum and apparently absent or hypoplastic labia majora: resulting from the pull of the intercrural pterygia which affects a flattening of these structures
      ii. Cryptorchidism: representing mechanical obstruction of the processus vaginalis from pull of intercrural web or some intrinsic defect of the gubernaculums testis which is unable to effect descent of the gonads
3. Pathogenesis
   a. The underlying pathogenesis of the secondary deformities and distortions, hypotrophies, disruptions, bony fusions, and incomplete or impeded morphogenetic movements is unknown
   b. A neuromuscular disease causing fetal akinesia (Chen et al. 1980; Bhargava et al. 2002) is suspected.
   c. Intrauterine crowding and oligohydramnios are contributory factors to joint contractures associated with MPS (Chen 2009).

Clinical Features

1. Short stature
2. Cutaneous and musculoskeletal
   a. Pterygia involving the following areas:
      i. Neck
      ii. Axillary
      iii. Antecubital
      iv. Popliteal
      v. Digital
      vi. Intercrural
   b. Multiple joint contractures
   c. Rib or vertebral anomalies
   d. Scoliosis/lordosis
   e. Rocker-bottom feet with vertical talus
3. Standing with a crouching or semi-crouching stance
4. Orofacial features
   a. A flat, sad, motionless facial appearance
   b. Epicanthal folds
   c. Ptosis
   d. Antimongoloid palpebral fissure
   e. Long philtrum
   f. Pointed, receding chin
   g. Down-turned angles of the mouth
   h. Cleft lip+/− palate
   i. Apparent low-set ears
5. Genitalia
   a. Males
      i. Small penis and scrotum
      ii. Cryptorchidism
   b. Females
      i. Apparent aplasia of the labia majora
      ii. A small clitoris

Diagnostic Investigations

1. Radiography
   a. Multiple joint contractures
   b. Fusion of cervical vertebrae
   c. Scoliosis/lordosis
   d. Flexion contractures of fingers
   e. Rocker-bottom feet with vertical talus
2. Pathological evaluations of muscle and nerve tissue: no consistent abnormality

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal recessive inheritance: 25%
      ii. Autosomal dominant inheritance: not increased unless a parent is also affected

   b. Patient's offspring
      i. Autosomal recessive inheritance: not increased unless the spouse is a carrier
      ii. Autosomal dominant inheritance: 50%
2. Prenatal diagnosis possible by ultrasonography for the family at risk
   a. Micrognathia
   b. Low-set ears
   c. Hypertelorism
   d. Cystic hygroma colli
   e. Rocker-bottom feet
3. Management (McCall and Budden 1992)
   a. Correction of the hand deformities
      i. Attention given to any deformities in the shoulder and elbow to maximize function of the limb before initiating correction of hand deformities
      ii. Intensive physiotherapy and occupational therapy preferable to surgery for management of the upper extremity and hand anomalies
   b. Correction of mild hip flexion contractures of $<30^\circ$ due to inguinal webbing and crouched stance: responding well to active and passive stretching programs
   c. Correction of popliteal webbing
      i. Physiotherapy.
      ii. Traction.
      iii. Popliteal skin web Z-plasty with serial casting or with cable grafting the sciatic nerve (to achieve further knee extension and independent ambulation).
      iv. Arthrodesis.
      v. Amputation.
      vi. Excision of a significant fibrous band extending from the ischium to the calcaneus allows significant improvement in extension.
   d. Correction of knee flexion contracture $<25^\circ$ without severe ambulatory limitations: conservative, consisting of a stretching program and night splints
   e. Correction of knee flexion contracture of 25–90°
      i. Physiotherapy followed by popliteal Z-plasty, fibrous band excision, and lengthening of all tense structures that are not neurovascular
      ii. Post-operative serial casting
      iii. Cable grafting or femoral shortening for neurovascular compromised cases
   f. Correction of knee flexion contracture of $>90^\circ$ which poses significant ambulatory difficulty
      i. Arthroses in extension
      ii. Disarticulation
   g. Correction of vertical talus
      i. Children 6 years or younger: treated with soft tissue procedures and/or Grice subtalar arthrodeses
      ii. Children over 6 years: undergo triple arthrodesis at age 12

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Fig. 1 (**a**–**f**) Two Honduran siblings (a 5-year-old girl and a 9-year-old boy) with multiple pterygium syndrome showing multiple pterygia involving neck, axillary, antecubital, popliteal, and intercrural areas. In addition, they had multiple joint contractures affecting hips, elbows, and interphalangeal, and popliteal joints; semi-crouching stance; and rocker-bottom feet due to vertical tali. Vigorous physiotherapy was performed initially for both upper and lower extremity contractures. Popliteal Z-plasty with release of the posterior capsule and excision of a fibrous band extending from the ischial tuberosity to the calcaneus resulted in better knee extension, but further correction was limited by tight neurovascular structures. Vertical tali were addressed surgically with triple arthrodeses on the boy at age 12, and soft tissue release combined with a Grice subtalar arthrodesis on the girl at age 6. Both children attained painless plantigrade feet at discharge

Fig. 2 (**a**–**i**) Three Nicaraguan siblings (parents are third cousins) with multiple pterygium syndrome showing similar features. Radiographs showed rocker-bottom feet with vertical talus and the fusion of cervical vertebrae. Patient 1 (a 7-year-old boy) had motionless facial appearance, cleft palate, multiple flexion contractures, and severe webbing at the antecubital and popliteal fossae, and interphalangeal regions. He also had severe foot deformities with calcaneus heels and vertical talus. Patient 2 (a 9-year-old girl) crawled at 4 years of age but had never walked. She was much more severely affected. Patient 3 (an 11-year-old boy) walked with difficulty but much less severely affected than younger brother and sister. Digital deformities were addressed surgically with some recurrence of original deformities. Hip flexion contractures were addressed with an active stretching program and prone positioning, resulting in satisfactory resolution. Popliteal webbing was treated by either physiotherapy alone and/or operative procedures. Bilateral congenital tali were treated by either bilateral talectomy or arthrodesis with partial talectomies

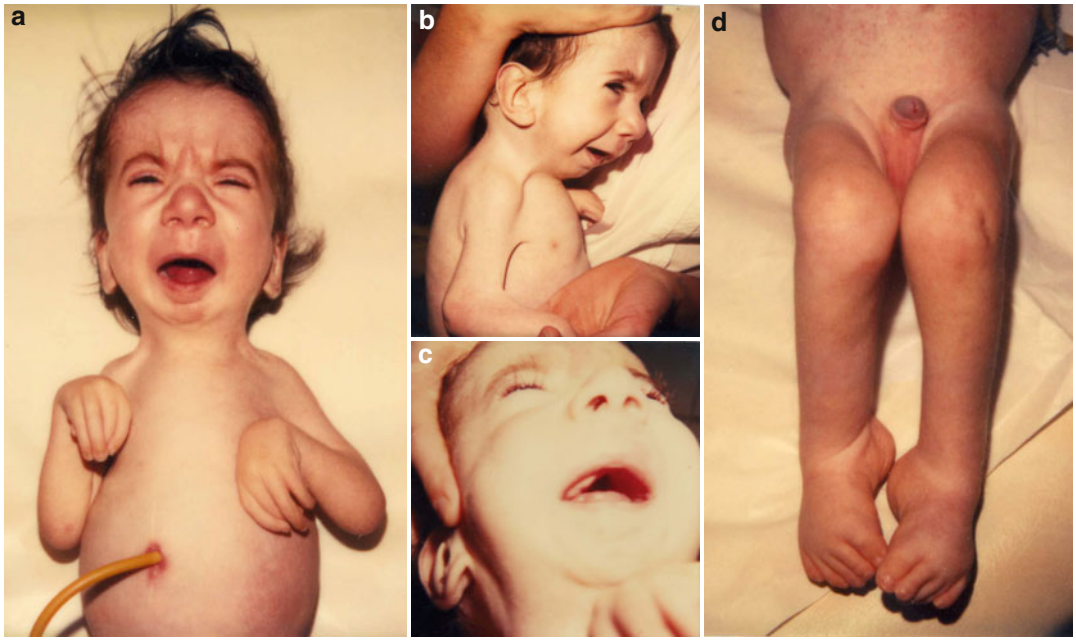

Fig. 3 (**a**–**d**) A boy with a sporadic case of multiple pterygium syndrome showing multiple pterygia, long philtrum, receding chin, cleft palate, low-set ears, and multiple contractures

Fig. 4 (**a**–**c**) An 11-year-old girl with typical Escobar syndrome with severe kyphoscoliosis

Myotonic Dystrophy Type I

Myotonic dystrophy type 1 (DM1) is the most common form of muscular dystrophy affecting adults with an estimated incidence of 1 in 8,000 among Caucasians (Brook et al. 1992).

Synonyms and Related Disorders

Myotonic dystrophy type 1 (dystrophia myotonica 1; Steinert disease); Myotonic dystrophy type 2 (dystrophia myotonica 2, proximal myotonic myopathy, proximal Ricker syndrome)

Genetics/Basic Defects

1. Inheritance: autosomal dominant with an anticipation phenomenon (Harley et al. 1993)
2. Molecular genetic perspective (Brook et al. 1992)
   a. Considerable variability of phenotype between affected individuals even within the same family
   b. An association of myotonic dystrophy with specific haplotypes in the population, indicating that most cases have resulted from a small number of genetic events
   c. Multisystemic nature of the phenotype
   d. An apparent increase in severity of symptoms and reduction in age at onset that is observed during transmission of the gene within families
3. Genetic defect: caused by an expanded CTG (cytosine-thymine-guanine) repeat in the dystrophia myotonica phosphokinase (*DMPK*) gene
   a. Encodes for a serine-threonine protein kinase
   b. Mapped on chromosome 19q13.3
4. CTG triplet repeat
   a. Transcribed and located in the 3′ untranslated region of an mRNA that is expressed in tissues affected by myotonic dystrophy
   b. Repeat size
      i. Highly variable in the normal population (5–36 triplets)
      ii. Undergoing expansion in myotonic dystrophy patients (50 to several thousand copies)
         a) Expansion of at least 50 repeats in patients who are minimally affected
         b) Expansion of up to several kilobase pairs in more severely affected patients
   c. Intergenerational instability (unstable CTG expansion at mitotic and meiotic levels with a bias toward length increase in the successive generations)
      i. Accounting for anticipation (the CTG repeat size increases in successive generations in parallel with increasing severity of the disease)
      ii. Accounting for somatic instability and mosaicism (the CTG repeat size varies considerably among different tissues and organs with coexistence in the same subject of cell lines with different CTG repeats)
   d. Genotype-phenotype correlations (Finsterer et al. 2001)
      i. Size of the CTG trinucleotide repeats generally correlated with the age of onset and clinical severity of the disease
      ii. Longer CTG repeat expansions correlate, in general, with an earlier age of onset and more severe disease.

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iii. Relation of cardiac abnormalities and CTG repeat size in myotonic dystrophy
  a) Increased cardiac involvement with increasing CTG repeat size in patients age 21–50
  b) The number of CTG repeats needed to develop a reasonable cardiac involvement is higher in young patients than in older patients.

Clinical Features

1. Highly variable phenotypic expression and age of onset
   a. The mildest form
      i. Seen in middle or old age (>50)
      ii. Characterized by cataracts and baldness with little or no muscle involvement
      iii. CTG repeats: 50–100
      iv. Occasionally difficult to diagnose: The pleomorphic manifestations, due to a dynamic mutation in the length of CTG repeat, lead to difficulty in clinical identification of asymptomatic or mildly affected patients.
   b. The classic (juvenile or adult) form
      i. The more common form
      ii. Usually becoming evident between the ages of 15 and 35 years
      iii. CTG repeats: 100–1,000
      iv. Phenotypically variable
      v. Characteristic clinical features
         a) Myotonia
         b) Muscle weakness
         c) Cardiac arrhythmias
         d) Male balding
         e) Hypogonadism
         f) Psychocognitive dysfunction
         g) Glucose intolerance
   c. The childhood form
      i. Age at onset: 1–10
      ii. CTG repeats: 500–>2,000
      iii. Clinical manifestations
         a) Hypotonia
         b) Learning difficulties
         c) Limited motor skills
   d. The most severe (congenital) form
      i. Recognized at birth or in the neonatal period
      ii. Pregnancy
         a) Maternal polyhydramnios
         b) Reduced fetal movement
         c) Breech presentation
         d) Prematurity
      iii. Associated with generalized muscular hypotonia
      iv. Respiratory distress
         a) Aspiration pneumonia
         b) Recurrent bronchitis
         c) Hypoventilation
         d) Sleep apnea
         e) Bronchiectasis
      v. Feeding difficulties
      vi. Dysphagia
      vii. Nasal regurgitation
      viii. Facial diplegia with a "tented-shaped" mouth
      ix. Delayed motor development
      x. Joint deformities
      xi. Mental retardation
      xii. High neonatal mortality
      xiii. Those survived invariably exhibiting the classical form of the disease in late childhood or adolescence
      xiv. Almost all congenital cases are exclusively maternally transmitted
      xv. CTG repeats: 1,000–5,000
      xvi. The phenomenon of anticipation often most strikingly manifested in a family producing a congenitally affected child
2. Neurologic manifestations
   a. Myotonia (100%) (Miller 2008)
      i. Delayed relaxation of muscles after an initial voluntary contraction or percussion.
      ii. Muscle stiffness that improves with repeated use of the muscle, the so-called warm-up phenomenon.
      iii. On examination, myotonia may be apparent from the first handshake, presenting with a delayed release of the hand. This can also be appreciated by asking the patient to repeatedly grip and release the examiner's fingers. Another helpful maneuver is to ask the patient to repeatedly close the eyes tightly. After the first closure, there may be lag in opening the eyes, but this will improve with repeated efforts.

iv. Myotonia may be provoked by percussion of muscle, e.g., by percussion of the thenar eminence. The muscle stiffens, often adducting the thumb.

b. Muscle weakness and atrophy
   i. Muscles most prominently affected
      a) Superficial facial muscles
      b) Levator palpebrae superioris
      c) Temporalis
      d) Sternocleidomastoids
      e) Distal muscles of forearm
      f) Dorsiflexors of foot
   ii. Other muscles commonly affected
      a) Quadriceps
      b) Diaphragm and intercostals
      c) Intrinsic muscles of hand and feet
      d) Palate and pharyngeal muscles
      e) Tongue
      f) External ocular muscles

c. Percussion myotonia and voluntary myotonia aggravated by cold
d. Dysarthria
e. Slow nasal indistinct speech
f. Foot drop
g. Step page gait
h. Contractures of the Achilles tendon
i. Diminished deep tendon reflexes
j. Cognitive and behavioral abnormalities

3. Craniofacial appearance
   a. Long thin face
   b. Flat, sagging, sad, and expressionless face
   c. Frontal bossing
   d. Hollow temple secondary to atrophy of temporalis
   e. Bilateral facial weakness (facial diplegia)
   f. Tented mouth
   g. Micrognathia
   h. Swan neck appearance (sternocleidomastoid muscle wasting)
4. Ocular findings
   a. Cataracts (>85%)
   b. Ptosis
   c. Extraocular weakness
   d. Peripheral retinal changes
   e. Coloboma of retina/choroid
   f. Optic atrophy
   g. Blepharospasms
   h. Decreased ocular pressure
5. Cardiac involvement (76%)
   a. An integral part of myotonic dystrophy targeting
      i. Almost selectively the conduction system
      ii. Less specifically the myocardium
   b. Electrocardiographic conduction abnormalities
      i. Manifesting with or without ventricular tachyarrhythmias or bradyarrhythmias
      ii. The first-degree atrioventricular (AV) block (most common)
      iii. Intraventricular conduction abnormalities (premature ventricular complexes like couplets and triplets)
      iv. Atrial arrhythmias (atrial fibrillation and flutter)
   c. A high incidence of sudden death
   d. Possible cardiomyopathy
   e. Congestive heart failure (6%)
6. Gastrointestinal findings
   a. Achalasia
   b. Gastroparesis
   c. Constipation
   d. Megacolon
   e. Gallstones
7. Genitourinary findings
   a. Dysuria
   b. Urinary retention
   c. Polycystic kidneys
   d. Testicular atrophy
8. Endocrine findings
   a. Hypogonadism
   b. Male infertility secondary to testicular atrophy
   c. Hypothyroidism
   d. Goiter/hyperparathyroidism
   e. Multiple endocrine neoplasia type 2A (pheochromocytoma and amyloid-producing medullary thyroid carcinoma)
   f. Dysmenorrhea
   g. Postprandial hyperinsulinemia
9. Orthopedic problems
   a. Arthrogryposis
   b. Talipes
   c. Kyphoscoliosis
10. Female patients
   a. Decreased total reproductive rate
   b. Obstetrical complications (Rudnik-Schöneborn and Zerres 2004)
      i. Higher rate of spontaneous abortions

ii. Ectopic pregnancies
iii. Abnormal placentation
iv. Urinary tract infections

11. Occasional accompanying benign or malignant neoplasms
    a. Pilomatrixoma
    b. Parathyroid adenoma
    c. Small bowel carcinoma
    d. Neurofibromatosis
    e. Thymoma
    f. Pleomorphic adenoma of the parotid gland
    g. Pituitary adenoma
    h. Ovarian cancer
    i. Ovarian cyst
    j. Laryngeal cancer not previously reported
12. Natural history
    a. Usually progressive
    b. Usually leading to severe disability within 15–20 years
    c. Greatly reduced life expectancy, particularly in the case of an early disease onset and proximal muscle involvement
    d. The high mortality rate reflecting an increase in deaths due to
        i. Respiratory diseases
        ii. Cardiovascular diseases
        iii. Neoplasms
        iv. Sudden deaths induced by cardiac arrhythmias
13. Differential diagnosis of myotonic disorders (Meola 2000; Miller 2008)
    a. Myotonic dystrophy type 2 (DM2)
        i. Clinical characteristics similar to those of DM1: an adult-onset muscular dystrophy associated with
            a) Myotonia (clinically and on EMG)
            b) Proximal weakness
            c) Frontal balding
            d) Polychromatic cataracts
            e) Cardiac arrhythmias
            f) Facial and respiratory muscles: relatively spared
            g) Insulin resistance
            h) Infertility
            i) Absence of congenital form of DM2 comparable with DM1
        ii. Molecular basis: DM2: caused by an expansion of a cytosine-cytosine-thymine-guanine (CCTG) repeat in the zinc finger protein 9 (ZNF9) gene on chromosome 3 (Liquori et al. 2001)
    b. Myotonia congenita
        i. Myotonia: prominent clinical symptom.
            a) Stiffness especially when first starting an activity in severe classic myotonia
            b) Perform activities at a normal or advanced level, including competitive sports, once warmed up
            c) Presents in early childhood, described by the parents as weakness and clumsiness in addition to or instead of stiffness
            d) Despite the reported difficulties, affected children appear "athletic," with increased muscle bulk, presumably because of the sustained muscle activity.
            e) The myotonic symptoms often improve with age but do not completely disappear.
        ii. Caused by a mutation in the gene encoding skeletal muscle chloride channel-1 (*CLCN1*) (Renner and Ptacek 2002). The chloride channel defect leads to an elevation of the resting membrane potential and thus a tendency toward repeated muscle contractions.
        iii. Inheritance: either autosomal dominant (Thomsen myotonia congenita) or autosomal recessive (Becker myotonia congenita).
    c. Schwartz-Jampel syndrome (chondrodystrophic myotonia)
        i. Caused by loss-of-function mutation in the *HSPG2* gene, which encodes perlecan, a heparan sulfate proteoglycans secreted into basement membranes (Nicole et al. 2000)
        ii. Clinical manifestations
            a) Severe myotonia: one of the first symptoms present in childhood. No warm-up phenomenon for the myotonia
            b) Short stature
            c) Muscular hypertrophy
            d) Diffuse bone disease
            e) Ocular and facial abnormalities
            f) Joint contractures

Diagnostic Investigations

1. Clinical examination to search muscle and nonmuscle manifestations (Meola 2000)
2. Lab: mildly elevated serum creatine kinase
3. Electromyography to identify subclinical myotonia
4. Slit-lamp examination to detect characteristic cataracts
5. Muscle biopsy
   a. Diagnostic but not indicated or useful for routine clinical evaluation
   b. Atrophic small type I fibers
   c. An increase in central nuclei
   d. Ringed fibers
6. Radiography
   a. Kyphosis of cervical spine
   b. Thin ribs observed in neonates suffering from myotonic dystrophy
7. Electrocardiogram abnormalities (60–70%) (Finsterer et al. 2001)
   a. ST abnormalities
   b. AV block I
   c. Increased QTc interval
   d. Tall R and/or S waves
   e. Left anterior hemiblock
   f. Supraventricular ectopic beats
   g. T wave abnormalities
   h. Pacemaker
   i. Missing R progression
   j. Abnormal U wave
   k. Left bundle branch block
8. Echocardiography (Finsterer et al. 2001)
   a. Septal thickness >11 mm
   b. Posterior wall thickness >11 mm
   c. Fractional shortening <30%
   d. E/A ratio >1
   e. Left ventricular end-diastolic diameter >57 mm
   f. Valve abnormalities
9. DNA testing for CTG repeat size: detects mutations in nearly 100% of affected individuals and is clinically available (Bird 2007)
   a. Gold standard for the diagnosis of DM1
   b. CTG repeat size
      i. Normal alleles: 5–34 CTG repeats
      ii. Premutation (mutable normal alleles): 35–49 CTG repeats
      iii. Full penetrance alleles (associated with disease manifestations): >50 CTG repeats
   c. Clinical testing by targeted mutation analysis
10. Presymptomatic carrier testing
    a. Leukocyte DNA analysis: provides an earlier opportunity to diagnose DM1 in family members at risk who are clinically asymptomatic
    b. Providing more aggressive monitoring program to detect
       i. Early cardiac conduction disturbance
       ii. Cataract formation
       iii. Respiratory difficulties
       iv. At risk of developing anesthetic complications, especially delayed-onset apnea

Genetic Counseling

1. Recurrence risk (Bird 2007)
   a. General principle for genetic counseling
      i. A normal molecular analysis excludes the risk of developing or transmitting myotonic dystrophy in essentially all situations.
      ii. For women who have had a child with congenital myotonic dystrophy, almost all subsequently affected pregnancies are likely to be severely affected.
      iii. Clinically affected women, in general, have around a 30% chance that an affected child would have congenital or severe childhood myotonic dystrophy. The risk of a congenitally affected child is related to maternal repeat size.
      iv. The risk for the healthy sib of a congenitally affected patient developing the disorder after childhood is low.
      v. For the adult healthy sib of an adult-onset case, the risk of carrying the mutation is also low (around 10%), with about half of this developing clinically significant disease.
   b. Patient's sib: recurrence risk depending on the genetic status of the parents
      i. Not increased if both parents are normal
      ii. Fifty percent risk if one parent has an expanded DMPK allele

c. Patient's offspring
   i. Offspring of an individual with an expanded allele (>34 CTG repeats) have a 50% chance of inheriting the mutant allele.
   ii. Disease-causing alleles may expand in length during gametogenesis, resulting in the transmission of longer CTG trinucleotide repeat alleles that may be associated with earlier onset and more severe disease than that observed in the parent.

2. Prenatal diagnosis
   a. Prenatal ultrasonography in congenital myotonic dystrophy
      i. Polyhydramnios
      ii. Talipes
      iii. Decreased fetal movements reflecting the neuromuscular failure of swallowing and movement
   b. Prenatal diagnosis possible by using mutation analysis (requires prior confirmation of the diagnosis of DM1 by molecular genetic testing of DMPK in an affected family member) and detection of the CTG repeat expansion with the *DMPK* gene in amniocytes or chorionic villi
   c. More challenging by using the CTG repeat test to determine whether the fetus is at risk for the severe form of myotonic dystrophy
      i. Generally, in amniocytes, congenital myotonic dystrophy is associated with CTG repeat expansion larger than that of the affected mother.
      ii. CTG repeat size may change over time in CVS or amniocentesis, providing different CTG repeat size at different gestational ages.
   d. Counseling of pregnant patients affected with myotonic dystrophy
      i. An explanation of the risk associated with anticipation, which is the tendency toward large intergenerational expansion of the CTG repeat during maternal transmission, resulting in offspring with congenital myotonic dystrophy
      ii. CTG repeat number provides only an approximate guide to prognosis or to pregnancy outcome. Most cases with over 2,000 repeats will have congenital or severe childhood-onset disease; most individuals with 50–100 repeats will not have significant neuromuscular disease.
      iii. An intergenerational contraction of the CTG fragment observed in approximately 7% of cases. Clinical anticipation was seen despite the reduced CTG repeat size, resulting in congenital myotonic dystrophy in the offspring.
      iv. Prenatal diagnosis (PND) is available; however, the decision to terminate affected pregnancies is difficult as the extent of disability is hard to predict from the size of the expansion.
   e. Preimplantation genetic diagnosis (PGD) genetic analysis: available and is carried out before the establishment of pregnancy (Kakourou et al. 2008)

3. Management
   a. No specific treatment available for the progressive weakness that is responsible for most of the disability in patients with myotonic dystrophy
   b. Patients with myotonic dystrophy usually do not seek treatment for the myotonia per se, or they are not compliant with medication regimens to treat it, either because myotonia is much milder than their other symptoms or because they avoid medical treatment as part of their personality (Conravey and Santana-Gould 2010).
   c. To alleviate myotonia by drugs
      i. Quinine, quinidine, dilantin, carbamazepine, procainamide, diamox to alleviate myopia not universally successful
      ii. Encouraging results with mexiletine (Logigian et al. 2010) and tocainide
   d. Avoid cold which may induce myotonia
   e. Prescription for orthoses, wheelchairs, or other assisted devices
   f. Treat cataracts, diabetes mellitus, hypothyroidism, and sleep apnea
   g. Avoid surgery and anesthesia (sensitive to narcotics and sedatives)

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Fig. 1 An adult (**a**) with myotonic dystrophy showing hard to release after shaking hand (**b**) and thenar myotonia after tapping (**c**)

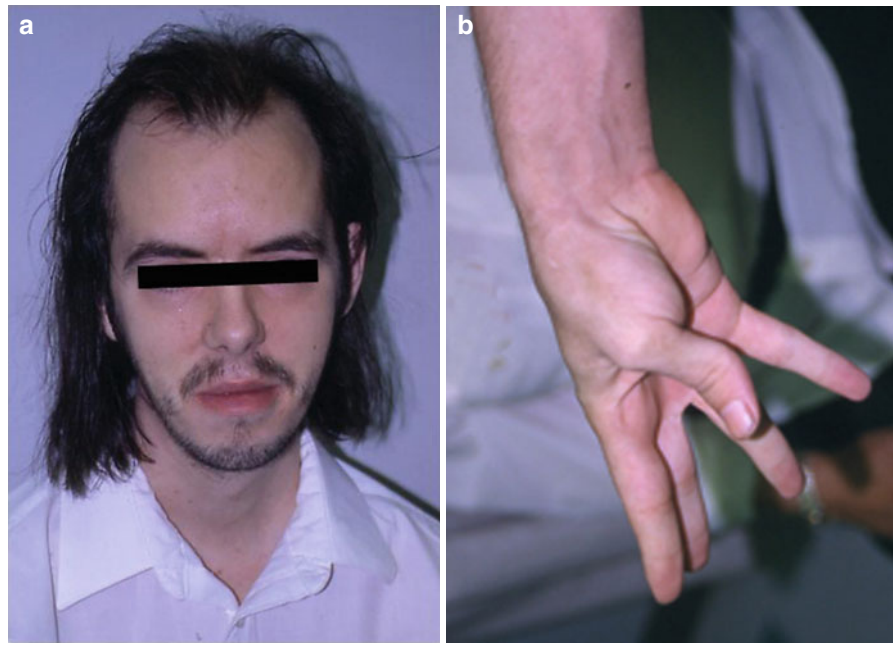

Fig. 2 (**a**, **b**) An adult with myotonia dystrophy showing long thin face with frontal bossing and thenar myotonia after tapping

Fig. 3 (**a**–**c**) A 23-year-old mother and her 21-month-old daughter with myotonia congenita type 1. The mother has myotonia (hard to relax after shaking hand), thenar myotonia after tapping, and absent tendon reflexes. The pregnancy was complicated by polyhydramnios, feeble fetal movement, and breech presentation. After scheduled cesarean section, the baby breathed only once and needed intubation for 5 days. She was very floppy and just started to walk about 2 months prior to the clinic visit. She chokes easily and does not chew and talk. On physical examination, in addition to hypotonia, there is a long and sagging face with marked tented-mouth. Molecular genetic testing of the daughter showed CTG repeats of 1,050

Nail-Patella Syndrome

In 1820, Chatelain first observed the nail-patella syndrome in a patient with a triad of abnormal nails, elbows, and knees. The hereditary nature of the syndrome was first described by Pye-Smith in 1883 in the English literature. The presence of iliac horns was first noted by Kieser in 1939 and later by Fong in 1946. In 1948, Mino et al. described the tetrad of abnormal nails, elbows, knees, and iliac horns for which the name hereditary onycho-osteodysplasia was coined by Duncan and Souter in 1963.

Synonyms and Related Disorders

Hereditary onycho-osteodysplasia

Genetics/Basic Defects

1. An autosomal dominant disorder with complete penetrance
2. *LMX1B*
   a. The only gene known to be associated with nail-patella syndrome
   b. A LIM-homeodomain transcription factor involved in normal patterning of the dorsoventral axis of the limb during development and early morphogenesis of the glomerular basement membrane

Clinical Features

1. Classic clinical tetrad
   a. Onychodysplasia: the most constant feature of the syndrome (approximately 98% of cases)
      i. Absent, hypoplastic, or dystrophic nails usually noted at birth
      ii. Bilateral or symmetrically involved
      iii. Longitudinally or horizontally ridged (grooved) nails
      iv. Thin or less often thickened nails
      v. Triangular lunules (lunulae): a characteristic feature of the syndrome
      vi. Most pronounced involvement in thumbnails, decreases in severity ulnarward
      vii. Dysplasia of toenails usually less marked, often affecting little toenails, and less frequent than that of the fingernails
   b. Knee dysplasia (approximately 74% of cases)
      i. Small, irregularly shaped, or absent patella that is prone to dislocate
      ii. May be asymmetrically involved
      iii. Hypoplastic patella often located laterally and superiorly, even though not actually dislocated
      iv. May be associated with prominent medial femoral condyles, hypoplastic lateral femoral condyles, and prominent tibial tuberosities
      v. Appearance of flattened profile of knee joints

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   c. Elbow dysplasia (approximately 70% of cases)
      i. May be asymmetrical
      ii. The deformity is characterized by hypoplasia of the capitellum, commonly by secondary dysplasia and dislocation, usually posteriorly, of the radial head, associated with limitation of rotation (pronation and supination) of variable degree.
      iii. Triceps hypoplasia with antecubital pterygia, a frequent accompaniment of the syndrome, further limiting extension resulting in cubitus valgus
   d. "Iliac horns"
      i. Clinically palpable
      ii. Generally symmetrical
      iii. Known to develop a secondary center of ossification
      iv. The iliac horns can be present at birth by X-ray examination
2. Other skeletal abnormalities
   a. Talipes equinovarus, talipes calcaneovalgus deformities, and flat feet
   b. Mild short stature
3. Associated nephropathy (30–50% of cases) (renal failure in approximately 5% of cases)
   a. Proteinuria
      i. Usually the first sign of renal involvement
      ii. With or without hematuria
      iii. May present at any age from birth onward
      iv. May be intermittent
      v. May remit spontaneously, remain asymmetric, progress to nephritic syndrome, and occasionally to renal failure
      vi. May be exacerbated during pregnancy
   b. Progression to chronic glomerulonephritis leading rarely to renal failure
      i. May occur rapidly
      ii. May occur after many years of asymptomatic proteinuria
4. Eye involvement
   a. Primary open-angle glaucoma
   b. Ocular hypertension
   c. Iris pigmentary changes: frequent observation of a zone of darker pigmentation shaped like a cloverleaf or flower around the central part of the iris (Lester's sign)
5. Gastrointestinal involvement (about one-third of cases)
   a. Constipation
   b. Irritable bowel syndrome
6. Neurological involvement
   a. Intermittent numbness, tingling, and burning sensations in the hands and feet in some cases
   b. Epilepsy (6% of cases)
7. Vasomotor problems in some cases
   a. Poor peripheral circulation, presenting as very cold hands and feet even in warm weather
   b. Raynaud's phenomenon
8. Dental problems
   a. Weak, crumbling teeth
   b. Thin dental enamel

Diagnostic Investigations

1. Diagnosis based on clinical and radiographic findings
2. Laboratory studies
   a. Urinalysis: proteinuria, hematuria
   b. Plasma urea, BUN, creatinine concentrations
3. Radiologic features
   a. Elbow involvement
      i. Dysplasia of the radial head
      ii. Hypoplasia of the lateral epicondyle and capitellum
      iii. Prominence of the medial epicondyle
      iv. Dislocation of the radial head, usually posteriorly
   b. Iliac horns
      i. Bilateral, conical, bony processes that project posteriorly and laterally from the central part of the iliac bones of the pelvis
      ii. Present in about 70% of cases
      iii. Considered pathognomonic of the syndrome
      iv. Pelvic X-ray
         a) Usually necessary for detection of iliac horns, but large horns may be palpable clinically
         b) Iliac horns: may be observed at birth
         c) An epiphysis at the apex of iliac horns: may be present in children
4. MRI for possible bone/soft tissue abnormalities
5. Ultrastructural (electron microscopic) abnormalities: the most specific histologic changes seen in nail-patella syndrome
   a. Collagen fibril deposition within the basement membrane and the mesangial matrix

   b. Irregular thickening of the glomerular basement membrane with electron-lucent areas giving a mottled "moth-eaten" appearance
6. Molecular genetic testing: *LMX1B* gene mutation analysis available clinically

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. An affected parent: a 50% risk
      ii. Clinically unaffected parents
         a) A low risk in a case of de novo mutation in the proband
         b) An increased risk if germline mosaicism exists in a parent (not been reported)
   b. Patient's offspring: a 50% risk
2. Prenatal diagnosis: demonstration of the disease-causing mutation previously identified in the proband on fetal DNA obtained from amniocentesis or CVS
3. Management
   a. Patella dysplasia: most patients asymptomatic, rarely require surgical treatment
   b. Physiotherapy for orthopedic complaints
   c. Surgical treatment
      i. Bilateral elbow soft tissue release
      ii. Bilateral radial head excisions
      iii. Foot and ankle reconstructive procedures for equinus, pes cavus, calcaneovalgus, congenital vertical talus, and clubfoot deformities
      iv. Congenital permanent dislocation of the patella
   d. Screening for proteinuria
   e. Screening for glaucoma

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Fig. 1 (**a**–**i**) A 10-year-old boy has classic nail-patellar syndrome. Note webbings of the neck and the elbows causing marked elbow contractures, abnormal muscle distribution of the upper extremities, nail hypoplasia, and absent patella. The radiographs show "iliac horn" sign of the pelvis and patella agenesis

Neonatal Herpes Simplex Infection

Hass in 1935 described a fatal case of neonatal herpes simplex virus (HSV) infection with hepatoadrenal necrosis and intranuclear inclusion bodies. Neonatal herpes is defined as the diagnosis of HSV infection in an infant within the first 28 days of life.

Synonyms and Related Disorders

Fetal/intrauterine herpes simplex infection

Genetics/Basic Defects

1. HSV-1 and HSV-2
   a. Belong to Herpesvirus family
      i. Herpes simplex viruses
         a) Enveloped, double-stranded DNA viruses
         b) Exist as two serotypes, 1 and 2 (HSV-1 and HSV-2)
      ii. Infections with HSV-1 generally involve the face and skin "above the waist" and are associated with orolabial disease. Most infections occur during childhood. HSV-1 also can cause genital infection, resulting more frequently from oral-genital contact.
      iii. Infections with HSV-2 usually involve the genitalia and skin "below the waist" in sexually active adolescents and adults, usually resulting from sexual intercourse. Most HSV disease in neonates is due to HSV-2. HSV-2 also causes oral lesions in approximately 25% of the infected population.
   b. Viruses are transmitted from infected to susceptible individuals during close personal contact.
   c. Recurrent HSV infections occur in over one-third of the world's population due to the rare fatal nature of the infection and a latency period.
   d. Infections in children and nonpregnant adults
      i. Recurrent herpes labialis: the largest reservoir of HSV infections in the community
      ii. Genital herpes
         a) A first-episode primary infection occurs in a person with no prior HSV-1 or HSV-2 antibody.
         b) A first-episode nonprimary infection occurs in a person with preexisting HSV-1 antibody acquiring HSV-2 genital infection.
         c) Recurrent infections can result from viral reactivation from latency and subsequent antegrade translocation of virus back to the skin and mucosal surfaces.
   e. Maternal genital infections
      i. Twenty-two percent of pregnant women are seropositive for herpes simplex virus (HSV)-2, and more than 2% of women acquire genital herpes during pregnancy.
      ii. Recurrent genital herpes infections: the most common form of genital HSV infections during gestation
      iii. The most devastating complication of genital HSV is infection of the neonate caused by contact with infected genital secretions at the time of delivery.
      iv. Woman with primary genital HSV disease: at highest risk of transmitting the virus to her baby
      v. Neonatal transmission occurs in the peripartum period, provided the gravid woman is shedding

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virus, either symptomatically or asymptomatically, at the time of delivery.

vi. Factors influencing transmission from mother to neonate
  a) Type of maternal infection (primary versus recurrent): Mothers with a first episode of genital HSV infection near term are at much greater risk of developing neonatal herpes than those whose mothers have recurrent genital herpes.
  b) Maternal antibody status
  c) Duration of rupture of membranes: Cesarean delivery within 4 h of membrane rupture in a woman with active genital lesions can reduce the infant's risk of acquiring HSV.
  d) Integrity of mucocutaneous barriers (e.g., use of fetal scalp electrodes)
  e) Mode of delivery (cesarean section versus vaginal): effective in the prevention of HSV transmission to the neonate from a mother actively shedding virus from the genital tract. Neonatal infection has occurred in spite of cesarean delivery performed prior to the rupture of membranes.

f. Incidence of neonatal disease: estimated at approximately 1 in 3,200 deliveries (an estimated 1,500 cases of neonatal HSV infection annually in the United States)

g. Transmission of HSV disease to neonates occurs in the following three distinct time intervals:
  i. Intrauterine (in utero): 5% infected with HSV in utero
  ii. Peripartum (perinatal): overwhelming majority (~85%) of infected neonates
  iii. Postpartum (postnatal): an additional 10% of infected neonates

h. Disease classification of HSV infections acquired either peripartum or postpartum: predictive of both morbidity and mortality
  i. Disease localized to the skin, eyes, and/or mouth (SEM disease, accounting for ~45% of cases of neonatal HSV)
  ii. Encephalitis, with or without SEM involvement (CNS disease, accounting for ~30% of cases of neonatal HSV)
  iii. Disseminated infection involving multiple organs, including the CNS, lungs, liver, adrenal glands, skin, eyes, and/or mouth (disseminated disease, accounting for ~25% of cases of neonatal HSV)

2. Two biologic properties of HSV that directly influence human diseases
  a. Latency: a period of reactivation of virus multiplication, resulting in clinically apparent disease (lesions) or clinically inapparent (asymptomatic, or subclinical) infection
  b. Neurovirulence: an affinity with which HSV is drawn to and propagated in neuronal tissue, resulting in profound disease with severe neurologic sequelae:
    i. Neonatal HSV central nervous system (CNS) disease
    ii. Herpes simplex encephalitis in older children and adults

Clinical Features

1. Intrauterine infection
  a. Incidence: approximately 1 in 300,000 deliveries
  b. In utero disease unlikely to be missed due to the extent of involvement of affected babies
  c. A triad of clinical findings
    i. Cutaneous manifestations
      a) Scarring
      b) Active lesions
      c) Hypo-/hyperpigmentation
      d) Aplasia cutis
      e) Erythematous macular exanthem
    ii. Ophthalmologic findings
      a) Microphthalmia
      b) Retinal dysplasia
      c) Optic atrophy
      d) Chorioretinitis
    iii. Neurologic involvement
      a) Microcephaly
      b) Encephalomalacia
      c) Hydranencephaly
      d) Intracranial calcification

2. Disseminated disease involving multiple organs, most prominently the liver and lungs and possibly with a central nervous system (CNS) component
  a. Incidence: approximately 25% of all children with neonatal HSV disease

   b. Has the earliest age of onset, often during the first postnatal week
   c. Encephalitis: about 60–75% of infants with disseminated disease
   d. Vesicular rash: over 20% of neonates with disseminated HSV disease do not develop cutaneous vesicles during the course of their illness
   e. Death relates primarily to the severe coagulopathy, liver dysfunction, and pulmonary involvement of the disease.
3. Localized CNS disease with or without SEM involvement: observed in almost one-third of all neonates with HSV infection and has the latest age of onset, usually between the second and third weeks after birth
   a. Seizures (both focal and generalized)
   b. Lethargy
   c. Irritability
   d. Tremors
   e. Poor feeding
   f. Temperature instability
   g. Bulging fontanelle
   h. Associated skin vesicles in 60% and 70% of babies classified as having CNS disease
   i. Death usually caused by devastating brain destruction, with resulting acute neurologic and autonomic dysfunction
4. SEM disease
   a. Incidence: approximately 45% of all cases of neonatal HSV disease
   b. Represents a spectrum of disease manifestations having more limited viral dissemination but without visceral involvement (e.g., liver, lung) as detected biochemically (e.g., elevated transaminase levels) or clinically (e.g., pneumonitis)
5. Factors affecting the severity of neonatal disease
   a. Prompt diagnosis: PCR assay to detect HSV DNA in neonates has improved early diagnosis of disease.
   b. Initiation of antiviral (intravenous acyclovir) therapy
      i. Reduces mortality and morbidity among neonates with skin, eye, and mouth disease
      ii. Unable to reduce morbidity associated with disseminated or CNS disease
6. Despite early intervention with high-dose antiviral therapy, 30% of infants with disseminated disease die, and 40% of survivors of CNS disease have severe neurologic damage. Therefore, prevention of neonatal infection is critical.

Diagnostic Investigations

1. Clinical diagnosis based on:
   a. Typical findings (HSV culture not necessary):
      i. Herpes labialis
      ii. Gingivostomatitis
      iii. Genital herpes
   b. Atypical HSV infections (culture and antiviral susceptibility testing needed to guide antiviral therapy)
      i. Immunocompromised patients
      ii. HSV conjunctivitis and keratitis: need an ophthalmologist consultation
2. Diagnostic evaluations obtained prior to initiation of acyclovir therapy
   a. HSV cultures: remains the definitive diagnostic method of establishing HSV disease
      i. Skin vesicles, if present
      ii. Oropharynx
      iii. Conjunctivae
      iv. Urine
      v. Blood
      vi. Stool
      vii. Rectum
      viii. Cerebrospinal fluid (CSF)
   b. Liver transaminase: Elevated levels suggest disseminated HSV infection.
3. Serologic testings
   a. Type-specific antibody assays to distinguish between HSV-1 and HSV-2 antibodies
   b. Identifies only past infection but cannot identify the site of HSV infection
   c. Patients with cold sores due to HSV-1 will test HSV-1 seropositive regardless of presence or absence of genital HSV-1 infection.
   d. Possible to identify serodiscordant couples in which the woman is HSV-2 seronegative and the partner is seropositive. Women in such couples are at risk for acquiring primary genital HSV infection during pregnancy and are thus at higher risk of transmitting the virus to their babies during birth.

e. Serologic studies, in general, play no role in the diagnosis of neonatal HSV disease.

4. Classification of genital HSV based on serologic and viral detection test results: important in pregnancy because the risk of perinatal HSV transmission varies accordingly
   a. Primary first episode: characterized by isolation of HSV-1 or HSV-2 from genital secretions in the absence of HSV antibodies in serum
   b. Nonprimary first episode: characterized by isolation of HSV-2 from genital secretions in the presence of HSV-1 antibodies in serum
   c. Reactivation disease: characterized by isolation of HSV-1 or HSV-2 from the genital tract in the presence of HSV antibodies of the same serotype as the isolate
5. PCR amplification
   a. Able to correctly diagnose neonatal HSV disease, especially in patients without overt manifestations such as skin vesicles
   b. Able to assess the response to therapy
      i. Having HSV DNA detected in CSF at or after the completion of intravenous therapy is associated with poor outcomes.
      ii. Repeat lumbar puncture of all patients with CNS HSV involvement is indicated at the end of intravenous acyclovir therapy to determine that the specimen is PCR negative in a reliable laboratory and to document the end-of-therapy CSF indices. Persons who remain PCR positive should continue to receive intravenous antiviral therapy until PCR negativity is achieved.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Unknown
      ii. No cases in siblings reported
   b. Patient's offspring
      i. Unknown
2. Prenatal diagnosis
   a. Genetic counseling complicated due to:
      i. Fetal infection may follow primary or recurrent disease.
      ii. Fetal infection can occur at any time in gestation.
      iii. Only approximately one third of cases have a history suggestive of maternal herpes infection during pregnancy.
   b. Isolation of the virus from amniotic fluid obtained at amniocentesis does not necessarily imply fetal infection.
   c. Currently no accurate risk estimate available for congenital malformations following maternal herpes infection during pregnancy
      i. Appears to be small
      ii. Highest risk for women with primary infection during the first trimester
3. Management
   a. Antiviral drugs
      i. Vidarabine (1-β-D-arabinofuranosyl-adenine): the first systemically administered antiviral medication with activity against HSV for which the therapeutic efficacy outweighed its toxicity
         a) Administered over prolonged infusion times and in large volumes of fluid
         b) Management of life-threatening HSV and varicella zoster virus infections, HSV encephalitis, and herpesvirus infections in immunocompromised patients
      ii. Acyclovir
         a) Lower dose: lower toxicity and improved ease of administration
         b) Higher dose: improved outcome in mortality and morbidity achieved with use of higher-dose acyclovir
   b. Antibody therapy
      i. Use of passive immunotherapy as an adjuvant to active antiviral interventions.
      ii. Neonates with higher neutralizing antibody titers: less likely to become infected with HSV following perinatal exposure and being more likely to have localized disease (and less likely to have disseminated disease) once they are infected
      iii. Intravenous gamma globulin currently not recommended for the management of neonates with HSV disease due to variable amount of anti-HSV antibodies present in conventional intravenous gamma globulin preparations
      iv. A monoclonal antibody directed against γD may be available for clinical investigation as an adjuvant therapeutic agent by

the NIAID Collaborative Antiviral Study Group in the future.

c. Prevention of neonatal HSV infections
   i. Prevention strategies
      a) Identification of women at risk for HSV acquisition during pregnancy by testing women and possibly their partners for HSV antibodies
      b) Provide counseling to prevent transmission to women in late pregnancy
   ii. Cesarean section
      a) Reduces the infant's risk of acquiring HSV in women with active genital lesions present at the time of delivery
      b) Limitations: 60–80% of babies who develop neonatal HSV disease are born to women without a history of genital herpes, and thus, infection in these babies may not be prevented by this approach, and women with recurrent infections who are shedding virus at the time of delivery are at low risk of their babies developing neonatal HSV disease.
   iii. Antiviral therapy during pregnancy
      a) Oral acyclovir near the end of pregnancy to suppress genital HSV recurrences becoming increasingly common in clinical practice
      b) Additional studies are needed to more definitively establish the effectiveness and safety of late-pregnancy maternal HSV suppression.
   iv. Vaccine development for genital herpes: A candidate HSV-2 gD subunit vaccine adjuvanted with alum combined with 3-deacylated monophosphoryl lipid A has recently demonstrated promising results in preventing HSV-1 or HSV-2 genital herpes disease and HSV-2 infection, efficacy limited only to women who were HSV-1 and HSV-2 seronegative prior to vaccination.

d. Avoid unnecessary invasive procedures in labor.
   i. Vaginal delivery in women with genital herpes but without lesions or symptoms at the time of labor
   ii. Avoid the following procedures to lessen the risk of HSV transmission, except when critical to obstetric care:
      a) Artificial rupture of membranes
      b) Fetal scalp electrodes
      c) Vacuum or forceps delivery

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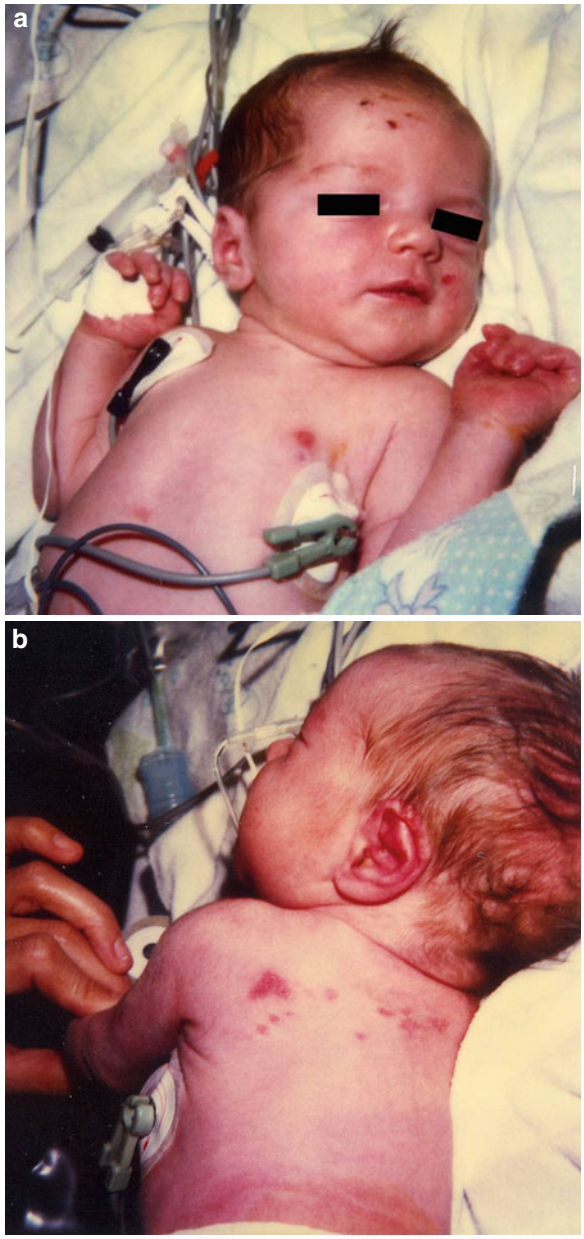

Fig. 1 (**a**, **b**) A neonate born with congenital herpes simplex infection showing generalized vesicular rash

Nephrogenic Diabetes Insipidus

Hereditary nephrogenic diabetes insipidus (NDI) is a rare disorder of defective vasopressin-stimulated water reabsorption via the luminal water channels in the cortical and medullary collecting ducts (Knoers and Deen 2001).

Genetics/Basic Defects

1. Causes of diabetes insipidus (Linshaw 2007)
   a. Central: hypothalamic/pituitary lesions leading to insufficient production or release of antidiuretic hormone (ADH)
      i. Postoperative brain surgery
      ii. Intracranial lesions (cysts, aneurysms, tumors of pituitary, brainstem)
      iii. Infiltrative malignancies (lymphoma, leukemia)
      iv. Infections, including encephalitis, meningitis, abscess
      v. Head trauma
      vi. Hypoxic injury
      vii. Congenital, inherited as an autosomal dominant disorder
   b. Nephrogenic: renal resistance (lack of response of the distal nephron) to ADH from lesions interfering with the renal concentrating mechanism
      i. Acquired metabolic aberrations
         a) Hypokalemia (chronic, Bartter syndrome)
         b) Hypercalcemia
         c) Hypercalciuria (rare)
         d) Diabetes mellitus
      ii. Medullary damage
         a) Chronic pyelonephritis
         b) Infiltrative disease (leukemia, lymphoma, amyloidosis)
         c) Sickle cell disease
         d) Cystinosis
         e) Other forms of chronic renal failure
         f) Obstructive uropathy
      iii. Drugs
         a) Lithium
         b) Demeclocycline
         c) Amphotericin B
         d) Diphenylhydantoin
      iv. Inherited
         a) X-linked recessive: approximately 90% of cases of hereditary nephrogenic diabetes insipidus
         b) Autosomal recessive: approximately about 9% of cases
         c) Autosomal dominant: about 1% of cases
2. X-linked inheritance
   a. Caused by mutations in the arginine vasopressin V2 receptor (*AVPR2*) gene on the X chromosome (mapped on Xq28), encoding the arginine vasopressin receptor type 2 (VR2): molecular basis for lack of concentration of urine
   b. Males who carry the defective gene
      i. Do not concentrate urine after administration of arginine vasopressin (AVP): defined as the excretion of increased (>30 ml/kg/day) volumes of diluted urine (<250 mmol/kg) (Fujiwara and Bichet 2005)
      ii. Tend to have more serious symptoms
         a) Polydipsia (excessive thirst)
         b) Polyuria (excessive urine production)

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   c. Females who carry the defective gene: can have variable (rarely severe) degrees of polydipsia and polyuria because of skewed X chromosome inactivation
3. Autosomal recessive inheritance
   a. Caused by aquaporin 2 (*AQP2*, mapped on 12q13) mutations
   b. Polyuria and polydipsia are usually present at, or shortly after, birth
   c. Disease tends to be more severe, with urine osmolality generally not exceeding approximately 200 mOsm/kg water.
4. Autosomal dominant inheritance
   a. Caused by *AQP2* mutations
   b. Clinical expression
      i. Tends to become noticeable after 6–12 months or even later
      ii. May not be as severe (urine osmolality may be higher)
      iii. Transient response to ADH may be present.

Clinical Features

1. Medical history (Linshaw 2007)
   a. Failure to thrive
   b. Extreme thirst
   c. Unexplained fever
   d. Irritability
   e. Constipation
   f. Impressive polyuria
   g. Vomiting
   h. Seizures
2. Physical features
   a. Dry mouth and eyes
   b. Poor skin turgor
   c. Sunken eyes and anterior fontanelle
   d. Mottled skin
   e. Decreased peripheral pulses
   f. Low blood pressure
   g. Multiple abdominal masses/fecaliths

Diagnostic Investigations

1. Laboratory features (Knoers 2007; Linshaw 2007)
   a. Hypernatremia: serum sodium concentration >143 mEq/L in the presence of a low urine specific gravity and in the absence of excessive sodium intake: highly suggestive of diabetes insipidus.
   b. Failure to concentrate the urine in the presence of high plasma vasopressin concentration and in the presence of parenteral administration of vasopressin or desmopressin: diagnostic of NDI.
   c. Hyperchloremia
   d. Metabolic acidosis
   e. Normal potassium concentration
   f. Hyperuricemia
   g. High serum and low urine osmolality
2. Molecular identification underlying X-linked NDI (*AVPR2*): immediate clinical significance because early diagnosis and treatment of affected infants can avert the physical and mental retardation that results from repeated episodes of dehydration (Fujiwara and Bichet 2005)
3. Molecular identification underlying autosomal recessive and autosomal dominant NDI (*AQP2*)

Genetic Counseling

1. Recurrence risk (Knoers 2007)
   a. Patient's sib
      i. X-linked recessive: risks of sibs depending on the genetic status of the proband's mother
         a) If the mother is a carrier: 50% of male sibs will be affected (inheriting the maternal *AVPR2* mutation); 50% of female sibs will be carriers
         b) A low recurrence risk but not zero due to possible germline mosaicism if the proband is the only one affected in the family and the disease-causing mutation cannot be detected in the DNA of the mother
      ii. Autosomal recessive inheritance: risk of recurrence 25%
      iii. Autosomal dominant inheritance
         a) Recurrence risk of 50% if a parent is affected
         b) A low recurrence risk if both parents are normal
   b. Patient's offspring
      i. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal.

   ii. Autosomal recessive inheritance
      a) Obligatory carriers for a disease-causing mutation in the *AQP2* gene
      b) A low recurrence risk unless the spouse is affected or a carrier
   iii. Autosomal dominant inheritance: a 50% risk of offspring affected (inheriting the *AQP2* mutation)
2. Prenatal diagnosis
   a. X-linked recessive: available for pregnancies at increased risk if the *AVPR2* mutation has been identified in an affected family member by amniocentesis of CVS if the fetal karyotype is 46,XY
   b. Autosomal recessive and autosomal dominant: available for pregnancies at increased risk for the *AQP2* mutation
   c. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation(s) has/have been identified.
3. Management (Linshaw 2007)
   a. Sufficient water to maintain normal electrolytes
   b. Low renal solute load to minimize water loss
   c. Adequate calories to support growth
   d. Pharmacotherapy: usually needed
      i. Thiazide
         a) Hydrochlorothiazide: 1–3 mg/kg/day bid
         b) Hypokalemia
         c) Hyponatremia
         d) Alkalosis
         e) Hypercalcemia
         f) Hyperglycemia
         g) Hyperuricemia
         h) Hepatitis
         i) Intestinal symptoms
         j) Bone marrow suppression
   e. Amiloride
      i. 20 mg/1.73 m^2/day bid–tid
      ii. Hyperkalemia
      iii. Headaches
      iv. Gastrointestinal discomfort
   f. Indomethacin
      i. 1.5–2.5 mg/kg/day tid
      ii. Gastrointestinal discomfort
      iii. Gastrointestinal bleeding
      iv. Headaches
      v. Renal toxicity
      vi. Hematopoietic adverse effects

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Fig. 1 A 3-year-old girl was evaluated because her father has nephrogenic diabetes insipidus. He has problems with dehydration, polyuria, and polydipsia. His mother is a carrier and his maternal grandfather died of nephrogenic diabetes insipidus. The girl was found to have a mutation in the *AVPR2* gene. The mutation detected is g692–693delCT where two bases (CT) in codon 111 are deleted. The deletion causes a frameshift mutation that begins with a change of the amino acid at position 111 and results in a premature termination of protein synthesis at codon 190.This mutation has been reported to cause nephrogenic diabetes insipidus (NDI). The genetic data along with the family history are consistent with this female being a carrier of X-linked NDI

Netherton Syndrome

Netherton syndrome is a rare hereditary disorder of keratinization. It was described by Comèl in 1949 and Netherton in 1958. The syndrome is sometimes called Comèl–Netherton syndrome. The incidence is about 1 in 200,000 (Bitoun et al. 2002b).

Synonyms and Related Disorders

Netherton disease

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Bitoun et al. 2002b)
2. Defective gene in Netherton syndrome
   a. Serine protease inhibitor, Kazal-type 5 (*SPINK5*) mapped on chromosome 5q31-32
   b. The protein encoded by *SPINK5* is highly expressed in thymus and mucous epithelia, thereby termed LEKTI for lymphoepithelial Kazal type–related inhibitor.
      i. LEKTI possibly plays a role in anti-inflammatory and/or antimicrobial protection of mucous epithelia.
      ii. LEKTI possibly have similar function in the epidermis.

Clinical Features

1. Clinical triad
   a. Congenital ichthyosis
      i. Extent of involvement: highly variable
      ii. Natural course
         a) At birth: usually normal appearing skin
         b) Within a few weeks of age: skin becomes erythematous and develops serpiginous double-edged scales typical of ichthyosis linearis circumflexa or ichthyosiform erythroderma.
   b. Hair abnormality
      i. Trichorrhexis invaginata/nodosa
         a) Sparse and brittle scalp hair with a characteristic "bamboo" shape under light microscope due to invagination of the distal part of the hair shaft to its proximal part
         b) The major diagnostic sign (considered pathognomonic) but may be difficult to detect in infancy and early childhood
         c) May not affect all hair and can be limited to the lateral part of the eyebrows
      ii. Pili torti
      iii. Eyelashes and eyebrows may be affected.
   c. Atopic manifestations (Bitoun et al. 2002b)
      i. Eczema-like rashes
      ii. Atopic dermatitis
      iii. Pruritus
      iv. Allergic rhinitis
      v. Asthma
      vi. Urticaria/angioedema
2. Prognosis: poor (Bitoun et al. 2002b)
   a. Frequent life-threatening complications during the neonatal period
      i. Hypernatremic dehydration
      ii. Hypothermia
      iii. Extreme weight loss

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iv. Recurrent infections
v. Bronchopneumonia
vi. Sepsis

b. Failure to thrive common during childhood resulting from
i. Malnutrition
ii. Metabolic disorders
iii. Chronic erythroderma
iv. Persistent cutaneous infections
v. Severe enteropathy with villous atrophy
vi. Growth retardation

c. Other abnormalities
i. Renal failure
ii. Aminoaciduria
iii. Congenital heart defects
iv. Hydroureter
v. Infantile pyloric stenosis
vi. Increased susceptibility to skin cancer
a) Squamous cell carcinoma
b) Vulvar cancer

Diagnostic Investigations

1. Clinical laboratory
   a. Increased serum immunoglobulin E levels
   b. Hypereosinophilia
   c. No consistent or significant abnormalities of immune function
   d. IgG abnormalities (both hypo- and hyper-IgG)
   e. T-cell and neutrophil defects may also occur.
   f. Selective humoral deficiency to bacterial polysaccharide antigens has been described.
   g. Specific IgE antibodies against airborne and food allergens frequently present
2. Dermatoscopy (trichoscopy) (Sun and Linden 2005; Burk et al. 2008; Rakowska et al. 2009)
   a. Trichorrhexis invaginata (bamboo hairs)
      i. A focal defect of the hair shaft that produces development of torsion nodules and invaginated nodules
      ii. The proximal element of the node overlaps the distal portion, causing an intussusception.
   b. Golf tee–like endings of hair shafts: If hair is pulled distally from this focal defect, a golf tee–like deformity is left. Hence, any hairs examined should be cut, rather than plucked.
   c. The hair shaft nodules caused by this defect are sometimes able to be seen by the naked eye. These hair defects can be found in scalp, eyebrow, or eyelash hairs. Grossly, scalp hair is described to be sparse and brittle.
   d. The hair shaft abnormality was reported to be secondary to intermittent incomplete formation of disulfide bonds in the keratogenous zone (Ito et al. 1984).
   e. Other hair shaft abnormalities
      i. Pili torti
      ii. Trichorrhexis nodosa
      iii. Helical hairs (Lurie and Garty 1995)
3. Immunohistochemistry using anti-LEKTI antibodies: shows a complete absence of LEKTI in the skin samples (Shimomura et al. 2005)
4. Histology and ultrastructural studies of skin sections
   a. Incomplete keratinization or defective cornification of the epidermis
   b. Dermal lymphocytic infiltrate
   c. Ultrastructure of the stratum corneum: characterized by premature degradation of corneodesmosomes with separation of corneocytes (Chao et al. 2005).
5. Molecular genetic testing of *SPINK5*: clinically available
   a. Mutation analysis of patients
   b. Carrier testing

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is a carrier of the gene
2. Prenatal diagnosis (Bitoun et al. 2002a)
   a. Ultrastructural examination of fetal skin biopsies for defective cornification of the epidermis is not reliable, since fetal skin keratinization does not begin until the 24th week of gestation, whereas in utero, fetal skin biopsy is usually performed between 19 and 22 weeks.
   b. DNA-based prenatal diagnosis on fetal DNA obtained from amniocentesis or CVS.
      i. *SPINK5* mutation detection
      ii. Indirect genotype analysis at the *SPINK5* locus using linkage analysis
         a) This approach is reliable since there is no evidence of locus heterogeneity.

   b) Presence of a large number of SPINK5 intragenic restriction fragment length polymorphisms (RFLPs) showing a high percentage of heterozygosity

3. Management
   a. No specific treatment available
   b. Emollients
   c. Keratolytics
   d. Antibiotics for recurrent infections
   e. Topical corticosteroids
   f. Topical tacrolimus and pimecrolimus with good control of skin disease without toxic effect (Saif and Al-Khenizan 2007)
   g. Medium dose of psoralen-UVA1 phototherapy may be effective and tolerated in adult.

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Fig. 1 A neonate (**a**) with Netherton syndrome showing erythroderma. The patient had markedly elevated serum total IgE levels of 409 IU/mL at age 8 months and 285 IU/mL at 14 months of age. Molecular genetic analysis of *SPINK5* showed a compound heterozygote with a mutation 316DelGA in exon 5 inherited from the mother, and a mutation 2441+1delGTGA in exon 25 inherited from the father. The same patient at age 3 years (**b**) showed generalized erythroderma and marked growth retardation (height age of 7 months and weight age of 4 months). Microscopic analysis of the hair (**c** and **d**, lower and higher magnification) showed trichorrhexis invaginata/nodosa (*bamboo hair*) (*pink arrows*), pili torti (*yellow arrow*), and fractured hair shaft at the site of invagination (*blue arrow*)

Neu–Laxova Syndrome

The Neu–Laxova syndrome is a lethal disorder characterized by multiple congenital malformations. Microcephaly, lissencephaly, absence of corpus callosum, facial anomalies (notably absent eyelids), short broad neck, peripheral edema, ichthyosis, limb anomalies, and other malformations are common findings. The syndrome was described first by Neu et al. in 1971 and Laxova et al. in 1972 (Neu et al. 1971; Laxova et al. 1972).

Genetics/Basic Defects

1. Inheritance: autosomal recessive inheritance (King et al. 1995)
2. Pathogenesis (Coto-Puckett et al. 2010): remains unknown and differing etiologies have been postulated:
   a. A form of neuroectodermal dysplasia given the CNS and skin findings (Lazjuk et al. 1979; Ejeckam et al. 1986; Muller et al. 1987; Naveed and Sreenivas 1990)
   b. CNS pathology described as a neuronal migration defect with arrest of development early at 12–14 weeks of embryogenesis (Muller et al. 1987; Ostrovskaya and Lazjuk 1988)
   c. A neurodegenerative disorder with abnormal cell death causing neuronal atrophy and depletion (Allias et al. 2004)
   d. Limb deformities: caused by failure of muscle, bone, nerve, and arterial development in early embryogenesis (Shved et al. 1985)
   e. Contractures: secondary to reduced fetal movements or fetal akinesia/hypokinesis (Fitch et al. 1982; Russo et al. 1989)
   f. Ichthyotic skin changes: the cause of the deformed limbs, reduced movement, massive edema, and IUGR (Karimi-Nejad et al. 1987; Russo et al. 1989)
   g. Mechanism of ichthyosis proposed as hypoproteinemia caused by protein leakage through skin fissures as the primary pathogenesis of Neu–Laxova syndrome (Karimi-Nejad et al. 1987)
   h. It is the restrictive dermopathy that leads the various authors to characterize Neu–Laxova syndrome as a malformation sequence

Clinical Features

1. Considerable intrafamilial and interfamilial variation in clinical features
2. Prenatal history
   a. Severe intrauterine growth retardation
   b. Polyhydramnios
3. Spectrum of skin lesions
   a. Edema over the dorsum of foot and hand, often associated with hypoplastic phalanges
   b. Thick, waxy, and stretched in appearance
   c. Peeling of skin, scaling, and extensive plaque formation over scalp, face, neck, back, and arm
   d. Translucent flexible membrane covering most of the skin
   e. Varying degrees of lamellar ichthyosis
4. Craniofacial features
   a. Receding forehead
   b. Ocular hypertelorism
   c. Exophthalmos (protruding eyes)
   d. Absence of the eyelids
   e. Flat, abnormal nose

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f. Eclabium
g. Cataract
h. Micrognathia
i. Cleft palate/lip
j. Hypodontia
k. Low-set, malformed ears

5. CNS abnormalities
   a. Microcephaly
   b. Lissencephaly
   c. Hypoplastic or abnormal cerebellum
   d. Agenesis or dysgenesis of the corpus callosum
   e. Decreased or absent gyri
   f. Dilatation or abnormal ventricles
   g. Dandy–Walker malformation
   h. Choroid plexus cysts
6. Limb anomalies
   a. Deformed digits
   b. Deformed limbs
   c. Flexion deformity
   d. Severe edema of the hands and feet
   e. Syndactyly
   f. Rocker-bottom feet
7. Other features
   a. Short broad neck
   b. Cystic hygroma
   c. Subcutaneous edema
   d. Small thorax
   e. Hypoplastic or atelectatic lungs
   f. Small abdomen
   g. Hypoplastic genitalia
   h. Short umbilical cord
   i. Absence of hair
   j. Muscle atrophy
8. Classification proposed by Curry (1982): may represent heterogeneity of the condition or different grades of severity, representing the wide spectrum of varying expressivity of the heterogeneous condition (Coto-Puckett et al. 2010).
   a. Group I
      i. Joint contractures
      ii. Partial syndactyly
      iii. Thin scaly skin
      iv. Mild ichthyosis
      v. Poor mineralization of bones
   b. Group II
      i. Massive swelling of hands and feet
      ii. More severe ichthyosis
      iii. Undermineralized bones leading to intrauterine fractures
   c. Group III
      i. Hypoplastic digits
      ii. Most severe ichthyosis (harlequin-like fetus)
      iii. Short limbs
      iv. Stick-like long bones
9. Prognosis
   a. Stillborn
   b. Die shortly after birth
10. Differential diagnosis
   a. Harlequin ichthyosis: see the chapter
   b. Restrictive dermatopathy (dermopathy) (Kulkarni et al. 2006; Khanna et al. 2008)
      i. A rare autosomal recessive disorder characterized by extreme tautness of the skin causing restricted intrauterine movement and a fetal akinesia deformation sequence
      ii. Uniformly mostly neonatally fatal
      iii. Diagnostic findings
         a) Skin tautness with near absence of the dermal elastic fibers, usually with no or only minor anomalies of the internal organs
         b) Abnormal face
         c) Absence of skin cracking (tight skin)
         d) Absence of skin edema
         e) Arthrogryposis multiplex
      iv. Secondary skeletal changes with variable radiographic findings which when present is pathognomonic of restrictive dermatopathy
         a) Poorly mineralized skull with large fontanelle
         b) Micrognathia
         c) Thin dysplastic clavicles
         d) Ribbon-like ribs
         e) Overtubulated humerus and forearm bones
   c. Lethal arthrogryposis with ichthyosis (Thakur et al. 2004)
      i. A lethal condition with joint contractures
      ii. Subcutaneous edema, ectropion
      iii. A severely flattened nose
      iv. “O”-shaped open mouth
      v. Extensive peeling of the skin (skin changes of ichthyosis)

Diagnostic Investigations

1. Radiography
   a. Multiple contractures
   b. Hemivertebrae
   c. Kyphoscoliosis
2. Histopathology of the skin
   a. Hyperkeratosis
      i. With or without parakeratosis
      ii. Associated with abundant subcutaneous tissue and excess of fat
   b. Myxomatous connective tissue associated with excess subcutaneous adipose tissue
   c. Epidermal and dermal atrophy
3. Ultrasound of the brain for CNS anomalies
4. Normal chromosomes

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: a lethal entity not surviving to reproductive age
2. Prenatal ultrasonography (Durr-e-Sabih et al. 2001; Rode et al. 2001)
   a. Severe growth retardation: a major feature
   b. Polyhydramnios
   c. Microcephaly/deficient calvarial ossification
   d. CNS abnormalities
   e. Abnormal facies including receding forehead
   f. Exophthalmos
   g. Cataract
   h. Cystic hygromas
   i. Pulmonary hypoplasia
   j. Contractures
   k. Excessive edema of the hands and feet
   l. Syndactyly
   m. Clubbing of the feet
   n. Absence of breathing movements, sucking, swallowing, or normal isolated arm and leg movements
   o. Restricted fetal movement
3. Management
   a. No specific treatment for the uniformly lethal disorder
   b. Mainly supportive with initial management of ventilatory, thermal, and nutritional support

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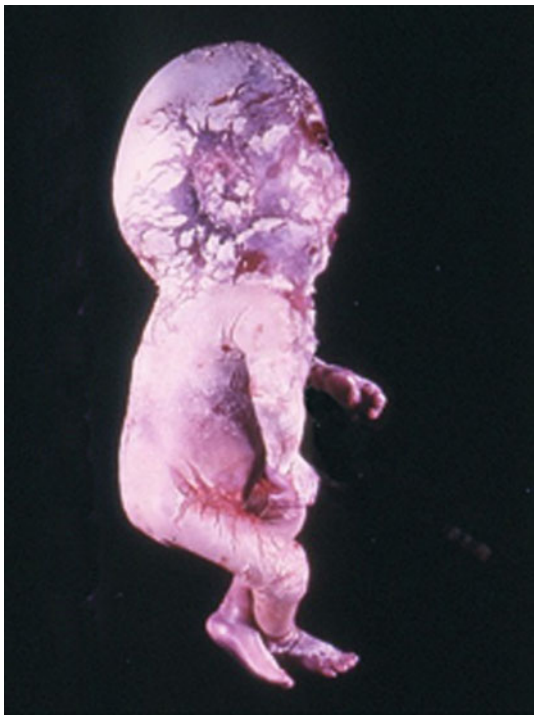

Fig. 1 An infant with Neu–Laxova syndrome showing severe ichthyosis (thick, cracked skin lesions forming deep fissures), characteristic facial features (absent eyelids, flattened nose, round gaping mouth, low-set ears with poorly developed pinnae), short broad neck, flexion contractures of the limbs, and short, small-caliber umbilical cord. Photomicrographs of skin (not shown) demonstrated a prominent hyperkeratosis of the epidermis and a thick layer of subcutaneous adipose tissue due to edema

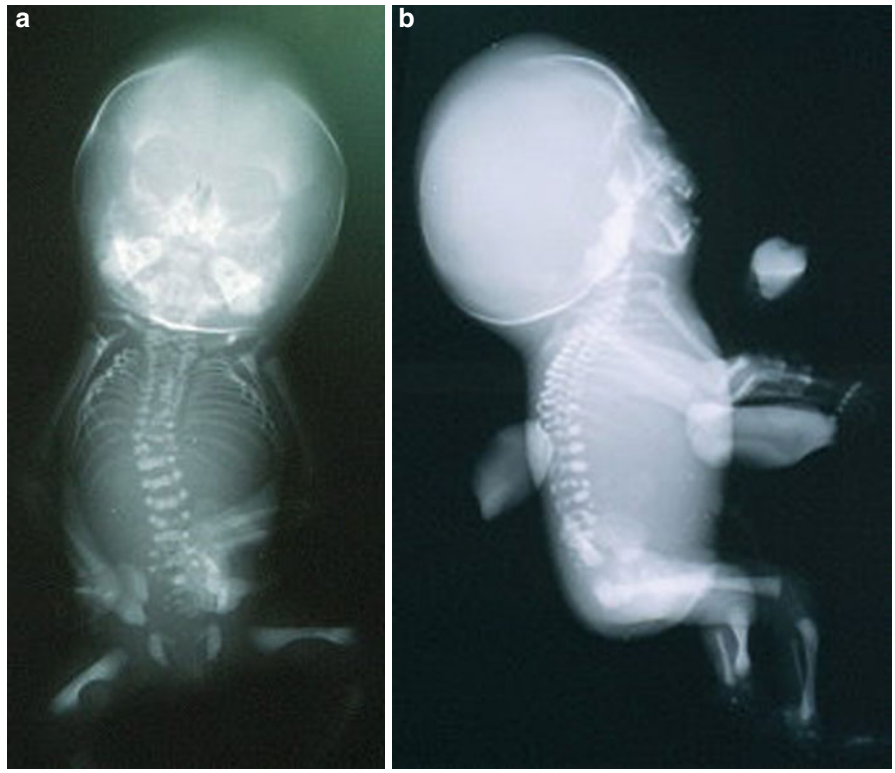

Fig. 2 (**a**, **b**) Radiographs showing hemivertebrae, kyphoscoliosis, and 11 pairs of ribs

Neural Tube Defects

Neural tube defects (NTDs) are among the most common severe congenital malformations of the central nervous system. Approximately 1 in 500 to 1 in 1,000 pregnancies result in NTDs. About 4,000 fetuses are affected each year in the USA. The incidence varies with geographic areas and ethnic groups. The incidence, however, appears to be decreasing recently.

Synonyms and Related Disorders

Anencephaly; Cranial meningocele; Cranio/spinal rachischisis; Cranium bifidum occultum; Encephalocele; Iniencephaly; Spina bifida

Genetics/Basic Defects

1. Caused by a defect in closure of the neural tube, which is normally closed by 28 days
2. Etiology: complex, involving environmental and genetic factors that interact to modulate the incidence and severity of the developing phenotype.
3. Specific causes are identified in less than 10% of affected infants.
   a. Chromosomal abnormalities
   b. Single gene mutations
   c. Teratogens
4. Defects in the neural tube closure linked to 5,10-methylenetetrahydrofolate reductase deficiency and defects in the metabolism of folic acid
5. Low erythrocyte folate in the first trimester of pregnancy: associated with an increased risk of neural tube defects
6. Mildly elevated homocysteine in some pregnant women who subsequently give birth to infants with NTDs (Akar 2000)
7. Genetic factor: *MTHFR C677T* polymorphism: a specific mutation known as *C677T* polymorphism
   a. More common in parents of children affected with NTDs
   b. This polymorphism affects the enzyme methylenetetrahydrofolate reductase (MTHFR), causing it to require more folic acid to work properly
8. Major epidemiologic finding in NTDs: the protective effect of perinatal folic acid supplementation that reduces risk by 60–70%
9. Genetic studies in NTDs
   a. Have focused mainly on folate-related genes and identified a few significant associations between variants in these genes and an increased risk for NTDs
   b. However, we are witnessing a rapid and impressive progress in understanding the genetic basis of NTDs, based mainly on the development of whole genome innovative technologies and the powerful tool of animal models (Bassuk and Kibar 2009).

Clinical Features

There are several morphologic types of NTDs: open NTDs (anencephaly, cranial or spinal rachischisis, iniencephaly, meningomyelocele, cranioectomesodermal hypoplasia), closed NTDs (cranial meningocele, cranial encephalocele, spinal meningocele alone or with spinal cord abnormality), and myelocystocele.

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1. Anencephaly
   a. Refers to an absence of the brain and the calvarium covering the brain
   b. The most severe form of NTDs
   c. Incidence: about 1/1,000 live births
   d. Responsible for about 50% of all NTDs
   e. Infants with anencephaly
      i. Stillborn
      ii. Die shortly after birth
   f. Anterior pituitary, eyes, and brainstem usually spared
   g. Remaining tissue covering the basal cranium: a highly vascular and friable membrane referred to as area cerebrovasculosa
   h. Striking craniofacial appearance
      i. Absent cranial vault
      ii. An angiomatous membranous mass lying on the floor of the cranium
      iii. An absent or backward sloping of the forehead
      iv. Frog-like eyes (ocular proptosis)
      v. Puffy eyelids
      vi. A flattened nose
      vii. Large folded-down ears
      viii. Often an open mouth
      ix. A short neck
   i. Syndromes associated with anencephaly
      i. Chromosomal disorders [e.g., r(13), trisomy 18, del(13q)]
      ii. Monogenic disorder (e.g., Meckel syndrome)
      iii. Disruptive sequences (e.g., amniotic bands, maternal hyperthermia)
      iv. Associations (e.g., spina bifida, holoprosencephalic face syndrome, craniofacial duplication)
2. Craniorachischisis or spinal rachischisis
   a. Rachischisis: refers to anencephaly with a contiguous spinal defect involving at least the cervical spine region and extending for varying degrees down the spinal column
   b. The area cerebrovasculosa and the area medullovasculosa fill the skeletal defects of the cranium and of the spinal column.
   c. Short neck
   d. Upward-turned face
   e. Ears touching the shoulders
   f. Frequent polyhydramnios
   g. Frequently stillborn
   h. Neurologic involvement
      i. Primarily limited to brainstem and spinal reflexes
      ii. Occasional seizures resembling infantile spasms
3. Iniencephaly (Balci et al. 2001)
   a. The name iniencephaly derived from an abnormality of the neck (inion) and the brain (cephaly)
   b. Triad
      i. Deficient cranial bone
      ii. Cervical dysraphism (rachischisis)
      iii. Fixed retroflexion of the fetal head and severe lordosis of the cervicothoracic spine
   c. Closed or open lesions
      i. A closed lesion when the occipital bone is not malformed
      ii. An open lesion when the occipital bone is hypoplastic
   d. Site of the neural tube lesion: at the level of the cervical spine
   e. Severity of lesion
      i. Spina bifida with intact skin
      ii. Meningomyeloencephalocele
      iii. Open rachischisis
   f. Associated CNS malformations
      i. Anencephaly
      ii. Encephalocele
      iii. Microcephaly
      iv. Hydrocephaly
      v. Holoprosencephaly
      vi. Posterior fossa defects
      vii. Spinal defects such as cervical dysraphism
      viii. Fixed cervical hyperlordosis
   g. Other associated malformations
      i. Diaphragmatic hernia
      ii. Omphalocele
      iii. Thoracic cage deformities
      iv. Hypoplastic lungs
      v. Genitourinary malformations
      vi. Cyclopia
      vii. Cleft lip and palate
      viii. Imperforate anus
      ix. Clubfoot
      x. Single umbilical artery
   h. Die within a few hours in most newborns
4. Cranium bifidum occultum
   a. The most benign type
   b. Generally asymptomatic
   c. Skull defects often close over time

d. Persistent parietal foramina (sometimes called "Caitlin marks" after the family for which it was described; transmitted as an autosomal dominant trait via a gene located on 11p)
e. Persistent wide fontanelle

5. Cranial meningocele
   a. Associated with a defect in the skull
   b. Associated with protrusion of the leptomeninges
6. Encephalocele
   a. A type of cephalocele (a herniation of cranial contents though a skull defect) that contains brain
   b. Incidence: 1/10,000 live births
   c. Occurring most frequently in the occipital region (80–90%) and commonly associated with a variety of syndromes, notably Meckel–Gruber syndrome and Walker–Warburg syndrome
   d. Anterior encephaloceles: found more commonly in Roberts syndrome
   e. An isolated malformation of frontal encephalocele: more commonly seen in southeast Asia
   f. Outcome depending on the position of the defect and on the associated anomalies
   g. Chromosome syndromes associated with encephalocele
      i. Trisomy 13
      ii. Trisomy 18
      iii. Del(13q)
      iv. Del(2)(q21 → q24)
      v. Dup(1q)
      vi. Dup(6) (q21 → qter)
      vii. Dup(7)(qter → p11)
      viii. Dup(8)(q23 → qter)
      ix. Turner syndrome
   h. Monogenic disorders associated with encephalocele
      i. Meckel syndrome
      ii. Cryptophthalmos syndrome
      iii. Silverman–Handmaker type and Rolland–Desbuquois type of dyssegmental dysplasias
      iv. Knobloch syndrome
      v. Chemke syndrome
      vi. Roberts syndrome
      vii. Walker–Warburg syndrome
      viii. van Voss–Cherstovy syndrome
   i. Disruptive sequences associated with encephalocele
      i. Maternal hyperthermia
      ii. Warfarin embryopathy
      iii. Amniotic bands
   j. "Associations" associated with encephalocele
      i. Absent corpus callosum
      ii. Dandy–Walker malformations
      iii. Arnold–Chiari malformation
      iv. Holoprosencephaly
      v. Craniosynostosis
      vi. Ectrodactyly
      vii. Frontonasal dysplasia
      viii. Hypothalamic-pituitary dysfunction
      ix. Klippel–Feil anomaly
      x. Iniencephaly
      xi. Myelomeningocele
      xii. Oculoauriculovertebral spectrum
7. Spina bifida cystica (the most common lesion)
   a. Myelomeningoceles (meningomyeloceles)
      i. A herniation of the spinal cord and/or nerves through a bony defect of the spine
      ii. Usually open defects in which meninges and/or neural tissue is exposed to the environment associated with leaking CSF
      iii. The most common type of spina bifida cystica (about 90%)
      iv. Approximately 20% of affected infants have additional congenital anomalies, such as gastrointestinal, cardiac, and urogenital malformations.
      v. Surviving infants with spina bifida likely have severe, lifelong disabilities, and psychosocial maladjustment.
      vi. Medical problems
         a) Paralysis
         b) Hydrocephalus
         c) Arnold–Chiari type II malformation (herniation of the cerebellar vermis and brainstem below the foramen magnum)
         d) Endocrine abnormalities
         e) Tethered cord
         f) Syringomyelia (cavitation of the spinal cord whose walls are composed of glial tissue)
         g) Syringobulbia
         h) Deformed limbs and spine
         i) Bladder/bowel/sexual dysfunction
         j) Learning disabilities
      vii. Neonates with Arnold–Chiari malformation presenting with:
         a) Stridor secondary to vocal cord paralysis
         b) Central apnea
         c) Aspiration

d) Dysphagia
e) Hypotonia
f) Progressive brainstem dysfunction
g) Myelopathy
h) Quadriparesis
i) Nystagmus
j) Strabismus
k) Poor sucking
l) Swallowing difficulties

b. Meningoceles
i. A saccular herniation of meninges and CSF through a bony defect of spine and usually covered by normal skin
ii. No herniation of the spinal cord or nerve roots into the dorsal dural sac
iii. A cystic mass full of cerebrospinal fluid
iv. Without associated neurologic problems such as hydrocephalus and Chiari II malformation

c. Lipomeningocele or lipomyelomeningocele
i. A lipomatous mass herniating through the bony defect and attaching to the spinal cord, tethering the cord and often its nerve roots
ii. Presentation with a skin-covered mass above the buttocks and eventual neurologic deficits
iii. Absent associated hydrocephalus

d. Myelocystocele
i. A large terminal cystic dilatation of the spinal cord secondary to hydromyelia giving rise to a large terminal skin-covered sac
ii. Constituting 4–6.5% of the skin-covered masses overlying the lower spine
iii. The majority of cases are dorsally located; only rarely (about 0.5%) are ventral in location
iv. The ventral type is an anterior sacral meningocele, most often presenting as a pelvic mass in females
v. Cervical myelocystocele
vi. Lumbar myelocystocele
vii. Terminal myelocystoceles accompanying midline abdominal and pelvic defects such as part of the OEIS (*o*mphalocele-*e*xstrophy of the bladder-*i*mperforate anus-*s*pinal defects) complex
viii. Chiari malformation less frequent since the lesion is covered by dura with regular hydrodynamics of the cerebrospinal fluid
ix. Other associated malformations
a) Genitourinary tract anomalies
b) Intestinal malrotation
c) Club feet
x. Differential diagnoses
a) Meningomyelocele
b) Lumbosacral and sacrococcygeal teratomas
c) Lipomas
d) Lipomyelomeningoceles
e) Hamartomas

e. Lifelong disability risks in infants with spina bifida
i. At risk for psychosocial maladjustment
ii. Medical problems resulting from the neurologic defects or from its repair
a) Paralysis
b) Hydrocephalus
c) Arnold–Chiari malformation
d) Endocrine abnormalities
e) Tethered cord
f) Syringomyelia
g) Syringobulbia
iii. Medical problems as sequelae of the neurologic deficits
a) Deformations of the limbs and spine
b) Bowel, bladder, and sexual dysfunction
c) Learning disabilities

8. Spina bifida occulta
a. A bony defect of the spine occurs most often at S1 and/or S2 and is covered by normal skin (a closed lesion)
b. No herniation of the meninges through the bony defect
c. Without associated hydrocephalus or Chiari II malformations
d. Paraspinal cutaneous lesions with high index of suspicion pointing towards the underlying spina bifida (Drolet 2000)
i. Hypertrichosis or hairy patches
ii. Lumbosacrococcygeal dimples and sinuses
iii. Acrochordons (skin tags): a small, flesh-colored to dark brown, sessile or pedunculated lesion consisting of a hyperplastic epidermis enclosing a dermal stalk of connective tissue
iv. True tails: a caudal midline appendage capable of spontaneous or reflex motion consisting of skin covering muscle, adipose, connective tissue, blood vessels, and nerves but lack vertebrae and abnormal tissue

v. Pseudotails: a caudal protrusion composed of adipose (lipoma), teratomatous elements, or cartilage
vi. Lipomas
vii. Hemangiomas: indicator for tethered cord syndrome
viii. Aplasia cutis congenita (congenital absence of skin) or scar
ix. Dermoid cyst or sinus: 12–35% of children with spina bifida occulta have sacrococcygeal dermoid cysts or sinuses, which rarely connect with the intraspinal canal. Lesions above these levels along the spine are more likely to connect with the intraspinal canal and increasingly associated with spina bifida occulta.

e. Paraspinal cutaneous lesions with low index of suspicion (Drolet 2000)
i. Telangiectasia
ii. Capillary malformation (port-wine stain)
iii. Hyperpigmentation (lentigines or café-au-lait-like lesions)
iv. Melanocytic nevi
v. Teratomas: most common in the sacrococcygeal region in infancy

f. Neurologic deficits (Ellenbogen 2001)
i. Weakness of leg or legs
ii. Leg atrophy or asymmetry
iii. Loss of sensation
iv. Painless sores
v. Hyperreflexia
vi. Unusual back pain
vii. Abnormal gait
viii. Radiculopathy
ix. Neurogenic bladder
x. Incontinence

9. Multiple NTDs at different sites (Ahmad et al. 2008): The presence of meningomyelocele and/or encephaloceles at multiple (two or more) sites along the vertebral axis is a very rare event occurring in 1% of cases
a. Double NTDs
b. Triple NTDs

Diagnostic Investigations

1. Neurological examination of neonates
a. Size, site, and level of the lesion
b. Motor and sensory level
c. Presence of associated hydrocephalus
d. Presence of associated symptomatic hindbrain herniation such as Chiari II malformation
e. Presence of associated orthopedic deformity
2. Neonatal cranial ultrasonography to demonstrate hydrocephalus
3. Radiography
a. Occult spinal disorders in children (Ellenbogen 2001)
i. Lamina defects
ii. Hemivertebrae
iii. Scoliosis
iv. Widening of interpedicular distance
v. Butterfly vertebrae
b. Generally to detect bony defects
4. CT
a. Cranial defects
b. Spinal defects
5. MRI: provide exquisite detail of both the cranial defect and the herniated contents
a. Cranial defects
b. Cerebral defects
i. Hydrocephalus
ii. Gray matter heterotopia
iii. Schizencephaly
iv. Gyral abnormalities
v. Agenesis and thinning of the corpus callosum
vi. Abnormal thalami
vii. Abnormal white matter
c. Herniated contents in Chiari malformations
d. Associated lesions
i. Diastematomyelia
ii. Syringomyelia
iii. Hydromyelia
iv. Tethered cord

Genetic Counseling

1. Recurrence risk
a. Affected first-degree relatives
i. 1 sib affected (5%)
ii. 2 sibs affected (10%)
iii. 3 sibs affected (21%)
iv. 1 parent affected (3–4.5%)
v. 1 parent and 1 sib affected (13%)

b. Affected second-degree relative: uncle/aunt, half sib (2%)
c. Third-degree relative: first cousin (1% or less)

2. Prenatal diagnosis (Cameron and Moran 2009)
   a. Risk assessment prior to biochemical and/or ultrasonic screening
      i. The most significant risk factor: a history of having a previous child affected with neural tube defect
      ii. Other independent (nongenetic) risk factors (Cameron and Moran 2009; Copp and Greene 2010)
         a) Valproic acid
         b) Folic acid antagonists (methotrexate, aminopterin, carbamazepine, fumonisin, trimethoprim)
         c) Vitamin A
         d) Maternal diabetes
         e) Maternal obesity
         f) Hyperthermia
         g) Micronutrient deficiencies (folate, inositol, vitamin B12, zinc)
   b. Two approaches used for NTD screening in low-risk population
      i. Biochemical testing of maternal blood for alpha-fetoprotein (AFP)
         a) Measurement of maternal serum alpha-fetoprotein (MSAFP): a useful tool for mass screening of pregnant women for NTDs
         b) All cases of anencephaly and about 65% of cases of spina bifida are identified by measurement of MSAFP and ultrasonography.
         c) Not effective in closed NTDs (10% of lesions) which do not increase AFP
         d) AFP needs to be expressed as multiples of the median (MoM), since the maternal serum level of AFP varies with gestation.
         e) Using 2.5 MoM as screen positive in singleton pregnancies, the detection rate for anencephaly is expected to be >95% and for open NTD between 65% and 80%.
         f) False-positive rates should lie between 1% and 3% (Bradley et al. 2005). A raised serum AFP is not diagnostic for open NTD as it can be associated with other abnormalities including gastroschisis, omphalocele, congenital nephrosis, and fetal demise.
      ii. Use of 2D/3D ultrasonography
         a) Used both as a screening test and as a follow-up test after positive results on MSAFP screening
         b) First trimester detection rates for anencephaly and encephalocele: typically quoted as >90% for anencephaly and encephalocele and lower rates for spina bifida (44%)
         c) Second trimester scanning improves the detection of spina bifida, typically to 92–95%
         d) Direct demonstration of the spinal defect
         e) Indirect signs: lemon sign (referring to a symmetrical bifrontal narrowing of the skull) and banana sign (cerebellar abnormality)
         f) Carefully evaluate the whole fetus because of associated malformations in around 20% (Stoll et al. 2007)
      iii. Fetal MRI (Saleem et al. 2009)
         a) An important adjunct to US in assessing NTD
         b) Can identify topography and contents of sacs, add CNS and non-CNS findings
         c) Influence management decision
   c. Prenatal diagnosis of iniencephaly by careful sonography
      i. Marked fixed retroflexion of the head and neck
      ii. Rachischisis
      iii. Extreme lordosis of the fetus
   d. Amniotic fluid alpha-fetoprotein (AFAFP) and amniotic fluid acetylcholinesterase (AFAChE): confirmatory tests for spina bifida

3. Management: complex and challenging
   a. Prevention
      i. Folic acid supplementation of 0.4 mg/day to all women capable of becoming pregnant: decrease the first occurrence of NTDs by at least 40%
      ii. Folic acid supplementation of 4 mg/day in families with previous children born with NTDs: decrease risk of recurrence by 70%
      iii. Periconceptional use of folic acid supplementation will prevent 50–70% of NTDs.
   b. Medical management
      i. Antibiotic prophylaxis to prevent meningitis and ventriculitis

ii. Urological management
iii. Management of rectal incontinence
iv. Preventable conditions
a) Urinary tract infections
b) Calculi
c) Skin ulcerations
d) Latex allergy and sensitization

c. Surgical treatment
i. Closing all but the prognostically worst cases
ii. Concurrent shunting of coexisting hydrocephalus often necessary
iii. Decompression of the posterior fossa and/or cervical cord in Chiari II malformations
iv. Spina bifida occulta: prophylactic surgical repair more effective than waiting for patients to experience a significant neurologic deficit such as a neurogenic bladder or leg weakness from these occult spinal lesions
v. Orthopedic management of scoliosis

d. Fetal spina bifida repair (Fichter et al. 2008)
i. Several reports of intrauterine repair of meningomyelocele with benefits to motor function and a decreased incidence of shunt-dependent hydrocephalus and a reversal of hindbrain herniations
ii. Especially fetuses treated before 26 weeks of gestational age, with small ventricles (<14 mm) at the time of surgery, and lesion levels below L2 seem to profit from fetal surgery
iii. However, the clinical relevance of the observed regression of Chiari II malformation is still in dispute and a positive effect on sensorimotor function could only be observed for patients with higher lumbar and thoracic spinal defects in the early postnatal period.

e. Rehabilitation programs
i. Physical therapy
ii. Occupational therapy
iii. Speech therapy
iv. Recreational therapy

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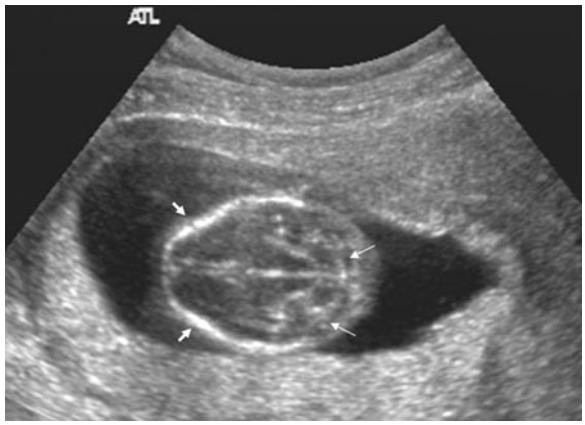

Fig. 1 Inward scalloping of the frontal bones, known as "lemon sign" (*short arrows*) and "banana sign" configuration of the cerebellum (*long arrows*), in a fetus with open spina bifida

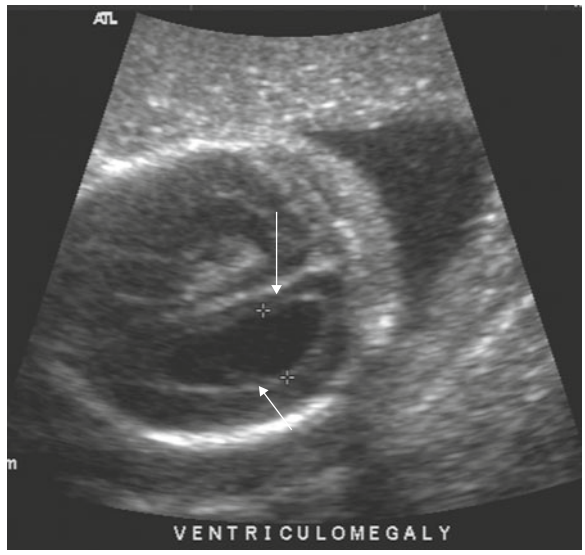

Fig. 3 Ventriculomegaly (*arrows*) observed in a fetus with lumbar meningomyelocele

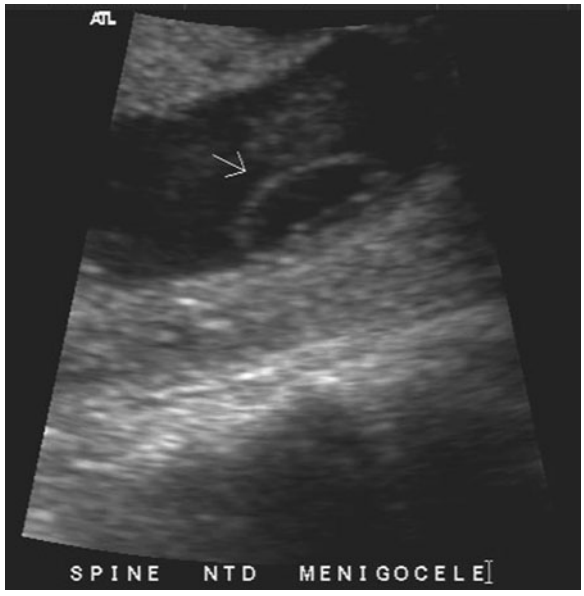

Fig. 2 A paraspinal unilocular cyst (*arrow*) in a fetus with lumbosacral meningocele

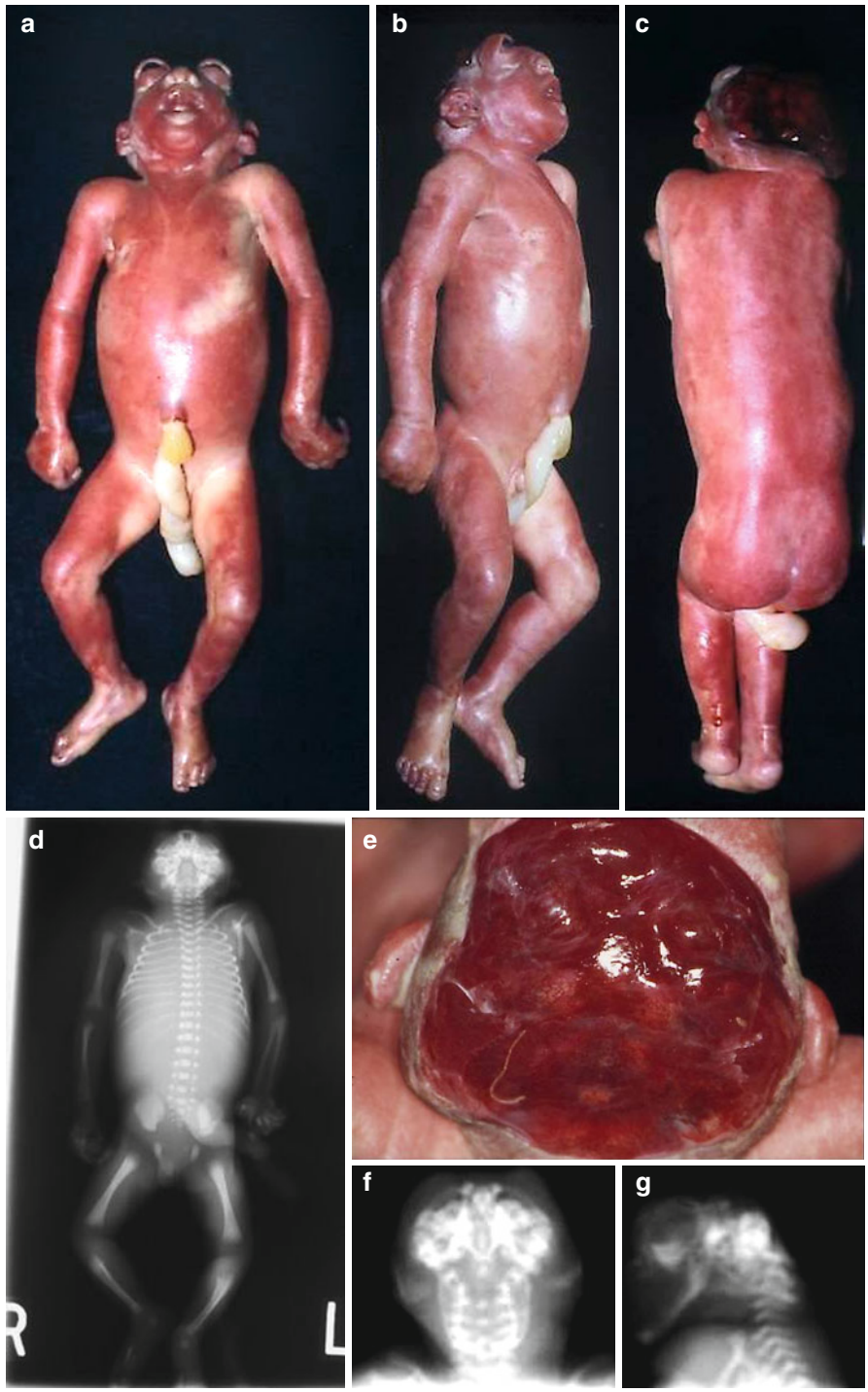

Fig. 4 (**a**–**g**) A stillbirth with classic anencephaly showing absent cranial vault, an angiomatous mass on the skull base, an absent forehead, protuberant, puffy "frog-like" eyes, an open mouth, large folded-down ears, and a short neck. Radiographs show the absent calvarium

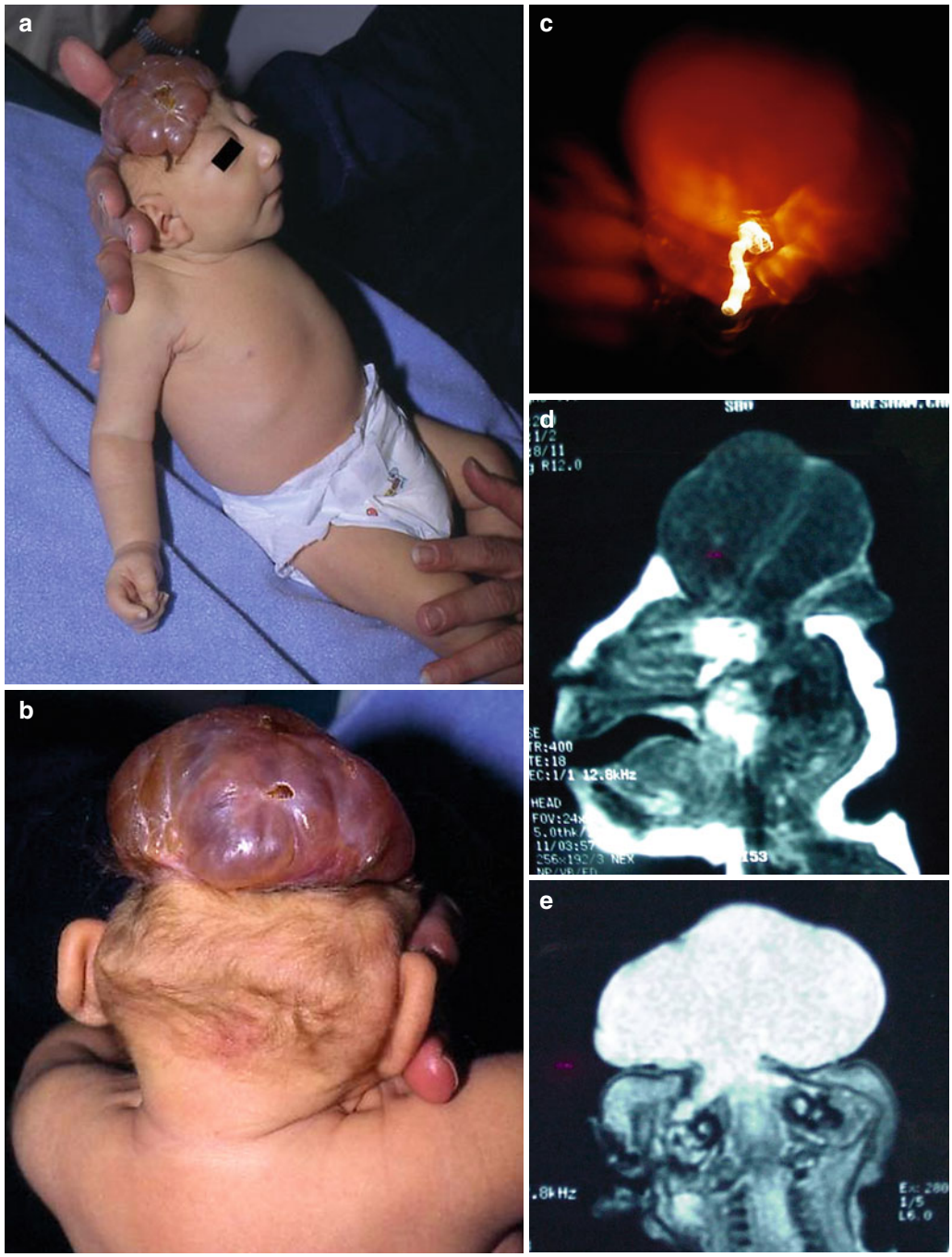

Fig. 5 (**a**–**e**) A newborn with anencephaly/meningocele showing the presence of a meningeal sac above the base of the skull without containing the brain tissue, illustrated by transillumination and MRI of the brain with or without contrast

Fig. 6 Another neonate with anencephaly/meningocele showing similar craniofacial anomalies

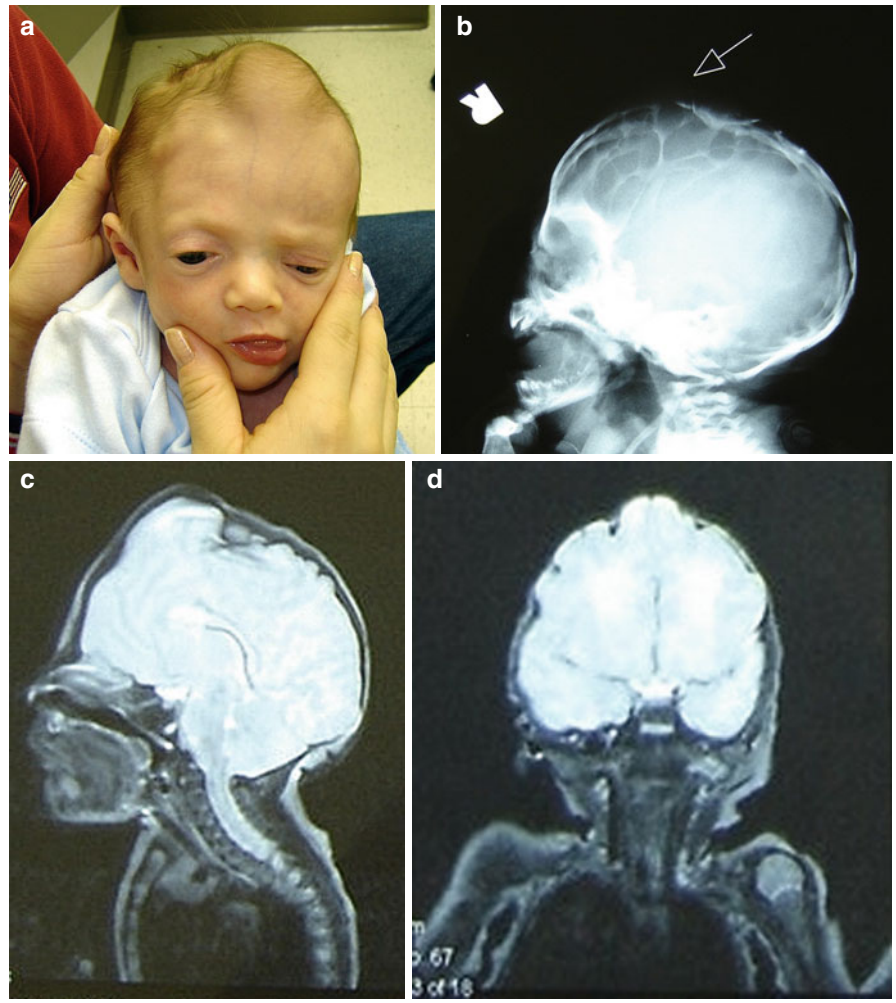

Fig. 7 (**a**–**d**) A 2-week-old infant with frontal encephalocele, illustrated by lateral skull radiograph and MRI of the brain

Fig. 8 (**a**, **b**) Newborns with an occipital encephalocele

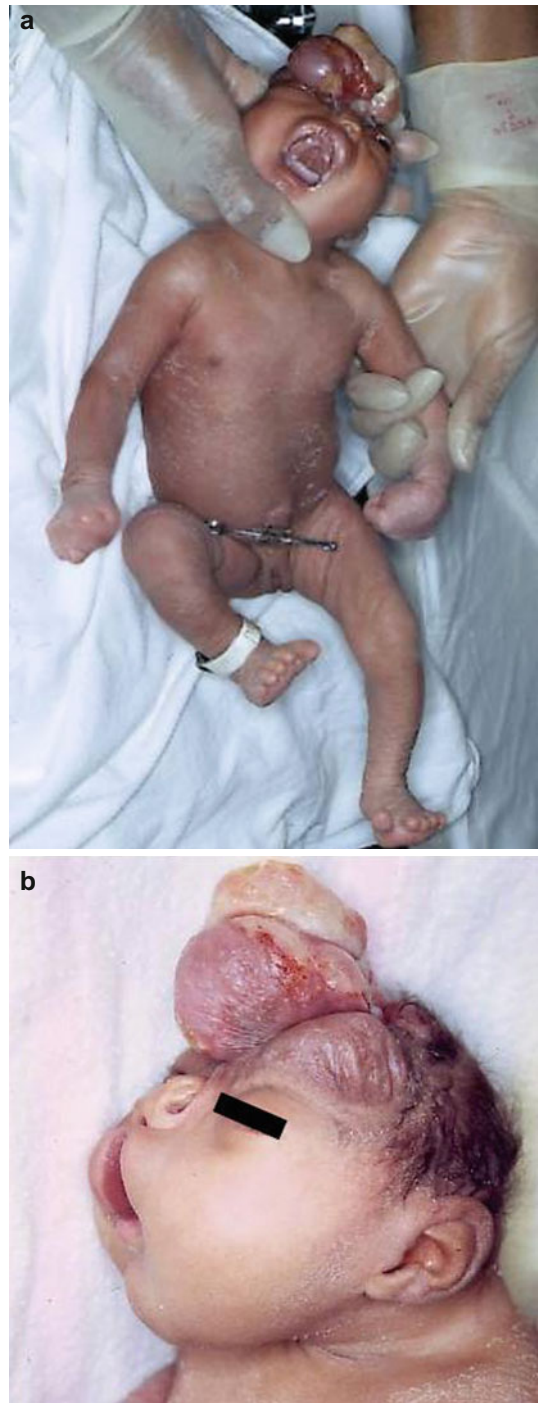

Fig. 9 (**a**, **b**) Encephalocele associated with amniotic band syndrome

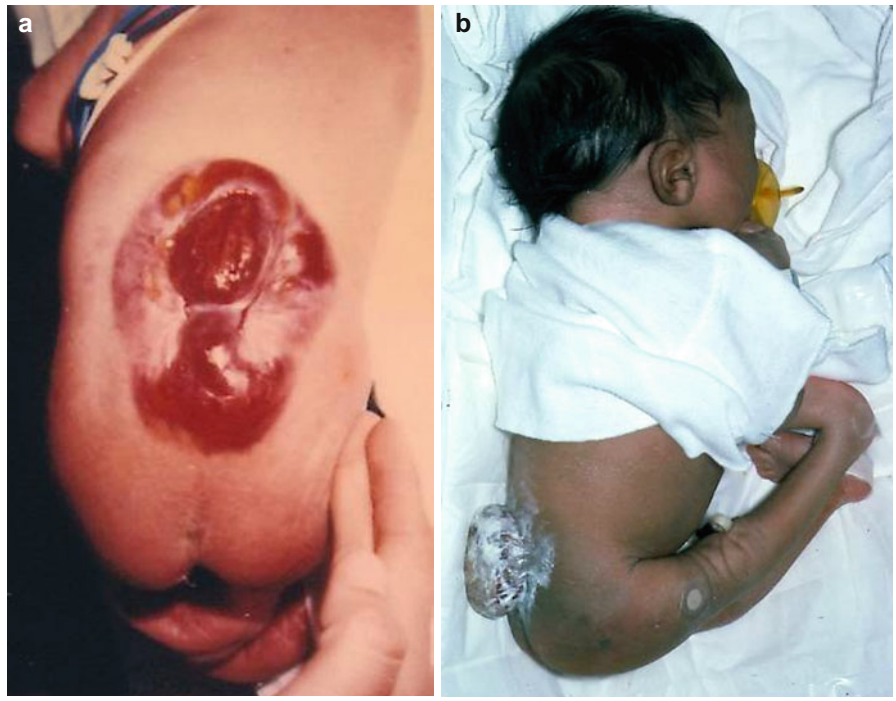

Fig. 10 (**a**, **b**) Newborns with a lumbosacral myelomeningocele

Fig. 11 (**a**, **b**) A fetus with trisomy 18 and open lumbosacral spina bifida

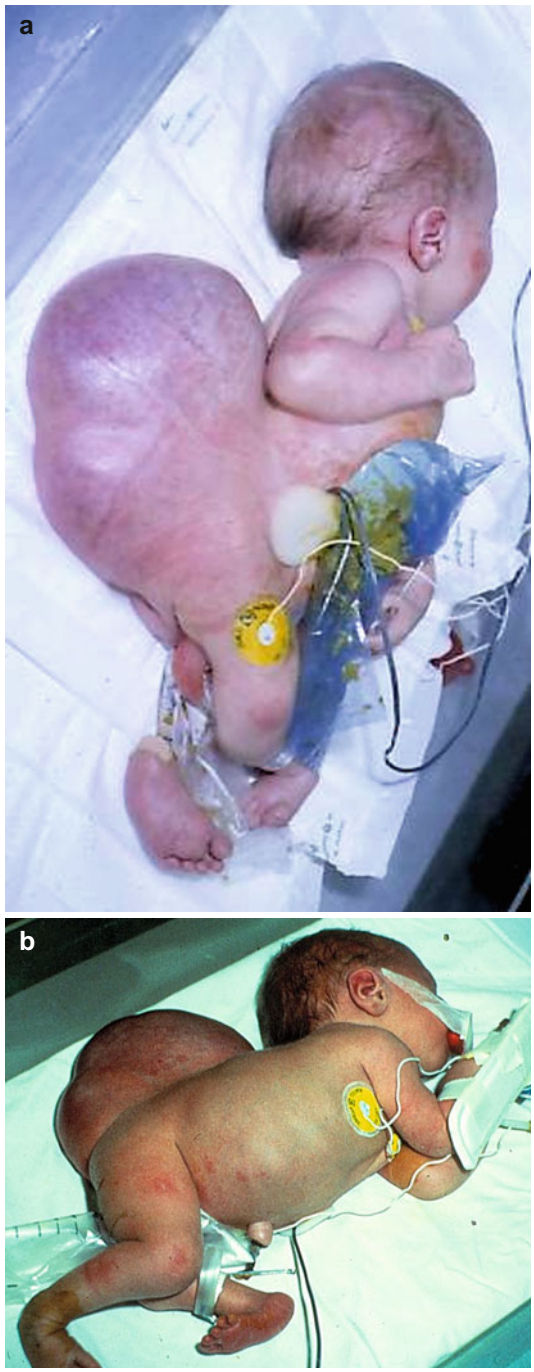

Fig. 12 (**a**, **b**) Two infants with a large lumbosacral myelocystocele covered with skin

Fig. 13 (**a**–**c**) A stillborn with iniencephaly showing deficient cranium, short neck, cervical rachischisis, fixed retroflexion of the head, and severe lordosis of the cervicothoracic spine

Fig. 14 (**a**, **b**) A stillborn with craniorachischisis showing anencephaly with a contiguous spinal defect involving cervical spine region and extending down the spinal column, short neck, upward-turned face, and ears touching the shoulders

Neurofibromatosis I

Neurofibromatosis I (NF1) was described in 1882 by von Recklinghausen (von Recklinghausen 1882) who gave the disease its first full description, including recognition that the tumors arose from the fibrous tissue surrounding small nerves, leading to his designation of these tumors as "neurofibromas." Thus, it is also called von Recklinghausen disease. It is one of the most common dominantly inherited genetic disorders affecting about 1 in 3,000 newborns and 1,000,000 people worldwide.

Synonyms and Related Disorders

Peripheral type neurofibromatosis; von Recklinghausen disease

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant
   b. High spontaneous mutation rate
      i. One of the highest in humans (1×10^{-4} per gamete per generation)
      ii. 50% of the cases are due to new mutations.
      iii. Most patients are expected to have different mutations due to the high mutation rate at the *NF1* locus.
   c. Full penetrance: essentially 100% in adults after careful examination by a slit-lamp examination
   d. Widely variable expressivity even among family members with the same mutation (Riccardi and Lewis 1998; Korf and Rubenstein 2005)
   e. Highly pleiotropic
2. The *NF1* gene
   a. Mapped to pericentromeric region of 17q11.2
   b. Entire sequence of the expressed *NF1* gene has been identified by a positional cloning strategy.
   c. A large size of the gene spanning over 350 kb of genomic DNA
   d. Consisting of at least 60 exons
   e. Translated into a 240-kDa protein, neurofibromin
3. Mutations of the *NF1* gene
   a. Most described mutations are unique to a particular family.
   b. Type of mutations (over 250 different mutations described)
      i. Stop codon
      ii. Substitutions
      iii. Deletions of only one or a few base pairs, multiple exons, or the entire gene
      iv. Insertions
      v. Intronic changes affecting splicing
      vi. Alterations of the 3′ untranslated region of the gene
      vii. Gross chromosomal rearrangements
   c. Severe truncation of the gene product in about 70% of the germ-line mutations
   d. *NF1* gene usually classified as a tumor suppressor gene since mutations in both *NF1* alleles are detectable in malignant tumors associated with NF1 and in benign tumors, such as neurofibromas.
4. Knudson two-hit hypothesis is also applicable to explain the mechanism by which the manifestations of *NF1* occur (Dupuis and Nezarati 2001).
   a. A mutated tumor suppressor gene (the first hit)
      i. Inherited from a parent
      ii. Presents in every cell of the body

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b. A second mutation (hit) in some somatic cells of the individual
   i. Knocks out the other copy of the gene
   ii. Resulting in complete loss of the gene product and unregulated cell growth/division
   iii. Resulting in a predisposition to cancer in the cells

5. Pathogenesis of NF1 (Boyd et al. 2009)
   a. Neurofibromin
      i. The *NF1* gene protein product
      ii. A tumor suppressor expressed in many cells, primarily in neurons, glial, Schwann cells and early in melanocyte development (Stocker et al. 1995)
      iii. A regulator of ras guanosine triphosphatase activity (GTPase-activating protein, GAP), and as such, serves as a regulator of signals for cell proliferation and differentiation (Korf and Rubenstein 2005)
      iv. Loss of function of neurofibromin may, therefore, remove this regulation and lead to uncontrolled cell proliferation
   b. Schwann cells in neurofibromas and melanocytes in café-au-lait macules
      i. Have a mutation in both *NF1* alleles, including a germ line and an acquired somatic mutation
      ii. Considered the primary tumor cell in their respective cutaneous manifestation
      iii. Based on these findings, it is likely that NF1 functions as a tumor suppressor gene (Maertens et al. 2007; de Schepper et al. 2008).
      iv. Both of these cell types are descendants of neural crest.
      v. The exact timing of the acquired mutation is unknown but is crucial in the development of the various manifestations.
         a) Experiments have shown that *NF1* gene inactivation at the neural crest stage and mature Schwann cell stage do not lead to tumor formation.
         b) However, in a progenitor intermediate step between these two stages, tumor formation occurs with *NF1* gene inactivation (Wu et al. 2008).

6. Marked heterogeneity in NF1
   a. Whole gene deletion with distinctive phenotype
      i. Early onset of cutaneous neurofibromas
      ii. Facial anomalies
         a) Macrocephaly
         b) Hypertelorism
         c) Ptosis
         d) Down-slanting palpebral fissures
         e) Short nose
         f) Low-set ears
         g) Micrognathia
      iii. Developmental delay
      iv. Other standard features of NF1
   b. Alternate forms of NF1 (conditions with incomplete/atypical features)
      i. Mixed neurofibromatosis
      ii. Localized neurofibromatosis
         a) Segmental neurofibromatosis (occasional localized café-au-lait spots, segmental distribution of dermal neurofibromas, no systemic manifestations, uncommon internal manifestations of neurofibromas)
         b) Gastrointestinal neurofibromatosis
         c) Familial spinal neurofibromatosis (multiple café-au-lait spots and neurofibromas involving spinal cord, lack dermal neurofibromas, and Lisch nodules)
         d) Familial café-au-lait spots (autosomal dominant café-au-lait spots in rare multigeneration families, lack of neurofibromas, axillary freckling, and Lisch nodules)
   c. Related forms of NF1 (conditions with additional features)
      i. Neurofibromatosis/Noonan syndrome (may or may not fit the criteria of NF1 but with features of Noonan syndrome)
      ii. Watson syndrome
         a) Multiple café-au-lait spots
         b) Pulmonary stenosis
         c) Intertriginous freckling
         d) Short stature
         e) Low intelligence

7. Several pathways are thought to be involved in the development of tumors associated with NF1 (Brems et al. 2009).
   a. Rat sarcoma viral oncogene homologue (RAS)–mitogen-activated protein kinase (MAPK): Neurofibromin is involved in the downregulation of RAS–MAPK pathway, and NF1 belongs to the group of RAS–MAPK disorders that include Noonan, cardiofaciocutaneous, Costello, LEOPARD, and NF1-like syndrome.

b. Mammalian target of rapamycin (mTOR)
c. P21 protein (Cdc42/Rac)–activated kinase 1 (PAK1)

8. Variable expressivity (one of the hallmarks of NF1)
   a. Intrafamilial variability (marked phenotypic differences may be observed within the same family).
   b. Interfamilial variability (full spectrum of the disease, mild to severe form, may be present in different families in which affected individuals have the same NF1 mutation).
9. Prototype of a pleiotropic congenital multiple dysplasia syndrome involving CNS, vascular and skeletal systems, and a predilection for hamartomas, dysplasia, and malignancies
10. Mosaicism resulting from somatic mutations
    a. Early somatic mutation gives rise to generalized disease, clinically indistinguishable from nonmosaic form.
    b. Late somatic mutation gives rise to localized disease often described as segmental form.
    c. Individuals with the mosaic form
       i. Less likely to have severe disease even with a generalized phenotype
       ii. Lower offspring recurrence risk than individuals with the nonmosaic form

Clinical Features

1. Extreme interfamilial and intrafamilial clinical variability
2. Often not diagnosed at birth, especially a new mutation case
3. Cutaneous manifestations
   a. Café-au-lait spots (analogy of the color to coffee with milk)
      i. Present in nearly all patients
      ii. Round or oval, discrete, well circumscribed, uniformly light brown–pigmented, macular lesions
      iii. Usually present at birth but continue to increase in number and size during the first decade
      iv. Six or more café-au-lait spots exceeding 0.5 cm in diameter in prepubertal children or exceeding 1.5 cm in broadest diameter in postpubertal individuals: the pathognomonic sign for NF1
   b. Hyperpigmentation patches may be associated with underlying plexiform neurofibromas, which are congenital in origin and which may lead to extensive localized hypertrophy.
   c. Freckles in the axillary, groin, and intertriginous areas (almost 90%): a helpful diagnostic feature
   d. Dermal neurofibromas, usually present in adults with NF1
   e. Xanthogranulomas (2–5%)
   f. Hemangiomas (5–10%)
4. Lisch nodules (asymptomatic pigmented iris hamartomas)
   a. An extremely important diagnostic feature
      i. A characteristic sign of NF1 present in 97% of postpubertal patient
      ii. Lesions typically not detected before 5 years of age
      iii. Often appear before development of neurofibromas
   b. Best observed with slit-lamp examination
   c. Raised, often pigmented nodules of the iris, pathologically representing hamartomas
   d. Never resulting in significant disease
5. Peripheral neurofibromas
   a. Benign histologically
   b. May involve viscera, such as bowel, bladder, and liver, causing bleeding and obstruction
   c. May result in functional compromise and cosmetic disfigurement
   d. Increase in size and number during puberty and pregnancy
6. Gross forms of neurofibromas (Woodruff 1999)
   a. Localized cutaneous neurofibromas (nodular or polypoid): the most common form of neurofibromas. Numerous localized cutaneous neurofibromas are the hallmark of NF1.
   b. Localized intraneural neurofibromas (causing fusiform enlargement of the affected nerve)
   c. Plexiform neurofibromas (25%)
      i. Diffuse lesion involving nerve, muscle, connective tissue, vascular elements, and overlying skin
      ii. Commonly leading to overgrowth of surrounding tissues during childhood
      iii. Usually congenital
      iv. Almost invariably apparent by 4 or 5 years of age
      v. One of the most common and debilitating complications of NF1

vi. Account for substantial morbidity, including disfigurement, functional impairment, and life-threatening complications
vii. Subject to transformation into malignant peripheral nerve sheath tumor (2–5%)

d. Diffuse neurofibromas involving skin and subcutaneous tissue
e. Massive soft-tissue neurofibromas (extreme neurofibromatous growth producing massive, diffuse infiltration of soft tissue of a body part, often a distal extremity, leading to localized gigantism, cape formation, or, at the extreme end of the spectrum, formation of disfiguring redundant soft-tissue masses)

7. Certain selected clinical features of NF1 in different age groups
   a. Infancy
      i. Pseudarthrosis
      ii. Seizures
      iii. Constipation
      iv. Congenital glaucoma
      v. Deafness
      vi. Optic gliomas
   b. Childhood
      i. Optic gliomas
      ii. Other brain tumors
      iii. Kyphoscoliosis
      iv. Genu valgum
      v. Seizures
      vi. Cognitive disorders
         a) Developmental delay
         b) Learning disabilities
         c) Mental retardation
      vii. Speech impediments
      viii. Short stature
      ix. Macrocephaly
      x. Early puberty
      xi. Hypertension
      xii. Embryonal tumors
      xiii. Leukemia
   c. Preadolescence and adolescence: worsening of previous problems such as
      i. Scoliosis
      ii. Cosmetic disfigurement
      iii. Major psychologic burden
      iv. Malignancy (neurofibrosarcoma)
   d. Early adulthood
      i. Increase in the number and size of cutaneous, subcutaneous, and plexiform neurofibromas
      ii. Cosmetic disfigurement
      iii. Functional compromise
         a) Pain
         b) Paralysis
         c) Gastrointestinal hemorrhage
         d) Renovascular hypertension
   e. Adulthood
      i. An increased risk of developing a specific cancer (2–5% of patients with NF1)
      ii. Neurofibrosarcoma and malignant peripheral nerve sheath tumor commonly arise in a plexiform neurofibroma in a young adult with symptoms of pain or rapid growth.
8. Skeletal involvement (50% of cases)
   a. Short stature (30%)
   b. Scoliosis
      i. Observed in approximately 20% of children with NF1
      ii. The most common skeletal defect
      iii. With or without classic dystrophic features such as vertebral scalloping and rib penciling
   c. Kyphosis
   d. Cervical spine abnormalities
   e. Spondylolisthesis
   f. Congenital pseudarthroses (3%), frequently with bowing of the tibia and fibula (2–5%)
      i. A peculiar and uncommon complication
      ii. First noted as bowing, particularly of the tibia and fibula, in young children
      iii. May progress to thinning of the cortex, pathologic fracture, and severe difficulties with nonunion of the fragments
      iv. May go on to form a pseudarthrosis, or false joint, leaving the limb severely compromised
   g. Macrocephaly (40%)
   h. Skull bony defects
      i. Posterosuperior orbital wall bony defect
      ii. Overgrowth of cranial bones
      iii. Craniofacial asymmetry
      iv. Sphenoid wing dysplasia (5–10%)
   i. Ocular hypertelorism
   j. Hemihyperplasia of a limb or digit
   k. Spina bifida
   l. Absent patella
   m. Elevated scapulas
   n. Congenital dislocation (hip, radius, ulna)

o. Clubfoot
p. Syndactyly
q. Complete or partial absence of the limb bones

9. Endocrine abnormalities
   a. Sexual precocity (2–5%, the most common endocrine abnormality)
   b. Hypopituitarism
   c. Hypogonadism
   d. Gigantism
   e. Acromegaly
   f. Delayed sexual development
   g. Obesity
   h. Hypoglycemia
   i. Diabetes insipidus
   j. Goiter
   k. Myxedema
   l. Hyperparathyroidism
10. Cardiovascular diseases
   a. Vasculopathy
      i. Asymptomatic throughout life in many patients
      ii. Symptomatic vasculopathy: uncommon
      iii. Affects vessels, from aorta to small arterioles, result in vascular stenosis, occlusion, aneurysm, pseudoaneurysm, rupture, or fistula formation
      iv. Renal arteries: the most frequently involved site
      v. NF1-associated cerebrovascular disease in children: presents with weakness, involuntary movements, headaches, or seizures as a result of cerebral ischemia
      vi. NF1-related cerebrovascular disease in adults: similar symptoms and signs as a result of intracranial hemorrhage
   b. Hypertension
      i. Extremely common in adult patients with NF1 (33%)
      ii. Causes
         a) Essential hypertension
         b) Renal artery stenosis
         c) Pheochromocytomas
   c. Congenital heart disease (0.4–6.4%)
      i. Pulmonary stenosis (recognized feature of Watson syndrome, NF1–Noonan syndrome, and individuals with large deletions of the NF1 gene)
      ii. Left heart obstruction (aortic stenosis or coarctation)
      iii. Other CHD
11. Neuropsychological impairment
   a. Cognitive impairments (30–65%)
   b. Learning disabilities (30–60%)
      i. Easy distractibility
      ii. Impulsiveness
      iii. Deficient visual–motor coordination
      iv. Language and vocabulary deficits
   c. Mental retardation (4–8%)
   d. Behavioral difficulties
   e. Hydrocephalus (5%)
   f. Neurosensory hearing loss (5%)
12. Tumor types associated with NF1 (Brems et al. 2009)
   a. Non–nervous system tumors
      i. Adulthood
         a) Gastrointestinal stromal tumor
         b) Somatostatinoma
         c) Pheochromocytoma
         d) Breast cancer
      ii. Childhood: rhabdomyosarcom
   b. Nervous system tumors
      i. Adulthood and childhood
         a) Astrocytoma
         b) Malignant peripheral nerve sheath tumor
      ii. Childhood: neuroblastoma
13. Miscellaneous complications
   a. Headache (10–20%)
      i. Bothersome but usually not a disabling complaint
      ii. Headache possibly indicates the presence of an intracranial tumor but no identifiable etiology in many patients.
   b. Generalized itching or itching localized to newly developing neurofibromas experienced by many individuals
   c. Constipation observed especially in patients with plexiform neurofibromas in the pelvic area which interfere with autonomic innervation of the colon and produce both bowel and bladder problems
14. Pathological manifestations of NF1 (Woodruff 1999)
   a. Epidermis (pigmented macule or café-au-lait spot)
   b. Iris (Lisch nodule, optic glioma)
   c. Skeleton (malformations)
   d. Blood vessels (mesodermal vascular dysplasias): Intrinsic lesions of arterial walls

(vasculopathy) are important manifestations of NF1. It appears to contribute to excessmortality of young patients with NF1.
   i. Asymmetric
   ii. Renal artery stenosis with consequent hypertension
   iii. Occlusion resulting in cerebral or visceral infarcts
   iv. Aneurysms resulting in hemorrhage
   v. Arteriovenous fistulae
e. Brain
   i. Glial hamartomas
   ii. Astrocytomas
f. Adrenal (pheochromocytoma)
g. Intestine
   i. Somatostatinoma
   ii. Gastrointestinal autonomic nerve tumor
h. Peripheral nerve sheath
   i. Neurofibromas
   ii. Malignant peripheral nerve sheath tumors

15. NIH diagnostic criteria
   a. National Institutes of Health consensus development conference identified seven important components of neurofibromatosis. Two or more of these components must be present for a diagnosis of neurofibromatosis.
      i. Six or more café-au-lait spots, which are more than 5 mm in diameter in prepubertal patients and more than 15 mm in diameter in postpubertal individuals
      ii. Two or more neurofibromas of peripheral nerves of any type or one plexiform neurofibroma
      iii. Freckling in the axillary or inguinal region
      iv. Optic glioma (age of presentation at preschool years)
      v. Two or more Lisch nodules (hamartomas of the iris)
      vi. A distinctive bony lesion such as dysplasia of the sphenoid at the base of the skull or pseudarthrosis or thinning of long bone cortex, with or without complete interruption of the bone
      vii. A first-degree relative (parent, sib, or offspring) affected with neurofibromatosis type 1 which was diagnosed according to the preceding criteria
   b. These diagnostic criteria have been shown to be both highly specific and sensitive for adults with NF1 (Gutmann et al. 1997).
   c. Because some of the criteria may not manifest until later in life, they are not as sensitive in children, especially those under the age of 8.
   d. A 2,000 retrospective review of nearly 1,900 cases of NF1 found that 46% of sporadic cases did not meet criteria by age 1; however, 97% met criteria by age 8, and all fulfilled them by age 20 (DeBella et al. 2000).
16. Syndromes related to NF1
   a. Neurofibromatosis type 2 (bilateral vestibular neurofibromatosis)
      i. Clinically and genetically distinct from NF1
      ii. *NF2* gene is mapped to chromosome 22.
      iii. Inheritance: autosomal dominant
      iv. Often with a small number of café-au-lait spots (rarely more than six)
      v. Often with one or two peripheral neurofibromas (usually not more)
      vi. Occasionally with Lisch nodules
      vii. Posterior subcapsular cataracts detected by ophthalmologic examination in a sizable proportion of patients
      viii. The hallmark of NF2: development of bilateral eighth cranial nerve tumors, properly called vestibular schwannomas rather than acoustic neuromas (by age 30 years in 95% of patients)
      ix. Other tumors of cranial and cervical nerve roots common
      x. NF2 much less common than NF1, affecting approximately 1 in 40,000 individuals
   b. Segmental or mosaic NF1
      i. Presence of NF1 features (café-au-lait spots, freckling and peripheral or plexiform neurofibromas, and Lisch nodules) in an individual with a segment of the body affected
      ii. Family history with invariably normal parents who, on rare occasions, can have a child with classic NF1
      iii. Presence of strong circumstantial evidence suggests somatic mutation of the *NF1* gene early in embryogenesis so that derivatives of that mutant line display the features of NF1.

iv. May transmit the disease if the mosaicism involves the germ line
v. Germ-line mosaicism for an *NF1* gene mutation has been observed in a clinically unaffected father of a child with new onset NF1.
vi. Somatic mosaicism for an *NF1* gene deletion has been detected in an individual with NF1.
vii. Possibility of demonstrating similar somatic mosaicism if cases of segmental NF1 are analyzed.

c. Watson syndrome
i. Pulmonary stenosis with café-au-lait spots
ii. Dull intelligence
iii. Short stature
iv. A small number of neurofibromas
v. Lisch nodules
vi. Deletions present in the NF1 gene in at least two families: no distinguishing aspect between the deletions causing Watson syndrome and those associated with more classic NF1

d. Neurofibromatosis 1–Noonan syndrome
i. A Noonan syndrome phenotype in patients with NF1 (about 12%)
ii. Clinical features in addition to NF1
a) Ocular hypertelorism
b) Down-slanting palpebral fissures
c) Low-set ears
d) Webbed neck
e) Pulmonic stenosis
f) Pectus excavatum
g) Mild hypertelorism
h) Short stature
iii. Relatives affected with NF1 present with or without concomitant features of Noonan syndrome.
iv. Current understanding: The phenotype of NF1 can include features overlapping with those described in Noonan syndrome, but these disorders are probably genetically distinct.

e. Predominance of spinal tumors and relatively few peripheral neurofibromas identified in rare families
i. Locus heterogeneity
ii. Not representing a distinct subtype of NF

17. Prognosis of NF1
a. Progression of the disease with time
b. Pregnancies in women with NF1
i. Normal pregnancies in most patients but serious complications have been noted in some patients.
ii. Rapid increase in the number and size of neurofibromas during pregnancy
iii. First onset of hypertension or marked exacerbation of pre-existing hypertension during pregnancy
iv. Delivery complicated by large pelvic or genital neurofibromas often necessitates cesarean section in pregnant women with NF1.

c. Anesthetic risk
i. Intraoral lesions compromising the airway (5%)
ii. Coexisting kyphoscoliosis (2%) and fibrosing alveolitis (20%) complicating the perioperative period
iii. Careful regional anesthesia to monitor the existence of neurofibromas affecting peripheral nerves and nerve roots
iv. Possible long-term muscular blockade following the use of suxamethonium and non-depolarizing muscle relaxants

d. Average life expectancy overall reduced by at least 15 years
i. Malignancy and hypertension contributing to increased morbidity in adults with NF1
ii. Risk for neurofibromatosis-related malignancy (8%)
iii. Most common malignancy: malignant peripheral nerve sheath tumors
iv. Better prognosis in patients with only mild and cosmetic symptoms of the disease

Diagnostic Investigations

1. Diagnosis of neurofibromatosis 1 based largely on clinical criteria despite progress in defining the molecular genetics of the disorder
2. Slit-lamp examination of the eyes to detect Lisch iris nodules

3. Radiography to detect bony abnormalities
   a. Skull
      i. Macrocephaly
      ii. Absence of the greater and lesser wings of the sphenoid
      iii. Absence of the orbital floor
      iv. Hypoplasia of the lesser wings of the sphenoid
      v. Enlarged orbits
      vi. Enlargement of cranial foramina
      vii. Enlargement of orbital margins
      viii. Sclerosis in the vicinity of the optic foramen (optic nerve sheath meningioma)
      ix. Facial asymmetry
      x. Hypoplasia of the paranasal sinuses
      xi. Mandibular abnormalities
      xii. Mandibular hypoplasia with flattening of the external contour
      xiii. Thinning of the ramus
      xiv. Coronoid hyperplasia
      xv. Widening of the lateral and medial coronoid spaces
      xvi. Calvarial defects adjacent the left lambdoid suture
      xvii. Osseous defects associated with multiple frontonasal osseomeningeal defects causing cerebrospinal fluid (CSF) rhinorrhea
   b. Chest
      i. Inferior rib notching
      ii. Twisted ribbonlike ribs in the upper thoracic cage
      iii. Posterior mediastinal masses secondary to intrathoracic meningoceles
      iv. Mediastinal and lung masses secondary to neurofibromas
      v. Dumbbell neurofibromas
      vi. Progressive pulmonary interstitial fibrosis leads to formation of bullae and honeycomb lung.
      vii. Increased incidence of spontaneous pneumothorax and hemothorax
      viii. Dilatation/enlargement of the central pulmonary arteries and peripheral pruning of vessels secondary to changes of interstitial lung disease and pulmonary hypertension
   c. Spine
      i. A sharply angled kyphoscoliosis centered at the thoracolumbar junction in 50% of patients
      ii. Enlargement of the intervertebral foramina
      iii. Scalloping of the vertebral bodies (anterior, posterior, lateral)
      iv. Hypoplasia of the vertebral pedicles
      v. Wedged-shaped vertebrae
      vi. Spondylolisthesis
      vii. Spinal clefts
      viii. Osteolysis
      ix. Spindling of the transverse processes
   d. Appendicular skeleton
      i. Bowing of long bones
      ii. Hyperplasia or hypoplasia of long and short bones
      iii. Pseudarthrosis
      iv. Erosions
      v. Periosteal dysplasia
      vi. Intramedullary longitudinal osteosclerotic streaks
      vii. Single or multiple cystic bone lesions
      viii. Focal gigantism
      ix. Protrusio acetabuli
      x. Dislocation of the hip
      xi. Dislocation of the radius and ulna
      xii. Absence of a patella
      xiii. Neuropathic arthropathy of the knee
   e. Gastrointestinal
      i. Neurofibromas within the stomach, small and large bowels, and rectum
      ii. Intussusception of the bowel presenting with intestinal obstruction
      iii. Bowel obstruction simulating Hirschsprung disease secondary to plexiform neurofibroma of the colon
      iv. Pseudoobstruction
      v. Biliary strictures and bile duct intraluminal neurofibromas rarely reported
   f. Urinary tract
      i. Renal collecting system and bladder intrinsically involved or extrinsically compressed or displaced by neurofibromas
      ii. Intravenous urogram providing useful information regarding the nature and site of obstruction and function
4. Echocardiography for pulmonic stenosis, aortic coarctation, or other CHD
5. CT imaging
   a. Solid fusiform masses
      i. Present in the distribution of nerves, with central areas of low attenuation and calcification

ii. May present in the paravertebral, laryngeal, mediastinal, abdominal, and pelvic/ischiorectal fossae
b. Plexiform neurofibromas seen as widespread sheets of nodular tissue
c. Paraspinal neurofibromas seen at every level, vary in size, may be dumbbell-shaped, or may comprise fusiform/spherical soft-tissue masses.
d. Mesenteric plexiform neurofibromas trap mesenteric fat within an entangled network.
e. Nonneoplastic cerebral and cerebellar calcification and choroid plexus calcification on cranial CT scans
f. Hydrocephalus in NF1 results from benign aqueduct stenosis or a glioma of the tectum/tegmentum of the mesencephalon.
g. Intracranial nerve sheath tumors with associated bone erosions
h. Meningiomas with associated changes in the calvarium/skull
i. Extrinsic bladder involvement, intrinsic infiltrative processes, or extrinsic compression of the renal collecting system by a neurofibroma
j. A role in the investigation of thoracic, abdominal, and pelvic complications of NF1

6. MRI imaging
   a. Brain
      i. T2 hyperintensities (60–70%)
      ii. Hamartomas in the brain
      iii. Optic nerve pathology
   b. Internal lesions
      i. Mediastinal masses
      ii. Spinal cord tumors
      iii. Deep plexiform neurofibromas
      iv. Neurofibromas of the brachial or sacral plexus
7. Histopathology
   a. Confirmation of neurofibromas
      i. Arisen from cells in the peripheral nerve sheath
      ii. Consist of a mixture of cell types, including Schwann cells, fibroblasts, mast cells, and vascular elements
   b. Verification of malignant transformation to neurofibrosarcoma
8. Linkage analyses using polymorphic markers that segregate with the disease in familial cases
9. Either FISH, loss of heterozygosity or southern blotting analyses reveal 5% of patients with large deletions of *NF1* gene encompassing part or the whole *NF1* gene.
10. Mutation analysis in sporadic and familial cases (Friedman 2009)
    a. Protein truncation test based on the detection of truncated proteins via in vitro transcription and translation from RT-PCR fragments spanning the entire *NF1* cDNA
       i. *NF1* mutations detected
          a) Nonsense mutations
          b) Frameshift mutations
          c) Splicing mutations
       ii. Method of exploring the RNA for changes that are compatible with mutations in the gene
       iii. Positive in 80% of the cases
    b. Gene sequencing: specific search of exon by exon for the mutation
11. Multi-step detection protocol: preferred because of the large size of the NF1 gene and the lack of mutation hotspots
    a. Testing methods
       i. Optimized protein truncation testing
       ii. Sequence analysis
       iii. FISH
       iv. Long-range RT-PCR
       v. Southern blot analysis
       vi. Cytogenetic analysis
    b. NF1 mutations detected
       i. Nonsense mutations
       ii. Frameshift mutations
       iii. Splicing mutations
       iv. Missense mutations
       v. Deletions
       vi. Other rearrangements
    c. Mutation detection rate in patients with a clinical diagnosis of NF1: >95%
12. Presymptomatic/preconceptional genetic testing: molecular characterization in familial and in sporadic cases
13. Limitation of genetic testing
    a. Lack of genotype–phenotype correlations: A positive test will not predict disease severity or outcome
    b. Two exceptions
       i. Complete loss of the *NF1* gene along with multiple contiguous genes

a) Occurs in 4–5% of patients with NF1 (Kluwe et al. 2004)
b) Patients with whole gene deletion present with a very large neurofibroma burden, more severe cognitive impairment, large hands and feet, dysmorphic facial features, and have a higher lifetime risk of developing malignant peripheral nerve sheath tumors (MPNST) (Leppig et al. 1997; De Raedt et al. 2003).

ii. A 3-base pair in-frame deletion in exon 17 of the *NF1* gene: Patients with this genetic mutation have an absence of cutaneous neurofibromas and appear to have a lower incidence of serious complications.

Genetic Counseling

1. Recurrence risk
   a. Patient's sibling
      i. Risk not increased unless a parent is affected or has gonadal mosaicism.
      ii. If a parent is affected, the risk to the sibs is 50%.
      iii. Possibility of germ-line mosaicism in a clinically normal parent: recurrence risk based on the percentage of the germ-line mosaicism
   b. Patient's offspring
      i. Risk: 50% of inheriting the disease with extremely variable disease manifestations
      ii. Risk of having a child with NF1 in a patient affected with segmental NF1
         a) A small but greater than the general population risk
         b) Some cases of segmental NF1 apparently being "transmitted" to offspring; the mechanism (if one exists) behind this is unclear (Boyd et al. 2009).
         c) Segmental neurofibromatosis is believed to be due to somatic mosaicism for a mutation in the NF gene. The mutation occurred postconceptionally and present in the limited population of cells. Gonadal cells may or may not have a mutation (Dupuis and Nezarati 2001).
2. Prenatal diagnosis
   a. Influence of knowledge of the disease in the reproductive decisions of affected individuals (Ars et al. 1999)
      i. Interest in prenatal test by 41% of the subjects considering becoming pregnant
      ii. Only 10% considering terminating an affected pregnancy
   b. Prenatal diagnosis of NF1 difficult to be made in the past due to the following reasons (Vitale et al. 2002):
      i. Large size of the NF1 gene
      ii. Lack of any hotspots where the mutations arise
      iii. Variable expression even within members of a family with NF1
      iv. Lack of a tight genotype–phenotype correlation
      v. High spontaneous mutation rate
   c. Currently available prenatal diagnosis
      i. Direct characterization of the mutation from a parent affected by NF1
      ii. Analysis of the genomic DNA mutation from the fetus either by amniocentesis or CVS
      iii. Indirect linkage analysis to familial cases using informative polymorphic markers
      iv. Protein truncation test
      v. Fluorescence in situ hybridization
   d. Molecular diagnosis, unfortunately, cannot predict clinical expression of the disease in the fetus.
3. Management
   a. Developmental assessment in children
   b. Medical management for itching, pain, depression, and other psychological and social problems
   c. Treatment of hypertension depending on the etiology
      i. Pheochromocytomas
      ii. Renal artery stenosis
   d. Laser or electrocautery for small discrete cutaneous or subcutaneous neurofibromas
   e. Surgical resection of tumors
      i. Resection of neurofibromas pressing on vital structures, obstructing vision, or rapidly growing lesions causing irritation, discomfort, and pain
      ii. Plexiform neurofibromas: extremely difficult to approach surgically and often recur after resection because of residual cells resting deeply in the soft tissues
      iii. Resection of spinal cord tumors: quite difficult but often is necessary to prevent progressive paraplegia or quadriplegia

f. Surgical treatment of disfigurement
   i. Excision of multiple neurofibromas
   ii. Reconstructive surgery for plexiform neurofibromas
g. Orthopedic care indicated for rapidly progressive scoliosis and for some severe bony defects
h. Optic pathway gliomas in most children with NF1 (Jett and Friedman 2010)
   i. Usually do not require treatment
   ii. Chemotherapy is the treatment of choice for progressive tumors.
   iii. Surgical treatment: reserved for cosmetic palliation in a blind eye
   iv. Radiotherapy usually avoided because of the risk of inducing malignancy or moyamoya in the exposed field
i. Treatment of congenital pseudarthrosis of the tibia: challenging (Vitale et al. 2002)
   i. Bracing mainly of early treatment before fracture develops
   ii. A knee-ankle-foot-orthosis when weight bearing
   iii. Intramedullary rod fixation, often in combination with autogenous bone grafting of the pseudarthrosis site
j. Advise high-risk pregnancy care to pregnant patient with neurofibromatosis
   i. Maternal hypertension
   ii. Aggravating features of neurofibromatosis

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Fig. 1 (**a**–**d**) Typical café-au-lait spots in different patients

Fig. 2 (**a**, **b**) Axillary freckles in a child and an adult

Fig. 3 (**a**–**c**) Café-au-lait spots and numerous localized cutaneous neurofibromas in three different patients

Fig. 4 (**a**–**e**) Diffuse cutaneous neurofibromas (nodular and polypoid shapes) in four patients affecting skin and subcutaneous tissue resulting in marked cosmetic disfigurements and functional disturbances

Fig. 5 (**a**–**c**) Neurofibromas involving vessels of the face and subcutaneous tissue of the fingers

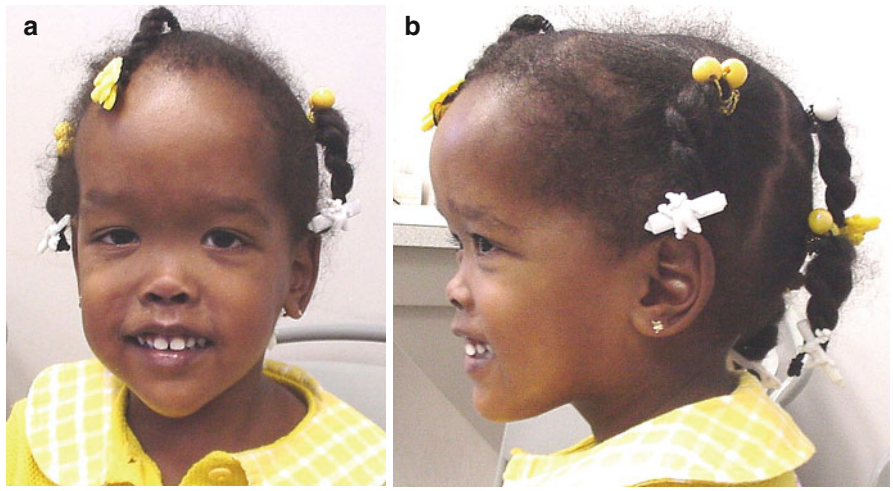

Fig. 6 (**a**, **b**) Macrocephaly with prominent forehead and depressed nasal bridge

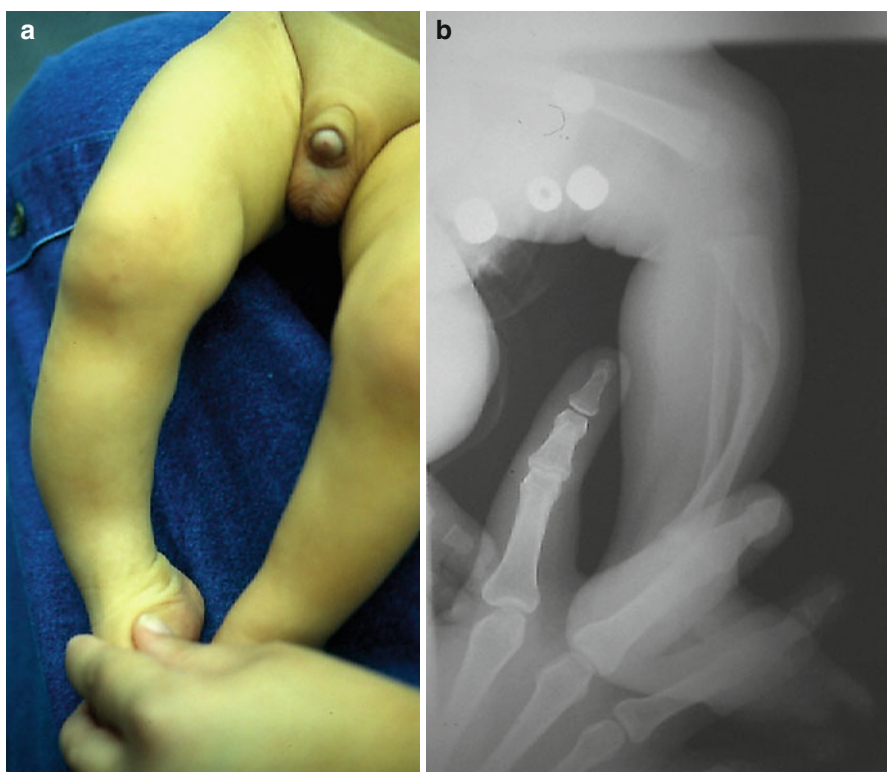

Fig. 7 (**a**, **b**) Pseudoarthrosis of right tibia manifesting as bowed leg

Fig. 8 (**a**, **b**) A child with NF1 having pseudoarthrosis of the left tibia and fibula resulting in fractures

Fig. 9 Localized intraneural neurofibromas of a median nerve, causing fusiform enlargement of the affected nerve

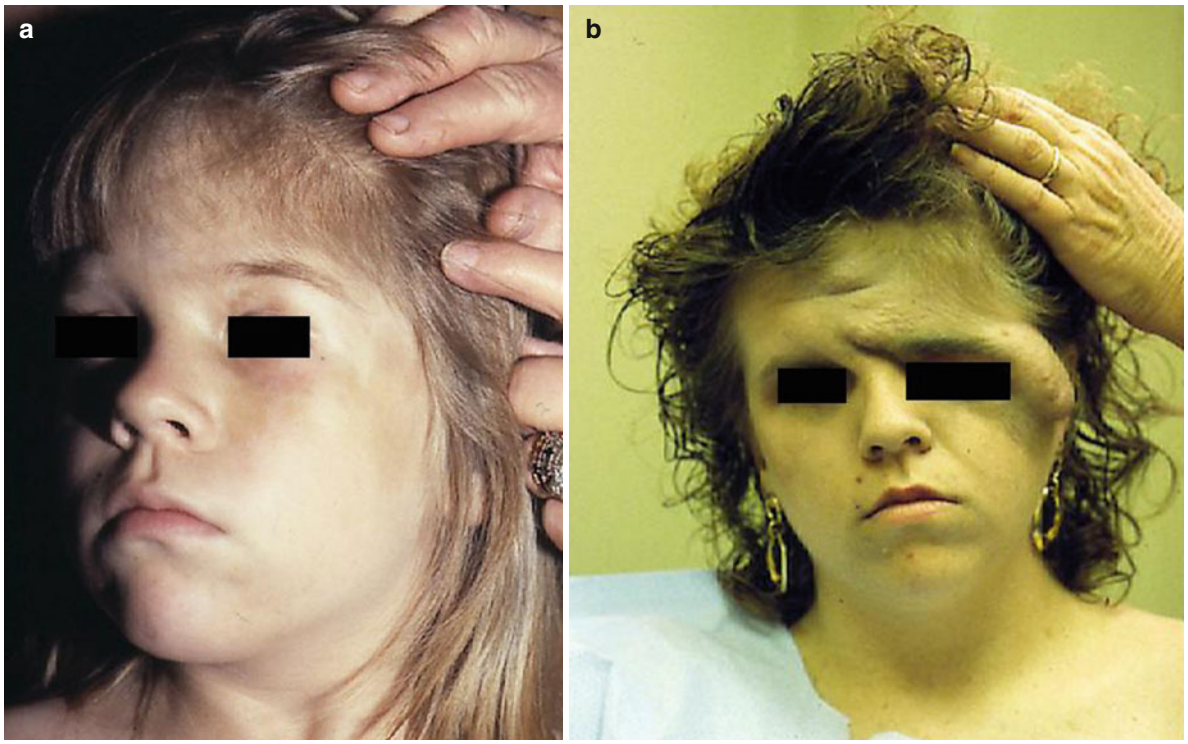

Fig. 10 (**a**, **b**) Plexiform neurofibromas affecting left orbital region in different ages

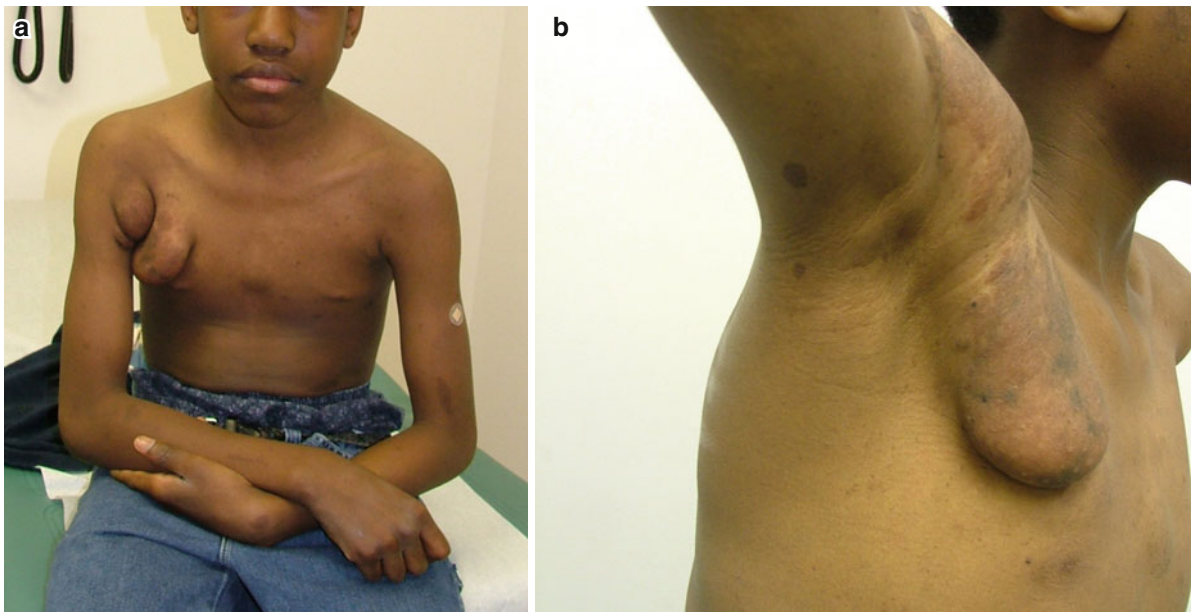

Fig. 11 (**a**, **b**) A 12-year-old boy with NF1 showing a large plexiform neurofibroma on the right upper chest

Fig. 12 (**a–d**) A man with NF1 showing plexiform neurofibromas on the left cheek, right upper back, and sole of the foot

Fig. 13 (**a–c**) Massive soft-tissue neurofibromas affecting two patients. Extreme neurofibromatous growth producing massive, diffuse infiltration of soft tissue of the thigh producing disfiguring redundant soft-tissue masses

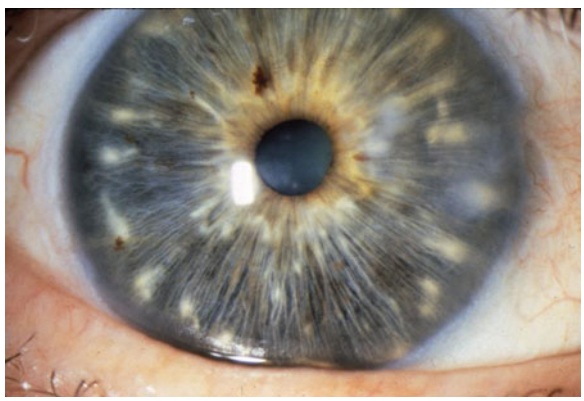

Fig. 14 Tannish white iris Lesch nodules in a patient with NF1

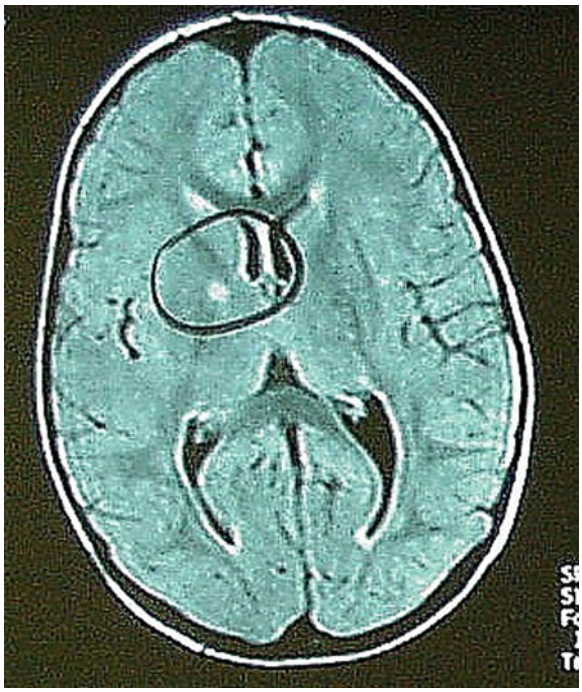

Fig. 15 MRI of the brain showing a hamartomatous lesion of the right globus pallidus. This patient has numerous cutaneous café-au-lait spots of varying size and typical axillary freckles. He was shown to have a truncating mutation in the segment 3 of the neurofibromin (NF1) gene

Fig. 16 (**a–d**) A 26-year-old female with segmental neurofibromatosis showing axillary freckles, multiple small neurofibromas, and hyperpigmentation, all involving the right side of the body. Left side of the body is spared, including left axilla which showed no freckles

Fig. 17 (**a–d**) A 36-year-old present with >8 large café-au-lait spots, bilateral axillary freckling, several cutaneous, intradermal, and subcutaneous neurofibromas. A heterozygous missense alteration in exon 13 of the NF1 gene was identified (c.2072 T>C) (p.Leu691Pro). The 2-year and 3-month-old daughter was found to have multiple café-au-lait spots with a single neurofibroma on the right scalp

Fig. 18 A 14-month-old infant was seen because of multiple café-au-lait spots without neurofibroma. A splice mutation was identified in the *NF1* gene, 6641 + 1 G > T, leading to skipping of exon 35. This finding confirms the diagnosis of NF1 in this patient

Fig. 19 A 13-year-old boy with multiple café-au-lait spots, axillary freckles, and small neurofibromas throughout the body. The molecular study revealed a recurrent deep intronic splicing mutation in the *NF1* gene (c.5749 + 322 A > G). This mutation leads to missplicing of intron 30. This finding confirms the diagnosis of neurofibromatosis I

Neurofibromatosis 2

Historically, neurofibromatosis 2 (NF2) has been previously known as bilateral acoustic neurofibromatosis or central neurofibromatosis. It has frequently been confused with the more common neurofibromatosis 1 (NF1), also known as von Recklinghausen disease or peripheral neurofibromatosis (MacCollin and Mautner 1998). Gardner and Frazier in 1930 were the first to persuasively argue that bilateral vestibular tumors can be clinically and pathologically distinguished from both von Recklinghausen neurofibromatosis and from sporadic tumors from studying a large family with 38 affected members over five generations.

The first clear description of NF2 was made by Wishart in 1822 (Wishart 1822). NF2 occurs in about 1 in 25,000 live births.

Synonyms and Related Disorders

Bilateral acoustic neurinoma; Bilateral acoustic neurofibromatosis; Bilateral acoustic Schwannomas; Central neurofibromatosis

Genetics/Basic Defects

1. An autosomal dominant disorder: resulting from a mutation in the *NF2* tumor suppressor gene on chromosome 22q12 (Asthagiri et al. 2009)
   a. Truncating mutations (nonsense and frameshifts): most frequent germ line event causing the most severe disease
   b. Single and multiple exon deletions are also common.
2. *NF2* tumor suppressor gene: consists of 17 exons that encode for a 69-kDa protein product called merlin (moesin-ezrin-radixin-like protein) or schwannomin (Rouleau et al. 1993; Trofatter et al. 1993)
3. Consistent with Knudson's two-hit hypothesis for tumorigenesis (tumor formation initiates when both alleles of this gene are inactivated) (Knudson 1971)
   a. Patients inherit a germ line mutation of one affected allele from a parent or acquire a de novo mutation of an allele at the postzygotic stage of embryogenesis.
   b. Subsequent development of tumors in susceptible target organs, such as nervous system, eyes, and skin, from cells that lose function of the wild-type (normal) *NF2* allele.
4. Abnormal or absent merlin function can disrupt tumor suppression in NF2.
5. High frequency of somatic mosaicism in patients with de novo mutations (Kluwe and Mautner 1998; Moyhuddin et al. 2003; Evans et al. 2007)
   a. Mutation takes place after conception in patients with mosaicism, resulting in two separate cell lineages.
   b. Patients with mosaicism tend to have mild generalized or even localized disease (e.g., unilateral vestibular schwannoma with ipsilateral tumors).
   c. Only a portion of the germ cells in a person with *NF2* mosaicism are likely to carry the mutation.
      i. Risk of transmission to offspring will be less than the expected one in two (50%) for an inherited mutation.
      ii. Children who inherit the mutation from a mosaic parent will probably have more severe disease than will the parent because the mutation will be present in all their somatic cells.

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Clinical Features

1. Young adulthood (age 20–30 years) (Asthagiri et al. 2009)
   a. Hearing loss from a vestibular schwannoma, often unilateral initially
   b. Accompanied symptoms
      i. Tinnitus
      ii. Dizziness
      iii. Imbalance
   c. A significant proportion of cases (20–30%) present with
      i. Headaches and/or seizures from an intracranial meningioma
      ii. Pain, muscle weakness, and/or paresthesia from spinal tumor
      iii. Cutaneous tumor induced symptoms
2. Children (up to 30%)
   a. May present with the same symptoms as adults
   b. More frequently present with the following:
      i. Visual disturbance
         a) Cataract
         b) Hamartomas
         c) Intracranial tumors
      ii. Skin tumors
      iii. Mononeuropathy
         a) Facial paresis
         b) Foot drop
      iv. Symptomatic spinal cord tumors
      v. Non-vestibular intracranial tumors
3. Lesions associated with NF2
   a. Neurological lesions
      i. Bilateral vestibular schwannomas (90–95%)
      ii. Other cranial nerve schwannomas (24–51%)
      iii. Intracranial meningiomas (45–58%)
      iv. Spinal tumors (63–90%)
         a) Extramedullary tumors (55–90%)
         b) Intramedullary tumors (18–53%)
      v. Peripheral neuropathy ($\leq$66%)
   b. Ophthalmological lesions
      i. Cataracts (60–81%)
      ii. Epiretinal membranes (12–40%)
      iii. Retinal hamartomas (6–22%)
   c. Cutaneous lesions
      i. Skin tumors (59–68%)
      ii. Skin plaques (41–48%)
      iii. Subcutaneous tumors (43–48%)
      iv. Intradermal tumors (rare)
4. Diagnostic criteria for NF2 including the NIH criteria with additional criteria (Manchester criteria which expanded the previous NIH diagnostic criteria and were designed to include patients with neither a family history of NF2 nor bilateral vestibular schwannomas, but who had multiple schwannomas or meningiomas). (Evans et al. 2005; Evans 2009a, b; Asthagiri et al. 2009)
   a. Major criteria
      i. Bilateral vestibular schwannomas or
      ii. First degree family relative with NF2 plus unilateral vestibular schwannoma or two NF2-associated lesions (meningioma, glioma, neurofibroma, schwannoma, or cataract)
   b. Additional criteria
      i. Unilateral vestibular schwannoma plus any two NF2-associated lesions (meningioma, glioma, neurofibroma, schwannoma, or cataract), or
      ii. Multiple meningiomas plus unilateral vestibular schwannoma or two other NF2-associated lesions (glioma, neurofibromas, schwannoma, or cataract)
5. Patient populations at risk for NF2 (Evans et al. 2005)
   a. First-degree relative with NF2 (affected parent, sibling, or children)
   b. People younger than age 30 years with a unilateral vestibular schwannoma or meningiomas
   c. People with multiple spinal tumors (schwannomas, meningiomas)
6. Recommended intervals for screening children of an affected parent (Evans et al. 2005)
   a. Ophthalmological examination yearly from infancy
   b. Neurological examination yearly from infancy
   c. Audiology with auditory brain stem evoked potentials yearly from infancy
   d. Presymptomatic genetic testing: one test from 10 years of age
   e. Cranial MRI at 10–12 years of age
   f. Spinal MRI at 10–12 years of age (every 2–3 years)
   g. For presymptomatic genetic testing, cranial MRI, and spinal MRI, screening may start

earlier than age 10 years in severely affected families and families in which early detection of disease would aid family preparation for future events related to NF2.

7. Variable expressivity of NF2 among individuals
   a. Varying size, location, and number of tumors.
   b. Although these tumors are not malignant, their anatomical location and multiplicity lead to great morbidity and early mortality.
   c. The average age of death is 36 years.
   d. Actuarial survival from the time of establishing the correct diagnosis is 15 years.
   e. Survival is improving with earlier diagnosis and better treatment in specialty centers (Baser et al. 2002; Evans et al. 2005).
   f. Underrecognized in children in whom skin tumors and ocular findings may be the first manifestations (NF2 is usually considered an adult-onset disease).
8. Penetrance: 100%
9. Differential diagnosis
   a. Main differential diagnosis of NF2: schwannomatosis (multiple schwannomas without the vestibular schwannomas that are diagnostic of NF2)
   b. Multiple non-cranial schwannomas: Some patients turn out to have mosaic NF2 (Moyhuddin et al. 2003; Evans et al. 2007).
   c. Neurofibromatosis 1
10. Prognosis is adversely affected by
    a. Early age at onset
    b. A higher number of meningiomas
    c. Having a truncating mutation

Diagnostic Investigations

1. Clinical and family history (Evans 2009a)
2. Physical examination including cutaneous and ophthalmic (slip lamp)
3. Craniospinal MRI
4. Hearing evaluation, including BAER
5. Chromosome analysis: Gross chromosomal changes are rare but may reveal a variety of chromosome abnormalities.
   a. Cytogenetically visible deletions encompassing the NF2 gene: may cause mental retardation and multiple congenital abnormalities (Barbi et al. 2002)
      i. Ring chromosome 22 (Tsilchorozidou et al. 2004)
      ii. Can cause multiple meningiomas and vestibular schwannomas fulfilling NF2 diagnostic criteria, NF2 locus itself is usually present within the ring, but the ring itself is frequently loss as a result of instability.
      iii. Apparently balanced chromosomal translocations disrupting the *NF2* gene causing NF2
      iv. Fluorescence in situ hybridization (FISH) to identify smaller deletions that remove multiple exons of the NF2 gene or the whole gene
6. Molecular genetic analysis
   a. Sequence analysis/mutation scanning of *NF2* gene (Evans et al. 2007)
      i. In 73% of families with NF2, sequence analysis identified a mutation in a member of the second generation.
      ii. In simplex cases (a single occurrence in a family), the mutation detection rate is approximately 60%.
      iii. Approximately 25–33% of mutations are not detected as a result of somatic mosaicism.
      iv. Mutations with mosaicism levels >10% can be detected in lymphocyte DNA.
      v. Identification of the remainder of mosaic mutations usually requires testing of tumor material.
   b. Deletion/duplication analysis
      i. Systematically detects whole exon deletions and duplications
      ii. Most large deletions and, less commonly, duplications of single exons or multiple exons can be detected by multiple ligation-dependent probe amplification (MLPA).
   c. Linkage analysis
      i. In families in whom no disease-causing mutation is identified, and at least two family members of different generations are affected.
      ii. Modified linkage analysis using both constitutional and tumor DNA can exclude NF2 in those children of a simplex case who have not inherited the allele lost in the tumor.

7. Presymptomatic genetic testing is an integral part of the management of NF2 families.
   a. At-risk relatives whose genetic status is unknown can be tested for presence of the *NF2* mutation (either constitutional or somatic mosaic) identified in an affected relative.
   b. In the rare instance in which an *NF2* mutation cannot be identified, linkage analysis can be used in families with at least two affected family members of different generations, or tumor DNA can be used to clarify the genetic status of children of a simplex case.

Genetic Counseling

1. Recurrence risk: presence of an affected parent in approximately 50% of individuals with NF2 (other 50% have NF2 as the result of a de novo mutation; 20–33% of simplex cases without family history are mosaic for an *NF2* mutation) (Evans 2009a)
   a. Patient's sib
      i. Affected parent: a 50% risk
      ii. Asymptomatic parents: a low risk since the age of onset of symptoms is relatively uniform within families
         a) A single case of germ line mosaicism in a clinically normal parent has been reported.
         b) Somatic mosaicism which may include germ line mosaicism is found in 25–33% of individuals with NF2 who are simplex cases.
   b. Patient's offspring
      i. The risk of disease transmission is 50% in the second generation and beyond.
      ii. The risk of transmission in people with new NF2 mutations is less than 50% due to mosaicism, in which only a proportion of cells have the mutated *NF2* gene (Evans et al. 1998; Kluwe and Mautner 1998).
2. Prenatal diagnosis and preimplantation genetic diagnosis: possible for at risk pregnancies, provided prior identification of the disease-causing mutation in the family
3. Management
   a. Surgery remains the focus of current management.
      i. Surgical removal of symptomatic cranial and spinal tumors
      ii. More difficult to determine the timing of removal of vestibular schwannomas
   b. Stereotactic radiosurgery, most commonly with the gamma knife, may be an alternative to surgery.
   c. Important to balance the use of microsurgery and radiation treatment, which can have a role in patients who have particularly aggressive tumors, or who are poor surgical risks, or who refuse surgery.
   d. Hearing preservation and augmentation with hearing aids or auditory rehabilitation with a cochlear or brain stem implant.
   e. Watchful waiting with careful surveillance and occasionally radiation treatment have a role.

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Fig. 1 (**a**, **b**) A 23-year-old female had resection of anterior fossa meningioma 2 years previously. She complained worsening headaches with intermittent vomiting and blurry vision recently. She underwent a posterior fossa craniectomy and resection of a large cervical medullary tumor, consistent with a spindle cell tumor (schwannoma). She also has history of bilateral hearing loss and balance dysfunction. Molecular genetic testing revealed a truncating mutation in the *NF2* gene (c.553delG) confirming the diagnosis of NF2 in this patient

Noonan Syndrome

Noonan syndrome (NS) is a relatively common but genetically heterogeneous autosomal dominant malformation syndrome. The incidence of Noonan syndrome is estimated to be 1 in 1,000–1 in 2,500 live births.

Synonyms and Related Disorders

Female pseudo-Turner syndrome; Male Turner syndrome; Turner phenotype with normal karyotype

Genetics/Basic Defects

1. Inheritance (Allanson 1987; Tartaglia et al. 2010)
   a. Autosomal dominant inheritance
   b. Many affected individuals with de novo mutations
   c. Affected parent recognized in 30–70% of families
2. Caused by mutations in the *PTPN11*, *SOSI*, *KRAS*, *RAF1*, *BRAF*, and *MEK1* (*MAP2K1*) genes: accounting for approximately 70% of affected individuals
   a. The gene *PTPN11* (protein tyrosine phosphatase, nonreceptor type 11), mapped on 12q24.1, encoding the protein tyrosine phosphatase SHP-2.
      i. Heterozygous point mutations in the gene *PTPN11* identified in the following:
         a) Families showing linkage to the *NS1* locus in 12q24
         b) Some sporadic cases with NS
      ii. All mutations detected to date: missense mutations
      iii. The majority of mutations found in exons 3 and 8, which correspond to the interacting regions of the N-SH2 and protein tyrosine phosphatase domains of the gene
      iv. Genotype-phenotype correlation of *PTPN11* mutations
         a) Increased frequency of *PTPN11* mutations observed in individuals with Noonan syndrome with pulmonary stenosis (70%)
         b) Infrequent frequency of *PTPN11* mutations observed in individuals with hypertrophic cardiomyopathy (6%)
   b. SHP-2 (encoded by *PTPN11*), SOS1, BRAF, RAF1, and MEK1 positively contribute to RAS-MAPK signaling and possess complex autoinhibitory mechanisms that are impaired by mutations.
   c. Similarly, reduced GTPase activity or increased guanine nucleotide release underlies the aberrant signal flow through the MAPK cascade promoted by most *KRAS* mutations.
3. Mutation in *SHOC2*
   a. Encodes a cytoplasmic scaffold positively controlling RAF1 activation.
   b. Has been discovered to cause a closely related phenotype previously termed Noonan-like syndrome with loose anagen hair.
   c. This mutation promotes aberrantly acquired N-myristoylation of the protein, resulting in its constitutive targeting to the plasma membrane and dysregulated function.
4. *PTPN11*, *BRAF*, and *RAF1* mutations
   a. Also account for approximately 95% of LEOPARD syndrome.
      i. A condition which resembles NS phenotypically

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ii. Characterized by multiple lentigines dispersed throughout the body, café-au-lait spots, and a higher prevalence of electrocardiographic conduction abnormalities, obstructive cardiomyopathy, and sensorineural hearing deficits

b. These recent discoveries demonstrate that the substantial phenotypic variation characterizing NS and related conditions can be ascribed, in part, to the gene mutated and even the specific molecular lesion involved.

Clinical Features

1. Clinical features (Allanson 1987)
   a. Growth
      i. Average length at birth: 47 cm
      ii. Generally normal birth weight but can be high due to subcutaneous edema
      iii. Prepubertal growth parallel to the third centile (40%) with a relatively normal growth velocity
      iv. Pubertal growth spurt often reduced or absent
   b. Craniofacial features: change with age (see below)
   c. Ocular abnormalities (observed up to 95% of cases)
      i. Strabismus
      ii. Refractive errors
      iii. Amblyopia
      iv. Nystagmus
      v. Anterior segment and fundal changes
   d. Congenital heart defects (two thirds of cases)
      i. Pulmonary valvular stenosis (50%)
      ii. Hypertrophic cardiomyopathy (20–30%): may be present at birth or appears in infancy or childhood
      iii. Atrial septal defect (10%)
      iv. Asymmetrical septal hypertrophy (10%)
      v. Ventricular septal defect (5%)
      vi. Persistent ductus arteriosus (3%)
      vii. Other cardiac defects
         a) Pulmonary artery branch stenosis
         b) Mitral valve prolapse
         c) Ebstein anomaly
         d) Single ventricles
   e. Genitourinary abnormalities
      i. Males: ranging from normal prepubertal virilization to delayed fertility and inadequate secondary sexual development associated with deficient spermatogenesis secondary to earlier cryptorchidism (60%)
      ii. Females: normal or delayed puberty but fertile in majority of cases
   f. Skeletal abnormalities
      i. Characteristic pectus deformity (see detail description below)
      ii. Common features
         a) Cubitus valgus (50%)
         b) Hand anomalies including clinobrachydactyly and blunt fingertips (30%)
         c) Vertebral and sternal anomalies (25%)
         d) Dental malocclusion (35%)
   g. Ectodermal abnormalities
      i. Various skin manifestations
         a) Café-au-lait patches (10%)
         b) Pigmented nevi (25%)
         c) Lentigines (2%)
         d) Keratosis pilaris atrophicans faciei
      ii. Several instances of neurofibromatosis and the Noonan phenotype documented
   h. Bleeding diathesis (about one third of cases with a coagulation defect)
      i. Factor XI deficiency
      ii. Von Willebrand disease
      iii. Platelet dysfunction which may be associated with trimethylaminuria
   i. Lymphatic abnormalities
      i. Congenital dysplasia, hypoplasia, or aplasia of lymphatic channels (20%)
      ii. General lymphedema
      iii. Peripheral lymphedema
      iv. Pulmonary lymphangiectasia
      v. Intestinal lymphangiectasia
      vi. Hydrops fetalis
      vii. Cystic hygroma
   j. Rare associated features
      i. Autoimmune thyroiditis
      ii. Pheochromocytoma
      iii. Ganglioneuroma
      iv. Malignant schwannomas
      v. Congenital contractures
      vi. Chiari malformation with syringomyelia
      vii. Skin and oral xanthomas
      viii. Odontogenic keratosis
   k. Behavioral and developmental abnormalities
      i. Failure to thrive in infancy (40%)
      ii. Motor developmental delay (26%)

iii. Learning disability with specific visual-constructional problems and verbal-performance discrepancy (15%)
iv. Language delay (20%) secondary to perceptual motor disabilities, mild hearing loss (12%), or articulation abnormalities (72%)
v. Intelligence
a) IQ: 64–127 with a median of 102
b) IQ: ten points below that of unaffected family members
c) Mild mental retardation reported in up to 35% of cases

2. Changing phenotype with age (Allanson 1987)
a. Newborn period
i. Marked edema
a) Contributing to a normal-to-high birth weight
b) Rapid reduction after birth simulating failure to thrive
ii. Excess nuchal skin
iii. Sloping and broad forehead
iv. Apparent ocular hypertelorism
v. Downslanting palpebral fissures
vi. A deep philtrum
vii. Mild retrognathia
viii. Posteriorly angulated ears with a thick helix
b. Neonatal period to 2 years
i. Head
a) Relatively large appearance
b) Flat malar eminence
c) Bitemporal narrowing accentuated by lateral supraorbital fullness
d) "Coarse" and occasional asymmetric facial appearance
ii. Eyes
a) Prominent and round
b) Ocular hypertelorism
c) Telecanthus
d) Lessening downslanting of the palpebral fissures
e) Occasional strabismus
f) Thick eyelid hooding the upper iris
g) Sharp arched eyebrows
iii. Nose
a) Depressed nasal root
b) Low nasal bridge
c) Wide nasal base
d) Bulbous nasal tip
e) Anteverted nares
f) Short columella
iv. Deep philtrum
v. Arched upper lip with high and wide peaks of the vermilion border
vi. Ears
a) Posteriorly rotated
b) Occasionally small or square
vii. Neck
a) Short
b) Less excess skin than in the newborn period
c) A low posterior hairline
viii. Often failure to thrive and hypotonia
ix. Occasional hepatosplenomegaly, swarthy skin, and wispy hair
x. 12–18 months of age
a) Changing body shape with stocky and square upper body
b) Occasional presence of an umbilical hernia or diastasis recti
c) The limbs becoming relatively longer and thinner secondary to resolving edema
d) Blunt finger tips
c. Childhood
i. Face
a) Appearance remaining coarse
b) Becoming more triangular as the chin lengthens
c) Forehead becoming lower and may be bossed
d) Flatter malar eminence
ii. Eyes
a) Less prominent eyes with reduced epicanthus
b) Increasing ptosis
c) Increasing lateral supraorbital fullness
d) Higher nasal root and bridge
iii. Full lips with sublabial protrusion
iv. Neck
a) Appearing longer
b) Accentuating webbing
c) Prominent trapezius
v. Thorax
a) Broad
b) An inverted pyramid shape
c) Increasing pectus

d) Upper chest length increases with relatively low-set nipples and axillary webbing which persist to adulthood.
vi. Scapula
a) Round shape
b) Winged scapulae
vii. Limbs
a) Thin
b) Marked cubitus valgus
c) Flat feet
viii. Skin
a) Lentigines
b) Nevi
c) Café-au-lait spots
ix. Often markedly curly or woolly hair
d. Teenage and young adulthood
i. Facial shape becoming increasingly triangular
ii. Facial features becoming sharper
iii. Less prominent eyes with occasional ptosis
iv. Nose
a) Thinner
b) A pinched root
c) Higher bridge
d) Wide base
e) Pointed tip
f) A longer columella
v. Eyebrows becoming sparse
e. Older adulthood
i. Prominent nasolabial folds
ii. Higher anterior hairline
iii. Occasional sloping forehead
iv. Transparent wrinkled skin
f. Prominent abnormalities at all ages
i. Striking blue or blue-green irides
ii. Increased number of fingertip whorls
iii. Posteriorly angulated ears with a thick helix
iv. Characteristic pectus deformity
a) Pectus carinatum superiorly
b) Pectus excavatum inferiorly

3. Disorders clinically related to Noonan syndrome (Tartaglia et al. 2010)
a. LEOPARD syndrome
b. Cardiofaciocutaneous syndrome
i. A rare sporadic multiple congenital anomalies/mental retardation syndrome characterized by:
a) Failure to thrive
b) Severe feeding problems
c) Developmental delay
d) Short stature
e) Distinguished face
f) Abnormalities of the skin gastrointestinal tract and CNS
g) Cardiac defects (pulmonary stenosis, hypertrophic cardiomyopathy)
ii. Genetically heterogeneous, with mutations in the *KRAS*, *BRAF*, *MEK1,* and *MEK2* genes occurring in approximately 60–90% of affected individuals
c. Costello syndrome
i. Clinical features
a) Prenatal overgrowth
b) Followed by postnatal feeding difficulties and severe failure to thrive
c) Distinctive "coarse" facial features
d) Mental retardation
e) Short stature
f) Cardiac defects (pulmonary stenosis, hypertrophic cardiomyopathy)
g) Musculoskeletal (joint laxity) and skin abnormalities
ii. Caused by germline missense mutations in the *HRAS* proto-oncogene
iii. Other causative genes: *KRAS*, *BRAF*, and *MEK1*
d. Neurofibromatosis-Noonan syndrome (NFNS)
i. Most individuals with NFNS harbor an *NF1* mutation and that a single mutation can be sufficient to engender the trait.
ii. Double heterozygosity for *NF1* and *PTPN11* mutations rarely causes NFNS, and it is not yet clear how frequently mutations in other NS disease genes co-occur with *NF1* defects in the disorder.
iii. These findings support the view that NFNS is genetically distinct from NS and emphasize the extreme phenotypic variability associated with lesions in the *NF1* gene.
iv. The identification of specific *NF1* alleles recurring in NFNS, the evidence that these alleles cosegregate with the condition in families, and the observation of a peculiar mutational spectrum strongly suggest that the term "NFNS" does characterize a phenotypic variant of NF1, which manifests with a lower incidence of plexiform neurofibromas, skeletal anomalies, and internal tumors, in association with

hypertelorism, ptosis, low-set ears, and congenital heart defects.
v. Some of the mutations identified in patients with NFNS have also been reported in NF1 without any feature suggestive of NS.

e. Legius syndrome
i. Previously known as neurofibromatosis type 1–like syndrome.
ii. An autosomal dominant disorder.
iii. Clinical features.
a) Multiple axillary freckling
b) Café-au-lait spots
c) Macrocephaly
d) NS–like facial dysmorphism in some individuals
iv. Caused by loss-of-function mutations of the *SPRED1* gene, which encodes a negative modulator of RAS-MAPK signaling (Brems et al. 2007).
v. *SPRED1* mutational analysis of sporadic or familial cases with a diagnosis of NF1 or with a phenotype suggestive of the disorder indicates that mutations account for approximately 0.5–1% of *NF1* mutation-negative cases.

Diagnostic Investigations

1. Growth curves for males and females with Noonan syndrome now available
2. Echocardiography for previously described congenital heart defects
3. Electrocardiography
   a. A wide QRS complex
   b. Left axis deviation
   c. Giant Q wave
   d. A negative pattern in the left precordial leads
4. Radiography: pectus deformity
5. Renal ultrasound for renal anomalies
6. Coagulation studies when needed
7. Chromosome analysis: normal karyotype
8. Molecular genetic testing available clinically
   a. Mutations in the gene *PTPN11* identified in 50% of patients (familial and sporadic cases)
   b. Germline mutations
      i. Detected in 59% of patients with familial Noonan syndrome
      ii. Detected in 37% of individuals with sporadic Noonan syndrome

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Fifty percentage if a parent is affected
      ii. Low risk (<1%) if parents are not affected unless gonadal mosaicism is present in a parent
   b. Patient's offspring: 50% affected
2. Prenatal diagnosis
   a. Ultrasonography for pregnancies at 50% risk: no definitive ultrasonographic diagnostic criteria early in gestation.
      i. Septated cystic hygroma
      ii. Scalp edema
      iii. Polyhydramnios
      iv. Facial features
         a) Posteriorly angulated, apparently low-set ears
         b) Depressed nasal bridge
      v. Pleural and pericardial effusions
      vi. Cardiac defects
         a) Pulmonic stenosis
         b) Hypertrophic cardiomyopathy
      vii. Ascites
      viii. Hydrops fetalis
   b. Molecular genetic testing of fetal DNA extracted from amniocentesis or CVS for *PTPN11* mutations. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.
   c. Preimplantation genetic diagnosis: may be available for families in which the disease-causing mutation has been identified.
3. Management
   a. Plotting of growth parameters on growth charts for Noonan syndrome.
   b. Ophthalmological care.
   c. Cardiac management of congenital heart defects and hypertrophic cardiomyopathy.
   d. Hearing evaluation and management.
   e. Physical and occupational therapies for hypotonia.
   f. Speech therapy for articulation deficiencies.
   g. Infant stimulation program for developmental delay.
   h. Multidisciplinary developmental intervention program.

i. Hearing aids for sensorineural hearing loss.
j. Orthopedic management of musculoskeletal abnormalities.
k. Growth hormone treatment of short stature: final height not improved substantially in most patients. When long-term GH therapy is intended to promote growth in children with NS, it has to be considered in relation to the genotype, the effective promotion of growth and the potentially increased tumor risk (Binder 2009).
l. Successful pregnancy possible in women with Noonan syndrome.

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Fig. 1 (continued)

Fig. 1 Two boys (**a**–**d**; **e**–**f**) with Noonan syndrome showing various features: downslanting palpebral fissures, hypertelorism, short and webbed neck with a low posterior hairline, pectus, and cubitus valgus

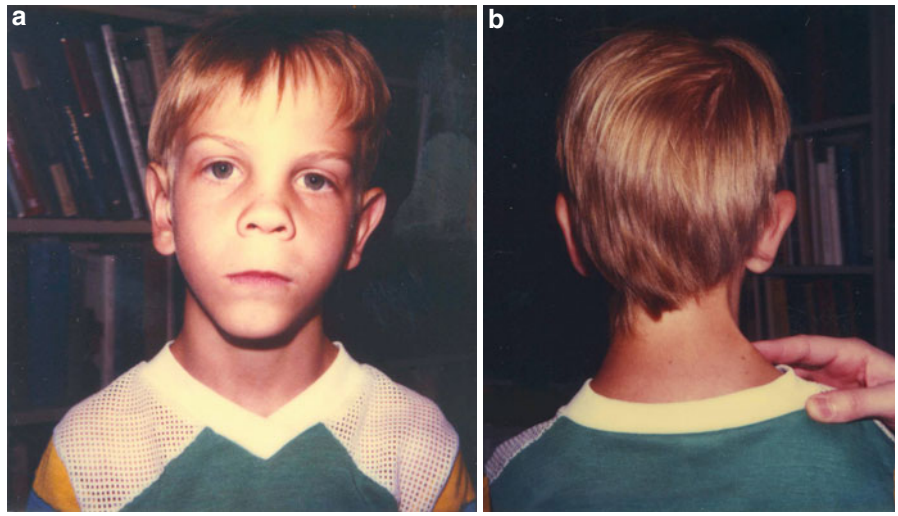

Fig. 2 (**a**, **b**) A boy with Noonan syndrome showing characteristic facial features and webbed neck

Fig. 3 Familial Noonan syndrome in a mother and a daughter

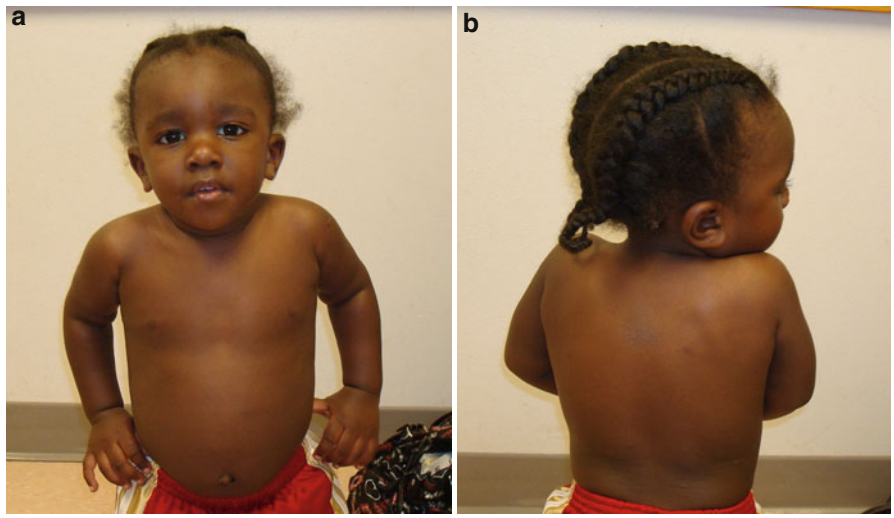

Fig. 4 (**a**, **b**) A 21-month-old boy was evaluated for possible Noonan syndrome because of antimongoloid slant of the palpebral fissures, depressed nasal bridge, slightly low-set ears, short neck, a shield-like chest with distally displaced nipples, and pulmonary stenosis. PTPN11 select exon analysis revealed a heterozygous G>A nucleotide substitution in exon 3, resulting in the replacement of a glycine codon (GGT) with a Serine codon (AGT) at amino acid position 60 of the tyrosine phosphatase SHP-2 protein (p.Gly60Ser or G60S) (c.178G>A)

Oblique Facial Cleft Syndrome

Oblique facial clefts are extremely rare congenital anomalies occurring in about 1/100 to 12/1,000 of facial clefts (Rintala et al. 1980).

Synonyms and Related Disorders

Mandibular process clefts; Naso-ocular clefts; Oculomaxillofacial dysplasia with oblique facial cleft; Oro-aural clefts; Oro-ocular clefts; Tessier clefts

Genetics/Basic Defects

1. Genetic heterogeneity (Richieri-Costa and Gorlin 1994).
   a. Sporadic in most cases
   b. A disruptive event resulting from amniotic band rupture sequence considered as a main etiological agent (Coady et al. 1998)
      i. Twenty six percentage of nonsyndromal craniofacial cleft displays congenital limb anomalies.
      ii. Thirteen percentage of nonsyndromal craniofacial cleft shows evidence of limb ring constrictions.
   c. Occasional association with malformation syndrome (e.g., Fryns anophthalmia-microphthalmia-oblique clefting syndrome)
   d. Rare autosomal recessive inheritance
2. Classification of facial clefts: A universally accepted classification scheme that fully encompasses, accurately describes, and integrates all the various types of orofacial and craniofacial clefts does not exist (Stellzig et al. 1997: Eppley et al. 2005).
   a. The American Association for Cleft Palate Rehabilitation (1962) divided facial clefts into four major groups according to the anatomic location.
      i. Mandibular process clefts
      ii. Naso-ocular clefts
      iii. Oro-ocular clefts
      iv. Oro-aural clefts
   b. Boo-Chai (1990) proposed a subdivision of the oro-ocular group into:
      i. Medial (Type I)
      ii. Lateral (Type II)
   c. Tessier (1976) presented an anatomic classification of the facial clefts by using numbers 0–14 anticlockwise to point the location of the cleft when the orbit is used as the central point.
      i. Commonly used by surgeons because it is purely descriptive and makes no pretense at causation and developmental relationships.
      ii. Proven validity in analyzing complex facial deformities.
      iii. Careful examination in confirming the diagnosis and in managing the patients.
      iv. The Tessier classification includes numbered clefts from 0 (midline cleft of the lip and nose) to 30 (clefting of lower face or a mandibular cleft).
      v. Tessier cleft numbers 4, 5, and 6 are oro-ocular clefts.
      vi. Tessier cleft numbers 7, 8, and 9 are lateral facial or commissural clefts.
      vii. The oblique clefts: indicated by Tessier cleft numbers 3 through 5 (Eppley et al. 2005).

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3. Classification of orofacial clefts (Tolarová and Cervenka 1998).
   a. Isolated anomaly (61.63%)
      i. Cleft lip
      ii. Cleft lip and palate
      iii. Cleft palate
      iv. Atypical facial cleft
   b. Sequence (3.9%)
      i. Robin sequence
      ii. Holoprosencephaly sequence
      iii. Frontonasal dysplasia sequence
      iv. Amyoplasia congenital disruption sequence
   c. Chromosome aberrations (8.79%)
      i. Trisomy 21 syndrome
      ii. Trisomy 13 syndrome
      iii. Trisomy 18 syndrome
      iv. Other trisomies
      v. Other chromosomal aberrations
   d. Monogenic syndromes (6.02%)
      i. Autosomal dominant
         a) Stickler syndrome
         b) Craniosynostosis syndromes
         c) Van der Woude syndrome
         d) Others
      ii. Autosomal recessive
         a) Smith-Lemli-Opitz syndrome
         b) Meckel syndrome
         c) Others
      iii. X-linked dominant
   e. Known environmental cause (0.2%)
      i. Fetal alcohol syndrome
      ii. Dilantin embryopathy
      iii. Congenital syphilis
   f. Associations (0.79%)
      i. CHARGE association
      ii. VATER association
   g. Multiple congenital anomalies (MCA) (18.5%)
      i. MCA of malformation origin
      ii. MCA of deformation origin
      iii. MCA of malformation and malformation origin
      iv. MCA of other combinations
   h. Conjoined twins
4. Oblique clefts
   a. Considered as late or secondary defects resulting from outgrowth of one or more bone centers in membranous bones
   b. Including certain types of Tessier classification (1976): oblique clefts corresponding to the numbers 3–6 distally or "southward" and 8–11 proximally or "northward" from the orbit in the extreme forms (Rintala et al. 1980)
   c. Arbitrary classification in some instances
   d. Presence of intermediate forms of facial clefts

Clinical Features

1. Clinical variability
2. Oblique facial clefts
   a. Naso-ocular clefts
      i. Whole stretch from the lip through the nose to the eyelid and orbit
      ii. Nasolacrimal duct always involved
      iii. Defective and upwardly dislocated ala nasi
   b. Oro-ocular clefts
      i. Type I (medial): cleft medial to infraorbital region of the nasolabial groove to end in the inner canthus or the lower eyelid
      ii. Type II (lateral): cleft extending from the angle of the mouth upward to the orbit ending in the lateral canthus or in a coloboma in the midportion of the lower eyelid
      iii. Twice as frequent as the naso-ocular types
   c. Bilateral clefts in 20–35% of cases
   d. Presence of complete or incomplete forms
   e. Possible involvement of palate and extending into the temporal region
3. Concordant clinical signs
   a. Short stature
   b. Sparse eyebrows
   c. Sparse eyelashes
   d. Lower lid coloboma
   e. Abnormal nose
   f. Involvement of the nasolacrimal duct
   g. Malar hypoplasia
4. Other variable clinical signs
   a. Mental retardation
   b. Anophthalmia/microphthalmia
   c. Hemimelia (possibly resulting from in utero vascular accident in some cases)
5. Associated anomalies
   a. Amniotic bands
      i. Amniotic band affecting premaxillary-nasal-ocular areas of the midface producing oblique tissue disruptions
      ii. Intrauterine amputation

iii. Constriction rings
iv. Distal lymphedema
v. Distal pseudosyndactyly
vi. Remnant of amniotic band still attached to the lesion

b. CNS abnormalities
i. Encephalocele
ii. Hydrocephaly

c. Aplasia cutis congenita
d. Talipes equinovarus

Diagnostic Investigations

1. Radiography for craniofacial anomalies
2. Three-dimensional CT scan for visualization of the extent and location of the cleft
3. MRI of the brain for CNS anomalies
4. Blood for chromosome analysis to rule out chromosome etiology

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Recurrence risk not increased since most cases are sporadic, especially in a case where amniotic band rupture sequence is considered to be the etiologic factor
      ii. Recurrence risk possibly increased in occasional cases of autosomal recessive inheritance
   b. Patient's offspring: not increased
2. Prenatal diagnosis: possible by ultrasonographic documenting oblique facial cleft associated with other commonly associated anomalies (CNS anomaly, anophthalmia, and findings of amniotic band disruption sequence)
3. Management
   a. Early orthopedic treatment
      i. To achieve both the proper alignment of the maxillary segments and a reduction of cleft width in cases of unilateral cleft lip, alveolus, and palate
      ii. Presurgical orthopedic devices to approximate the distorted segments and to facilitate lip closure in the treatment of maxillary clefts
   b. Surgical repair of facial cleft (Chiong et al. 1981)
      i. General principle
         a) Accurate approximation of each tissue layer
         b) Meticulous layered closure to prevent loss of anatomical continuity and a depressed scar along the site of the operative procedure
         c) Multiple Z-plasty when the repair crosses lines of minimal skin tension or when there is loss of length
      ii. Closure of the cleft and reconstruction of the underlying bony deficiencies at a very early age
      iii. Followed by subsequent correction of orbital hypertelorism between the ages of 2–5 years
      iv. Followed by orthognathic correction of maxillary and mandibular deformities in the teens
   c. Multidisciplinary approach to early intervention

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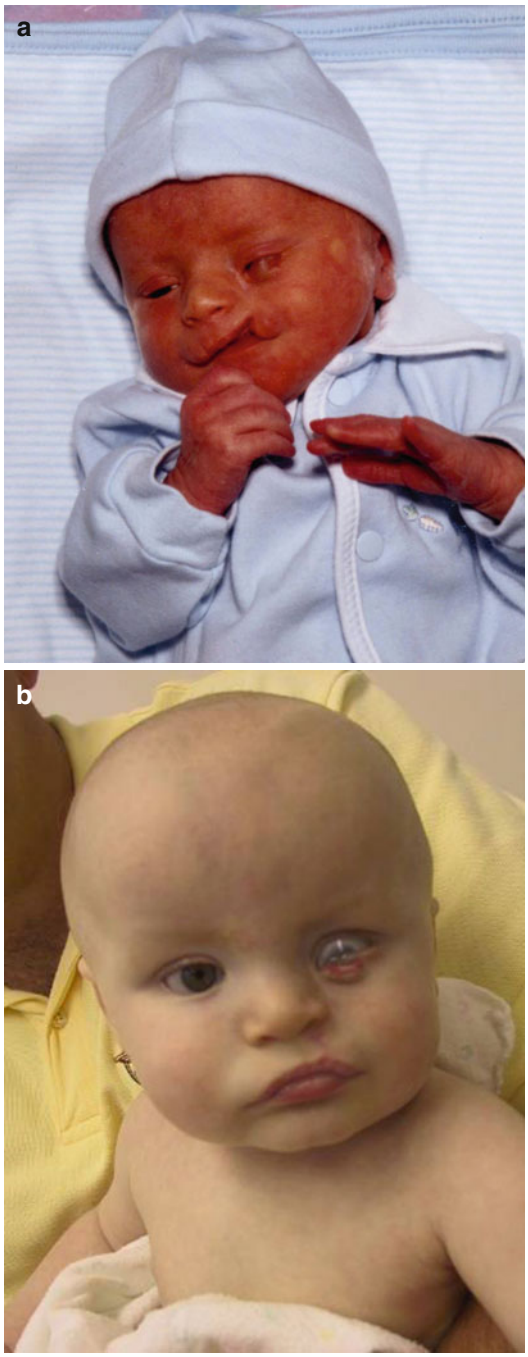

Fig. 1 (**a**, **b**) An infant with oblique facial cleft syndrome (at birth and postoperative) showing unilateral oro-ocular cleft with cleft beginning at the angle of the mouth and ending in a coloboma of the lower eyelid and corneal opacity

Fig. 2 (**a**, **b**) An infant with oblique facial cleft syndrome showing extensive unilateral oro-naso-ocular cleft and encephalocele

Fig. 3 (**a**–**c**) A newborn with oblique facial cleft syndrome associated with amniotic band syndrome and cutis aplasia congenita of the scalp showing bilateral frontonasal clefts, scalp defect, pseudotail, hypertelorism, anophthalmia, clubhands, digital amputation, constriction bands, and an amniotic band still attached to the left finger. The infant also had hydrocephalus, atrial septal defect, and clubfoot

Fig. 4 (**a**–**d**) A 4-year- and 11-month-old boy was seen for Tessier complex orofacial cleft. He was born without right eyeball, absent right nostril, and large oblique orofacial cleft. The photographs show before and after operations

Fig. 5 (**a**–**d**) An infant with Tessier number 7 cleft with a 3D reconstruction CT

Oligohydramnios Sequence

Oligohydramnios is defined as deficiency of amniotic fluid, i.e., decrease in the volume of amniotic fluid. It may result from decreased urinary production or excretion, or fluid loss from rupture of membranes. The incidence is estimated to be 0.5–8% of all pregnancies.

Genetics/Basic Defects

1. Associated maternal conditions (Peipert and Donnenfeld 1991)
   a. Ureteroplacental insufficiency
      i. Antiphospholipid antibodies
      ii. Chronic hypertension
      iii. Collagen vascular diseases
      iv. Diabetic vasculopathy
      v. Maternal hypovolemia
      vi. Preeclampsia/pregnancy-induced hypertension
   b. Drugs
      i. Prostaglandin synthetase inhibitors
      ii. Angiotensin converting enzyme inhibitors
   c. Placental
      i. Abruption
      ii. Twin-to-twin transfusion
   d. Maternal hydration status
2. Associated fetal conditions
   a. Renal malformations
      i. Bilateral agenesis
      ii. Bilateral cystic dysplasia
      iii. Unilateral cystic dysplasia/agenesis
      iv. Meckel syndrome
      v. Infantile polycystic kidneys
      vi. Renal tubular dysgenesis (Lacoste et al. 2006)
         a) Probably an underrecognized disorder
         b) An autosomal recessive disorder
         c) Should be considered for fetuses who present early oligohydramnios, normal or nearly normal kidneys on ultrasound examination, and skull ossification defects
      vii. Posterior urethral valves
      viii. Renal hypoplasia
      ix. Horseshoe kidney
   b. Other congenital anomalies
      i. Amniotic band syndrome
      ii. Branchio-oto-renal syndrome
      iii. Cystic hygroma
      iv. Encephalocele
      v. Endocardial fibroelastosis
      vi. Holoprosencephaly
      vii. Hypophosphatasia (homozygous dominant form)
      viii. MURCS association
      ix. Sacral agenesis (caudal regression)
      x. Sirenomelia
      xi. VATER association
      xii. Others
   c. Chromosome abnormalities
      i. Trisomy 13
      ii. Trisomy 18
   d. Twin-to-twin transfusion syndrome ("stuck twin syndrome")
      i. A complication of monochorionic diamniotic twinning

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ii. One twin stucked because of severe oligohydramnios and compressed by the significant polyhydramnios associated with its co-twin
iii. Perinatal mortality associated with severe oligohydramnios/polyhydramnios sequence in a monochorionic twin pregnancy before 28 weeks: 70–100%

e. Intrauterine growth retardation
f. Intrauterine fetal demise
g. Postmaturity possibly caused by a decline in placental function
h. Rupture of membranes: the most common cause of oligohydramnios
   i. Preterm
   ii. Prolonged
i. Idiopathic

3. Dynamic of amniotic fluid
   a. Presence of amniotic fluid throughout gestation
      i. Enables normal development of the fetal respiratory, gastrointestinal, and urinary tracts and musculoskeletal system
      ii. Continued fetal growth in a nonrestricted, sterile, and thermally controlled environment
      iii. Amniotic fluid volume is gestational-age dependent.
   b. Factors contributing to the formation and removal of amniotic fluid
      i. Formation
         a) Fetal urination
         b) Tracheal secretions
         c) Intramembranous pathway including transfers between amniotic fluid and fetal blood perfusing the fetal surface of the placenta, fetal skin, and umbilical cord
         d) Transmembranous pathway involving direct exchange across the fetal membranes between amniotic fluid and maternal blood within the uterus
      ii. Removal: fetal swallowing
   c. Significance of oligohydramnios
      i. A sign of potential fetal compromise
      ii. Associated with an increased incidence of adverse perinatal morbidity and mortality, especially in conjunction with the following:
         a) Structural fetal anomalies
         b) Fetal growth restriction
         c) Post dates pregnancies
         d) Maternal disease

Clinical Features

1. Consequences of severe fetal constraints secondary to early and prolonged oligohydramnios
   a. Potter facies: associated with renal agenesis and any other cause of severe oligohydramnios
      i. Hypertelorism
      ii. Deep crease under the eyes
      iii. Epicanthal folds
      iv. Flat nose
      v. Receding chin
      vi. Low-set, aberrantly folded ears
   b. Lung hypoplasia
      i. Respiratory insufficiency
      ii. Death
   c. Limb positional anomalies
      i. Arthrogryposis
      ii. Spade-like hands
      iii. Talipes equinovarus
   d. Intrauterine growth retardation: one of the most common complications associated with sever oligohydramnios
2. Presence of fetal abnormalities in cases associated with severe oligohydramnios (Shipp et al. 1996)
   a. 50.7% in the second trimester
   b. 22.1% in the third trimester
   c. Rate of aneuploidy: at least 4.4%
3. Correlation of the rate of survivors and the gestation when the severe oligohydramnios is diagnosed
   a. 10.2% survivors in the second trimester
   b. 85.6% survivors in the third trimester

Diagnostic Investigations

1. Ultrasonography
   a. Ultrasonographic modalities to assess oligohydramnios
      i. Single deepest vertical pocket (range: <0.5 to <3 cm)
      ii. Two-diameter pocket (vertical X horizontal <15 cm)
      iii. Amniotic fluid index (AFI) (range: <5 to <8 cm)
   b. Defines oligohydramnios
      i. Amniotic fluid index less than 7 cm
      ii. Absence of a fluid pocket of 2–3 cm in depth
   c. Assesses fetal growth

   d. Visualizes fetal kidneys, collecting system, and bladder
   e. Improves fetal structures by amnioinfusion
2. Chromosome analysis for aneuploidy
3. Autopsy for verification of etiology

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: depends on etiology
   b. Patient's offspring: depends on etiology
2. Prenatal diagnosis
   a. Ultrasonography
   b. Amniocentesis
3. Management
   a. Maternal bed rest
   b. Maternal hydration
   c. Serial amnioinfusions to prevent pulmonary hypoplasia (complications including preterm labor, amnionitis, and perinatal deaths)
   d. The risks of maintaining the fetus in utero must be weighed against the morbidities and mortalities of premature delivery.
   e. Bilateral renal disease with oligohydramnios indicates significant global fetal renal dysfunction and is a risk factor for the development of pulmonary hypoplasia. This is in striking contrast to the dramatic progress that has been made in neonatal intensive care including pulmonary management.
   f. Recent advances in treatment of infants and children with chronic kidney disease and end-stage renal disease has improved prognosis and also for infants with renal insufficiency considerably (Klaassen et al. 2007).

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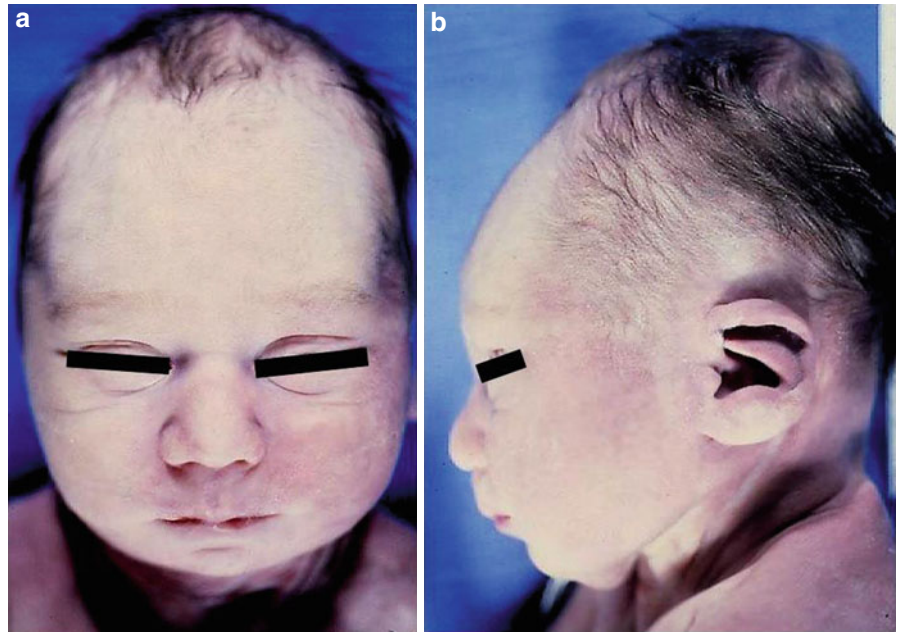

Fig. 1 (**a**, **b**) An infant with renal agenesis and oligohydramnios showing characteristic Potter facies

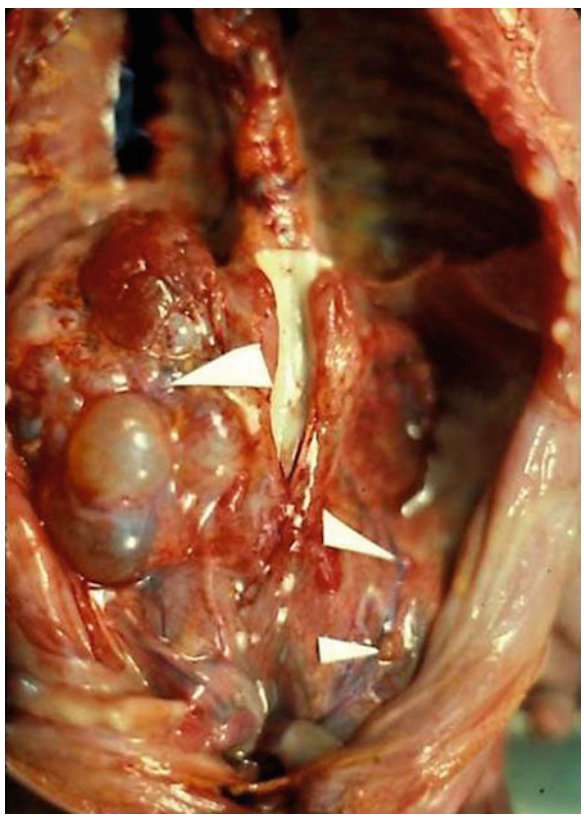

Fig. 2 Multicystic/dysplastic kidneys (*arrows*) causing oligohydramnios

Fig. 3 (**a**–**d**) An infant with caudal regression showing Potter facies, anal atresia, arthrogryposis, and talipes equinovarus

Omphalocele

Omphalocele is a congenital herniation of viscera into the base of the umbilical cord, covered by a membranous sac. The incidence of omphalocele is approximately 1 in 4,000 births.

Genetics/Basic Defects

1. Embryogenesis: Failure of the cranial, caudal, and lateral folds to fuse before myotome invasion is the most likely explanation for the failure of physiologically herniated midgut returning to the abdomen during the first trimester.
2. Inheritance
   a. Usually sporadic
   b. Single-gene disorders associated with omphalocele (Chitayat et al. 1997)
      i. Autosomal recessive disorders
         a) Agonadism with multiple internal malformation
         b) Agonadism, XY, with mental retardation, short stature, retarded bone age, and multiple extragenital malformations
         c) Craniostenosis-mental retardation syndrome of Lin and Gettig
         d) Hydrocephalus with associated malformation
         e) Hydrolethalus syndrome
         f) Malpuech facial clefting syndrome
         g) Omphalocele-exstrophy-imperforate anus-spinal defects (OEIS): also known as exstrophy of the cloaca occurring in about 1 in 100,00–400,000 pregnancies (Carey et al. 1978)
         h) Omphalocele-cleft palate
         i) Opitz C syndrome
      ii. Autosomal dominant disorders
         a) Beckwith–Wiedemann syndrome
         b) Omphalocele
         c) Shprintzen syndrome
      iii. X-linked recessive disorders
         a) Cranioorodigital syndrome
         b) Melnick–Needles osteodysplasty
         c) Omphalocele
         d) Simpson–Golabi–Behmel syndrome
         e) Thoracoabdominal syndrome
   c. Other malformation syndromes associated with omphalocele
      i. Caudal regression
      ii. Cornelia de Lange syndrome
      iii. Amniotic band syndrome
      iv. Limb body wall complex
      v. Megacystic microcolon
      vi. Schisis association
      vii. Skeletal dysplasias
   d. Chromosome disorders associated with omphalocele (25%) (Frolov et al. 2010)
      i. Trisomy 1q
      ii. Trisomy 3q
      iii. Trisomy 13
      iv. Trisomy 18
      v. Trisomy 21
      vi. Trisomy 16
      vii. Add(15)
      viii. Turner syndrome
      ix. Del(4q)
      x. Del(9)(p22)
      xi. Del(18p)

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xii. Del(21p)
xiii. Diploid-triploid mixoploidy
xiv. Inv(2)(p11q12)
xv. Inv(3)(p13q11)
xvi. Inv(16)(p11.1q11.2)
xvii. 47,XXX

Clinical Features

1. General features
   a. Prematurity
   b. IUGR
2. Herniated sac
   a. Size ranging from 2 to 10 cm
   b. Covering avascular sac consists of fused layers of peritoneum and amnion.
   c. Contents of hernia include thoracic and abdominal viscera.
      i. Liver
      ii. Large intestine
      iii. Small intestine
      iv. Stomach
      v. Gall bladder
      vi. Urinary bladder
      vii. Pancreas
      viii. Spleen
      ix. Internal genitalia
   d. The sac may be torn or ruptured (10–20%).
   e. Necrotizing enterocolitis and malabsorption only if sac is ruptured
3. Umbilical cord inserting into the apex of the sac
4. At increased risk for associated anomalies or syndromes (45–67%)
   a. Cleft lip/palate
   b. Gastrointestinal abnormalities
      i. Diaphragmatic hernia
      ii. Midgut volvulus
      iii. Meckel diverticulum
      iv. Intestinal atresia
      v. Intestinal duplication
      vi. Intestinal malrotation
      vii. Colonic agenesis
      viii. Imperforate anus
   c. Congenital heart defects
   d. Neural tube defects
   e. Genitourinary: exstrophy of the bladder
   f. Limb defects: absent radial ray
   g. Beckwith–Wiedemann syndrome
      i. Macroglossia
      ii. Hypoglycemia
      iii. Organomegaly
      iv. Gigantism
   h. Epigastric omphalocele associated with pentalogy of Cantrell
      i. Cardiac abnormalities
         a) Ventricular septal defect most common
         b) Occasional diverticulum of the left ventricle
      ii. Sternal cleft
      iii. Omphalocele
      iv. Anterior diaphragmatic hernia
      v. Ectopia cordis
5. Prognosis depending on:
   a. Size of the omphalocele
      i. Better prognosis with smaller defects
      ii. Intractable respiratory insufficiency in newborns with large omphaloceles
   b. Presence or absence of the associated anomalies
   c. Presence of chromosome anomalies

Diagnostic Investigations

1. Routine blood work
2. Abdominal radiography
3. Abdominal ultrasound
4. Echocardiography
5. Chromosome analysis
6. Initiate studies for associated single-gene disorder or malformation syndrome

Genetic Counseling

1. Recurrence risk: depends on the mode of transmission and associated chromosome anomalies
2. Prenatal Diagnosis
   a. Elevated maternal serum alpha-fetoprotein
   b. Prenatal 2D ultrasonography
      i. Maternal polyhydramnios
      ii. A circumscribed mass containing liver and/or intestines at the cord insertion site
      iii. Covering sac composed of amnion and peritoneum
      iv. Ruptured omphalocele: a rare complication

v. Identifies other malformations and allows diagnosis of recognizable syndromes such as pentalogy of Cantrell and prune belly syndrome

c. Prenatal 3D ultrasonography
   i. A useful complement to 2D ultrasonography
   ii. Improved definition of omphalocele
   iii. Identifies other malformations and allows diagnosis of recognizable syndromes such as pentalogy of Cantrell and prune belly syndrome
   iv. Allows isolation and better evaluation of the anomalous structure of interest when there is oligohydramnios or fetal contact with the uterine wall or placenta
d. Fetal echocardiography for evaluation of cardiac anomalies
e. Fetal MRI (Mann et al. 2008)
   i. Useful for viewing anatomical details where visualization is limited by maternal body habitus or amniotic fluid volume (Pumberger et al. 2003)
   ii. Volumetric calculations of lung volume (Cannie et al. 2006)
   iii. Evaluation of abdominal contents (Takada et al. 2006)
f. Amniocentesis
   i. Elevated amniotic fluid alpha-fetoprotein
   ii. Positive acetylcholinesterase
g. Chromosome analysis
   i. Amniocentesis
   ii. CVS
   iii. Fetal blood sampling

3. Management (Mann et al. 2008)
   a. Mode of delivery: Owing to the potential intrapartum risk of dystocia, sac rupture, and trauma to abdominal viscera, delivery of fetuses with giant omphaloceles should be by cesarean section.
   b. Attempts at primary repair: difficult due to a small abdominal cavity resulting from extraabdominal location of the viscera in utero
   c. Emergency care
      i. Insertion of an orogastric tube
         a) To decompress the stomach
         b) To prevent swallowed air from causing bowel distention
      ii. Cover the intact omphalocele sac with a sterile dressing and protect it from injury or rupture: Rupture of the sac increases the risk of infection and can lead to intestinal or hepatic trauma but, worse, destroys options for delayed closure strategies.
      iii. Administer intravenous fluids and parenteral antibiotics
      iv. Assess cardiorespiratory status and additional anomalies
   d. Direct primary closure of the abdominal wall for small omphalocele (2 cm)
   e. Staged closure: using a Dacron-reinforced Silastic silo as a temporary housing for the bowel for medium to large omphalocele

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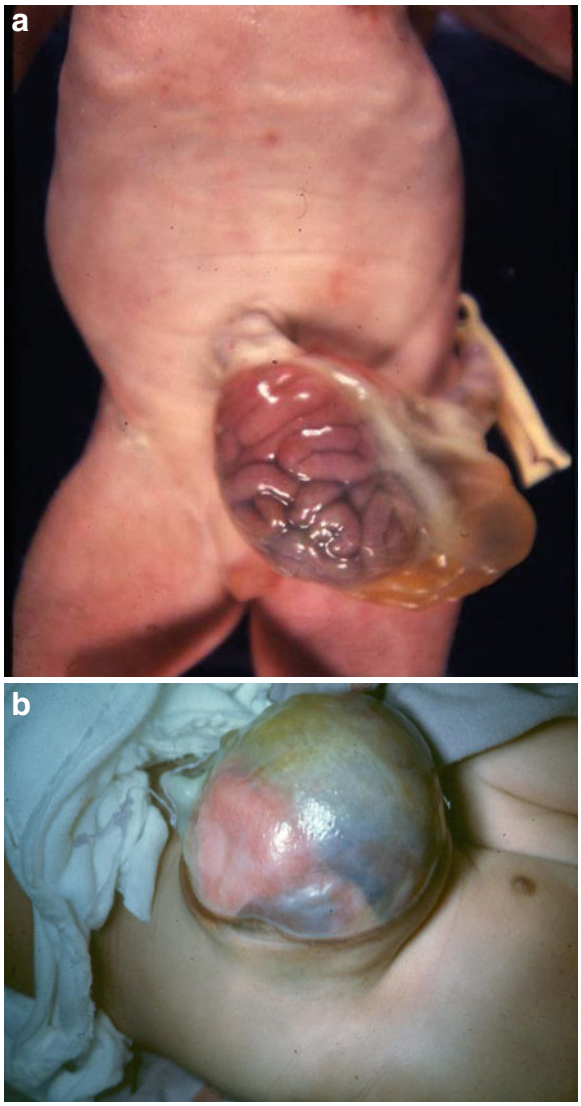

Fig. 1 (**a**, **b**) Two infants with omphalocele showing a sac containing bowel and other abdominal contents

Fig. 2 A 16-week-old fetus with omphalocele showing a sac containing bowel

Fig. 3 A fetus with omphalocele showing the umbilical cord attaching to the apex of the sac

Fig. 4 A neonate with a large ruptured omphalocele. The remnant of omphalocele sac is visible between the herniated viscera and the abdominal wall. The infant had body stalk anomaly

Oral–Facial–Digital Syndrome

In 1941, Mohr reported a family in which the propositus had oral (high-arched palate, lobate tongue with papilliform outgrowths), facial (broad nasal root, hypertelorism), and digital (syndactyly, brachydactyly, polydactyly of the hands and feet) findings. This report was the first description of an oral–facial–digital syndrome (OFD). Mohr concluded that the condition was due to sex-linked recessive sublethal gene. A later report of the same family identified a similarly affected individual born to consanguineous parents, thus leading to the conclusion that the condition was inherited as an autosomal recessive trait, now known as OFD II or Mohr syndrome.

A similar phenotype, described by Papillon-Leage and Psaume in 1954, was identified as an X-linked dominant trait, now known as OFD I. After the identification of OFD I and OFD II, the phenotype spectrum was further expanded with extra oral–facial–digital manifestations, leading to the definition of the new types. To date, 13 types have been distinguished based on the characteristic clinical manifestations. The oral–facial–digital syndromes result from the pleiotropic effect of a morphogenetic impairment affecting almost invariably the mouth, face, and digits.

Synonyms and Related Disorders

Orofacialdigital syndrome (OFD); OFD I (papillon-Leage-Psaume syndrome); OFD II (Mohr syndrome); OPD III (Sugarman syndrome); OFD IV (Mohr-Majewski syndrome); OFD V (Thurston syndrome); OFD VI (Varadi-Papp syndrome); OFD VII (Whelan syndrome); OFD VIII (Edwards syndrome); OFD IX (Gurrieri syndrome); OFD X (Figuera syndrome); OFD XI (Gabrielli syndrome); OFD XII (Moran-Barroso syndrome); OFD XIII (Degner syndrome)

Genetics/Basic Defects

1. OFD I (Papillon-Leage–Psaume syndrome): X-linked dominant (lethal in males): *OFD1* is the only gene currently known to be associated with oral–facial–digital syndrome type I.
2. OFD II (Mohr syndrome): autosomal recessive
3. OFD III (Sugarman syndrome): autosomal recessive
4. OFD IV (Mohr–Majewski syndrome, Baraitser–Burn syndrome): autosomal recessive
5. OFD V (Thurston syndrome): autosomal recessive
6. OFD VI (Varadi–Papp syndrome): autosomal recessive
7. OFD VII (Whelan syndrome): autosomal or X-linked dominant
8. OFD VIII (Edwards syndrome): possibly X-linked recessive
9. OFD IX (Gurrieri syndrome): autosomal recessive
10. OFD X (Figuera syndrome): autosomal dominant
11. OFD XI (Gabrielli syndrome): possibly autosomal recessive
12. OFD XII (Moran–Barroso syndrome): possibly autosomal recessive
13. OFD XIII (Degner syndrome): possibly autosomal recessive

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Clinical Features

1. OFD I (Papillon-Leage–Psaume syndrome) (Gurrieri et al. 2007)
   a. Characterized by anomalies of the face, oral cavity, and digits with a high degree of phenotypic variability even within the same family, possibly due to different degrees of somatic mosaicism resulting from random X-inactivation
   b. Abnormalities of the oral cavity: primarily affecting the tongue, palate, and teeth
      i. Lobed tongue often described as bifid or trifid
      ii. Tongue nodules, usually hamartomas or lipomas, also occur in at least one third of individuals.
      iii. Ankyloglossia attributable to a short lingual frenulum common
      iv. Cleft hard or soft palate, submucous cleft palate, or highly arched palate: occurring in more than 50% of affected individuals
      v. Trifurcation of the soft palate reported
      vi. Alveolar clefts and accessory gingival frenula are common. These fibrous bands are hyperplastic frenula extending from the buccal mucous membrane to the alveolar ridge, resulting in notching of the alveolar ridges.
      vii. Dental abnormalities include missing teeth (most common), extra teeth, enamel dysplasia, and malocclusion.
   c. Craniofacial abnormalities
      i. Median pseudoclefting of the upper lip
      ii. Irregular margin of the lips
      iii. Facial asymmetry
      iv. Downslanting palpebral fissures
      v. Ocular hypertelorism
      vi. Telecanthus
      vii. Micrognathia
      viii. Broadened nasal ridge
      ix. Hypoplasia of the malar bones and nasal alar cartilages
      x. Frontal bossing
      xi. Vanishing milia of the face and ears, usually disappear before the third year of life
      xii. Dryness, brittleness, and/or alopecia of the scalp hair
   d. Digital abnormalities
      i. Brachydactyly
      ii. Syndactyly of varying degrees
      iii. Clinodactyly of the fifth finger
      iv. The third (i.e., middle finger) showing variable radial or ulnar deviation
      v. Duplicated hallux (great toe) occurs in fewer than 50% of affected individuals, but if present is usually unilateral.
      vi. Preaxial or postaxial polydactyly of the hands occurring in 1–2% of affected individuals
      vii. Radiographs of the hands often demonstrate fine reticular radiolucencies, described as irregular mineralization of the bone, with or without spicule formation of the phalanges.
   e. Other associated anomalies
      i. CNS anomalies
         a) Microcephaly
         b) Intracerebral cysts
         c) Agenesis of the corpus callosum
         d) Cerebellar agenesis with or without Dandy–Walker malformation
         e) Type 2 porencephaly (schizencephalic porencephaly)
         f) Pachygyria and heterotopias
         g) Hydrocephalus
         h) Cerebral or cerebellar atrophy
         i) Berry aneurysms
      ii. Intelligence: about 50% of individuals with OFD1 with some degree of mental retardation or learning disability
      iii. Polycystic kidney disease: occurring in fewer than 50% of individuals with OFD1. Renal cysts can develop from both tubules and glomeruli, most often in adulthood.
2. OFD II (Mohr syndrome)
   a. Oral anomalies
      i. Cleft tongue
      ii. Tongue hamartomas
   b. Facial anomalies
      i. Bifid nasal tip
      ii. Median cleft of the upper lip
      iii. Ocular hypertelorism

c. Digital anomalies
   i. Bilateral upper extremity hexadactyly
   ii. Polysyndactyly of big toes
d. Features overlapping with OFD I
   i. Orofacial manifestations: tongue nodules, midline clefts of the lip, thick frenula, and dystopia canthorum
   ii. Digital manifestations: clinobrachydactyly, syndactyly, and polydactyly
e. Subtle clinical differences between types I and II
   i. Greater thickness of the alveolar ridge that in type I, which is normal in type II
   ii. Presence of hair and skin abnormalities in type I
   iii. Presence of bilateral polysyndactyly of the halluces in type II rather than unilateral polysyndactyly, which is usually found in type I
   iv. Conductive hearing impairment may occur in type II
   v. Central nervous system can also be affected in this form mainly with porencephaly and hydrocephaly
f. Distinctive difference in the mode of inheritance: OFD type II is caused by mutations of an as yet unidentified autosomal recessive gene vs. X-linked dominant inheritance in OFD type I.
g. Expanding phenotype spectrum in OFD type II: congenital heart defects such as atrioventricular canal and endocardial cushion defects
h. A Y-shaped central metacarpal, usually considered typical of OFD type VI, has also been reported in patients with clinical characteristics falling within the OFD II spectrum, suggesting the existence of transitional OFD types that may turn out to be allelic forms once the genetic defects of all OFD types are discovered.

3. OFD III (Sugarman syndrome): only two reports of this condition
   a. Oral, facial, and digital abnormalities
   b. Continuous alternating (ceaseless seesaw) winking of the eye lids
   c. Myoclonic jerks
   d. Polydactyly: postaxial
4. OFD IV (Mohr–Majewski syndrome, Baraitser–Burn syndrome) (oral–facial–digital syndrome with tibial defects)
   a. Minor facial anomalies
   b. Oral frenula, tongue nodules with or without lobulation
   c. Digital anomalies, including polydactyly and club feet
   d. Long bone anomalies limited to tibial defects (tibial dysplasia)
   e. Hearing loss
   f. Expansion of phenotypic spectrum
      i. Occipitoschisis
      ii. Brain malformation
      iii. Ocular colobomas
      iv. Intrahepatic cyst
      v. Renal cysts
      vi. Anal atresia
      vii. Joint dislocations
5. OFD V (Thurston syndrome)
   a. The mildest form within the OFD group
   b. Midline cleft lip
   c. Bilateral postaxial polydactyly of the hands and feet
   d. Reported exclusively in individuals of Indian ethnicity
6. OFD VI (Varadi–Papp syndrome)
   a. Distinguished features
      i. First report in endogamic gypsies
      ii. Oral, facial, and digital abnormalities
      iii. Cerebellar findings (vermis hypoplasia/aplasia, Dandy–Walker anomaly)
      iv. Y-shaped metacarpals: forked third or fourth metacarpals, indicating central polydactyly
      v. Expanded phenotype spectrum
         a) Penile agenesis
         b) Abnormal clavicles
         c) Absent pituitary gland
         d) Hypothalamic hamartoma with precocious puberty which is almost constantly found in Pallister–Hall syndrome, an autosomal dominant condition characterized by postaxial polydactyly, imperforate anus, and hypothalamic hamartoma. The phenotypic overlap between OFD VI and Pallister–Hall

syndrome has been noted, and lumping of the two conditions as the same entity has been proposed.
   e) GLI3 mutations identified in Pallister–Hall syndrome suggest that GLI3 analysis should also be carried out in patients with OFD VI to find out if these two conditions are allelic.
   f) A single report of neuropathologic findings in OFD VI showed disruption or dysgenesis of glial architecture, suggesting a primary glial cell defect. This observation is interesting in light of the recent discovery that OFD I is caused by a failure of the ciliary system, which is involved in cellular migration during embryogenesis.
7. OFD VII (Whelan syndrome): a single report of mother and daughter
   a. Facial (asymmetry), oral, and digital (polydactyly of hands and feet) anomalies
   b. Laryngeal anomalies
   c. Ear anomalies
   d. Hydronephrosis
   e. Possibly same entity as OFD 1 since mother and daughter later developed cystic kidney disease, although mutation analysis for OFD I failed to detect a pathogenic mutation
8. OFD VIII (Edwards syndrome)
   a. Clinically overlapped with OFD II
      i. Short tibia
      ii. Dystopia canthorum
   b. Distinguished from OFD II by X-linked recessive inheritance
9. OFD IX (Gurrieri syndrome)
   a. Retinal anomaly: a distinctive feature
   b. Digital anomalies: usually consist of hallucal duplication detectable radiologically
   c. Dandy–Walker malformation
10. OFD X (Figuera syndrome)
   a. Orofacial findings
   b. Digital findings
      i. Oligodactyly
      ii. Preaxial polydactyly
   c. Limb anomalies
      i. Mesomelic limb shortening, specifically due to radial hypoplasia
      ii. Fibular agenesis
11. OFD XI (Gabrielli syndrome): in addition to the oral, facial, and digital anomalies, this type is characterized by following craniovertebral anomalies
   a. Oral, facial, and digital anomalies
   b. Additional anomalies
      i. Midline cleft involving the palate, vomer, ethmoid, and crista galli
      ii. Apophysis
      iii. Vertebral malformations
         a) Fusion of vertebral arches in C1, C2, and C3
         b) Clefts of vertebral bodies
12. OFD XII (Moran–Barroso syndrome)
   a. Oral, facial, and digital anomalies
   b. Myelomeningocele
   c. Stenosis of the aqueduct of Sylvius
   d. Cardiac anomalies
13. OFD XIII (Degner syndrome)
   a. Oral, facial, and digital anomalies
   b. CNS anomalies
      i. Psychiatric symptoms (major depression)
      ii. Epilepsy
      iii. Brain MRI findings of leukoaraiosis (patched loss of white matter of unknown pathogenetic origin, possibly of ischemic nature, considered to increase the risk of stroke)

Diagnostic Investigations

1. Diagnostic approach
   a. First, ascertain oral, facial, and digital findings.
   b. Obtain family history to determine if a mode of inheritance can be established.
   c. In patients with clear X-linked dominant transmission and even in sporadic female patients, it is necessary to rule out mutations in the OFD1 gene.
   d. Additional studies to delineate specific type, given the fragmentary nosology of OFD
      i. Brain MRI
      ii. Abdominal ultrasound
      iii. Skeletal survey
      iv. Ophthalmologic evaluation
      v. Audiometric test
      vi. Chromosome analysis to detect submicroscopic rearrangements by array-CGH analysis
2. Diagnosis of OFD I
   a. Established at birth in some infants on the basis of characteristic oral, facial, and digital anomalies

b. Diagnosis is suspected in some patients only after polycystic kidney disease is identified in later childhood or adulthood
c. Molecular genetic testing (sequencing) of *OFD1*, the only gene currently known to be associated with OFD I: clinically available for confirmatory diagnostic testing and prenatal diagnosis of OFDI

3. Diagnosis of OFD VII (includes unilateral cleft lip and hydronephrosis, only been described in one mother–daughter pair, who were later found to have a mutation in *OFD1*): either allelic to OFD1 or demonstrates variable expression of OFD1

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal recessive (OFD types II, III, IV, V, VI, possibly types XI, XII, XIII)
         a) A 25% risk
         b) A 50% risk of being a carrier
      ii. Autosomal dominant (OFD X)
         a) A small recurrence risk if neither parent is affected
         b) A 50% risk if one parent is affected
      iii. X-linked dominant with male lethality (OFD I, OFD VII)
         a) Approximately 75% of affected individuals are simplex cases (no family history of OFD1).
         b) A female proband with OFD1 may have the disorder as the result of a de novo gene mutation; however, the proportion of cases caused by de novo mutations is unknown.
         c) If no family history of OFD1 exists, the risk that the unaffected mother of an affected female will have another female with OFD1 is less than 1%.
      iv. X-linked recessive (OFD VIII): risk to the sibs depending on the carrier status of the mother
         a) Mother is a carrier: a 50% of risk of having a male sib with OFD VIII
         b) Mother is not a carrier: a low recurrence risk
   b. Patient's offspring
      i. Autosomal recessive: a low recurrence risk unless the spouse is also affected or a carrier
      ii. Autosomal dominant: a 50% risk if the spouse is normal
      iii. X-linked dominant with male lethality
         a) At conception, the risk to the offspring of females with OFD1 of inheriting the disease-causing OFD1 allele is 50%; however, most male conceptuses with the disease-causing allele miscarry.
         b) At delivery, the expected sex ratio of offspring: 33% unaffected females, 33% affected females, and 33% unaffected males.
      iv. X-linked recessive
         a) No sons will be affected
         b) All daughters will be carriers
2. Prenatal diagnosis
   a. Prenatal ultrasound
      i. Prenatal diagnosis of OFD type II reported in a fetus
         a) Polydactyly with bifid thumbs in both hands
         b) Bilateral polysyndactyly of halluces
         c) Lateral polysyndactyly and bilateral pes equinovarus
      ii. Prenatal diagnosis of OFD type IV (Mohr–Majewski) possible: findings showing overlap between OFD type II (Mohr) and lethal short-rib–polydactyly syndrome type II (Majewski)
      iii. Prenatal ultrasound examination may detect structural brain malformations and/or duplication of the hallux.
   b. Molecular genetic analysis: prenatal diagnosis for families in which the disease-causing mutation has been identified is clinically available.
3. Management
   a. Surgery
      i. Cleft lip/palate
      ii. Tongue nodules
      iii. Accessory frenula
      iv. Polysyndactyly
      v. Removal of accessory teeth
      vi. Orthodontia for malocclusion
   b. Management of renal disease and seizures
   c. Speech therapy
   d. Special education
   e. Surveillance
      i. Annual monitoring of renal function
      ii. Speech and hearing assessment if cleft palate is present

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Fig. 1 Patient 1 with OFD I. Note the lingual frenulum and hypoplastic alar nasi

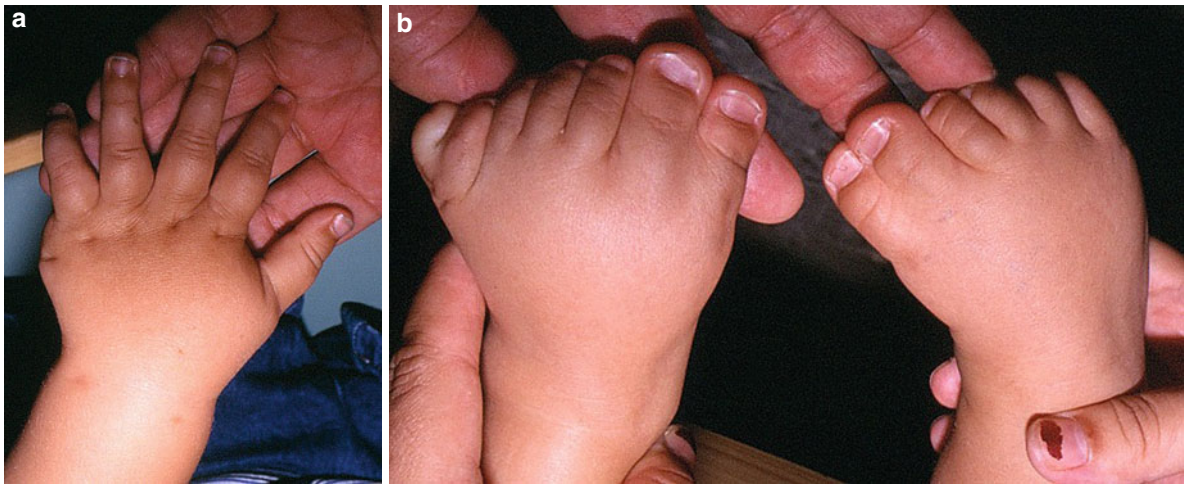

Fig. 2 (**a**, **b**) The patient's bilateral postaxial polydactyly of both hands, duplicated hallux of both feet, and postaxial polydactyly of the *left* foot

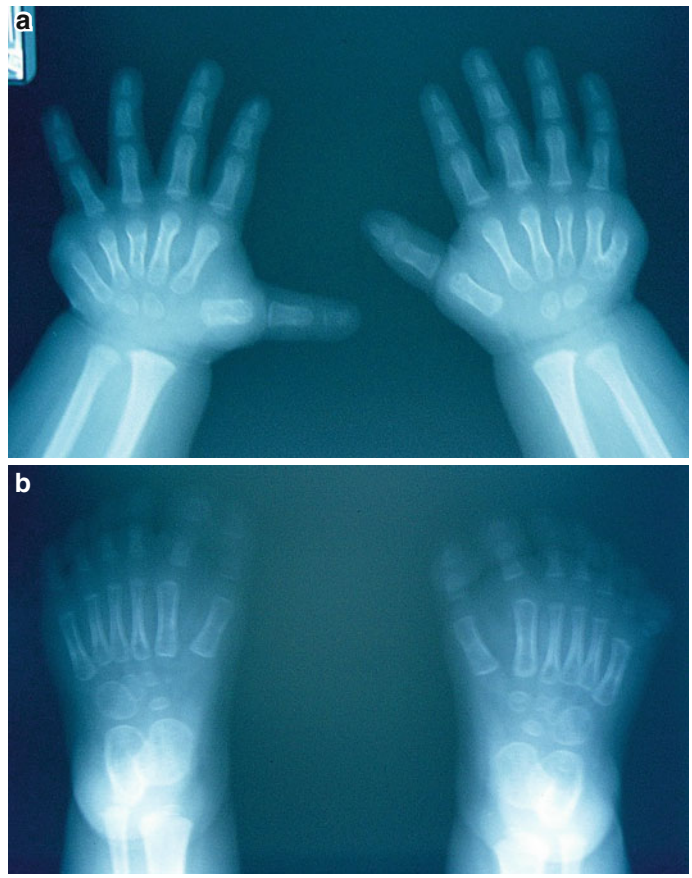

Fig. 3 (**a**, **b**) Radiographs of hands and feet of patient 1

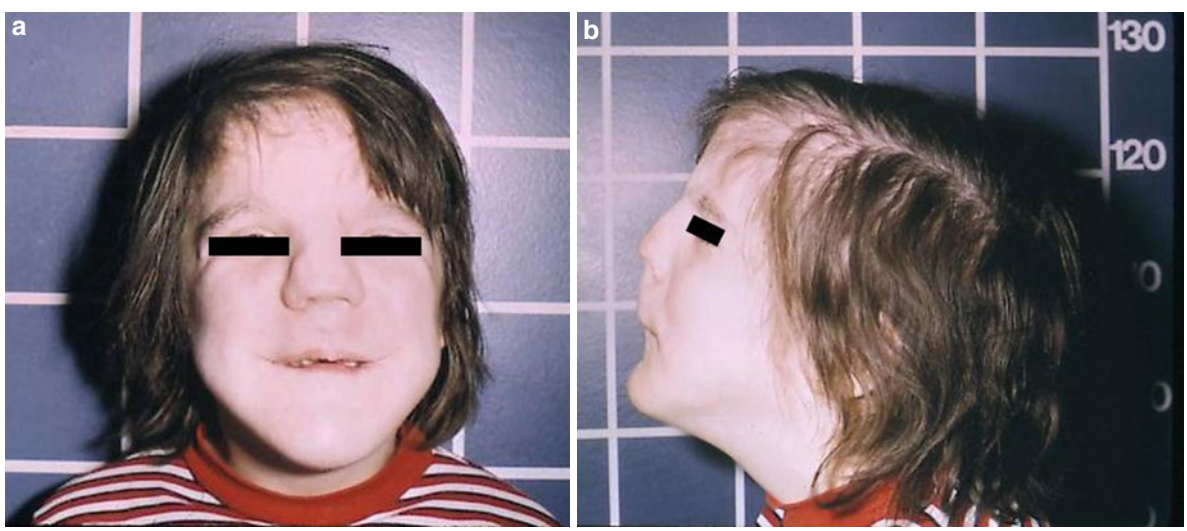

Fig. 4 (**a**, **b**) Patient 2 with OFD II. Note bifid nasal tip, medial cleft of the *upper* lip, and ocular hypertelorism

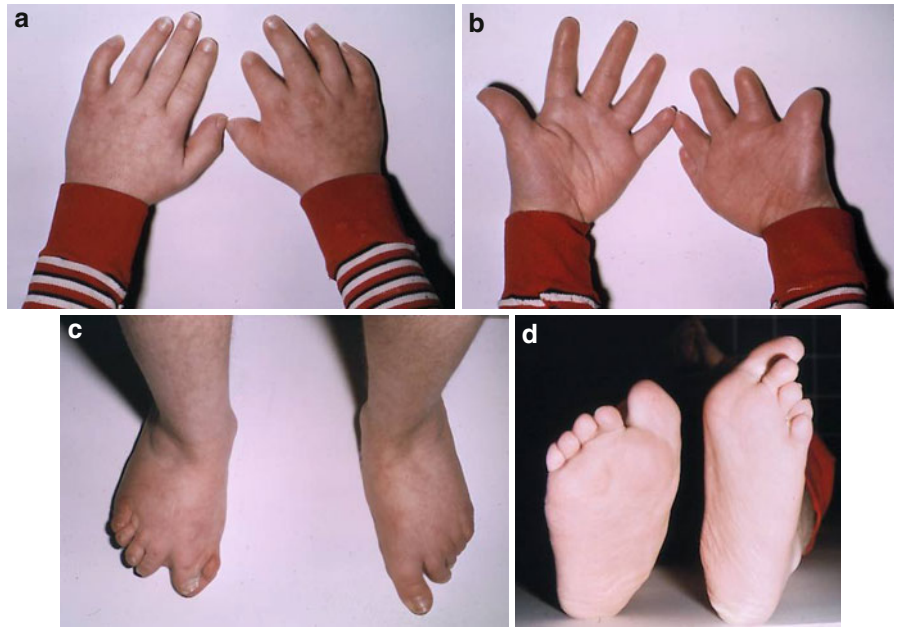

Fig. 5 (**a**–**d**) Note the clinobrachydactyly and syndactyly of the hands and polydactyly of the *right* hallux

Fig. 6 (**a**–**d**) Patient 3 with OFD II. Note the ocular hypertelorism, bifid tip of the nose, lingual frenulum, and brachysyndactyly

Fig. 7 (**a**–**d**) Patient 4 with unclassified OFD. Note frontal bossing, ocular hypertelorism, strabismus, pseudocleft of the upper lip, preaxial polydactyly of the hands, hepatomegaly, and genu valgum

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a generalized, hereditary disorder of connective tissue involving bone, tendon, ligament, fascia, and dentin, resulting from mutations affecting the amount or structure of type I collagen. OI affects about 1 in 10,000 individuals.

Synonyms and Related Disorders

Osteogenesis imperfecta with blue sclerae; Osteogenesis imperfecta with normal sclerae; Perinatal lethal osteogenesis imperfecta; Progressively deforming osteogenesis imperfecta with normal sclerae

Genetics/Basic Defects

1. Clinicopathological classification (Glorieux 2008; Basel and Steiner 2009): The classification system of Sillence et al. (1979b) divides OI into four severity-based types with type IV representing the most clinically diverse group. It is from this heterogeneous group that types V, VI, VII, and VIII have been identified on the basis of distinct clinical and histological features (Glorieux et al. 2000, 2002; Ward et al. 2002). The most clinically relevant characteristic of all types of OI is bone fragility, the severity of which increases in the order type I < types IV, V, VI, VII, VIII < type III < type II. Heredity follows an autosomal dominant pattern in types I through V, and is autosomal recessive in types VI, VII, and VIII. Mutations affecting collagen type I are usually present in types I through IV and types VII and VIII, but are absent in types V and VI. This classification scheme is likely to change as additional information is gathered on newly described forms caused by *CRTAP* and *LEPRE* mutations.
   a. OI I
      i. Autosomal dominant disorder
      ii. Fresh mutation in 15% of cases
      iii. The most common and mildest form of osteogenesis imperfecta
      iv. Estimated prevalence at between 1 in 10,000 and 1 in 25,000, or may be more frequent because of its relatively mild presentation and the possibility of underdiagnosis
   b. OI II
      i. Autosomal dominant disorder (new mutations in almost all instances)
      ii. The most severe form, resulting in death in the perinatal period
      iii. Autosomal recessive disorder (rare)
      iv. Further subdivided into IIA, IIB (same as type III), and type IIC
      v. Estimated frequency of 1 in 20,000–1 in 60,000 births
   c. OI III
      i. Autosomal dominant disorder
      ii. Autosomal recessive disorder (uncommon)
      iii. The rarest form of OI
      iv. Known as the progressive deforming form
   d. OI IV
      i. Autosomal dominant
      ii. The most clinically diverse group
      iii. Represents the moderately severe spectrum of OI
      iv. Marked intra/interfamilial variability of expression

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e. OI V
   i. The moderately deforming form
   ii. Associated mutations: unknown
f. OI VI
   i. The moderately to severely deforming form
   ii. Associated mutations: unknown
g. OI VII
   i. Overlaps with types II and III; milder forms also documented
   ii. Associated mutations: hypomorphic expression of *CRTAP*
h. OI VIII
   i. Overlaps with types II and III; milder forms also documented
   ii. Associated mutations: *LEPRE1*

2. Molecular basis
   a. Type I collagen
      i. Found in the skin, bone, tendons, and ligaments
      ii. Composed of three α chains (two α_1 chains and one α_2 chain)
      iii. Each α chain forms a helix which consists of three amino acids per turn.
      iv. The chains are held together by disulfide bonds at the C-terminal ends of the protein.
      v. There are three amino acids per turn in the helix.
      vi. Every third amino acid is glycine, giving a repeat of Gly-X-Y, where X and Y represent other amino acid residues.
         a) About 10% of the X residues are proline
         b) About 10% of the Y residues are hydroxyproline
      vii. A mutant collagen is produced by missense mutations that result in a substitution of the glycine residue by another amino acid.
   b. OI I
      i. Affected individuals produce only 50% of the normal amount of type I collagen, produced by the normal allele.
      ii. Mechanisms
         a) Splicing in α_1 gene
         b) Null mutation in α_1 gene
   c. OI II, OI III, and OI IV
      i. Affected individuals produce only 25% of the normal amount of type I collagen and 75% of mutant or defective collagen.
      ii. Mechanism: A missense mutation arises in the α_1 gene resulting in a defective α_1 chain which is incorporated into the final collagen molecule and destroys its function.
      iii. Severity of the disease
         a) Related to the position of the missense mutation within the gene and the amino acid substitution that occurs
         b) Generally, the disease is more severe when the mutation is closer to the C-terminal end of the protein.
   d. OI VII
      i. The disease has been assigned to chromosome 3p22–24.1 (Labuda et al. 2002).
      ii. Co-localizing with the gene encoding CRTAP, a cartilage-associated protein, whose expression is 90% reduced in homozygote patients (Morello et al. 2006)
3. OI VIII: caused by *LEPRE1* mutations
4. Allelic connective tissue disorders (Basel and Steiner 2009)
   a. Several patients have been described with joint hypermobility and skin laxity, a clinical phenotype more in keeping with Ehlers-Danlos syndrome but who have an increased disposition to fractures.
   b. Mutations not involving the glycine residues within the triple helix of COL1 and mutations involving cysteine residues have been described in a subset of these patients (Maifait et al. 2007, 2006; Cabral et al. 2007).
   c. N-terminal mutations in COL1 appear to result in abnormal protein folding, which leads to a milder OI/Ehlers-Danlos syndrome p (Makareeva et al. 2006).
5. Very few individuals or families share the same mutation, although more than hundreds of unique mutations of the type I collagen genes have been identified.
6. Phenotypic variations among different families and within same family

Clinical Features

1. OI type I (mild type) (Glorieux 2008)
   a. Fractures
      i. Rarely fracture in utero or in the perinatal period
      ii. Usual onset of fractures: when the child begins to walk

iii. A few to more than 50 fractures before puberty
iv. Number of fractures gradually decreases after puberty.
v. Involve any bones of the body, but primarily long bones of the arms and legs, ribs, and small bones of the hands and feet
vi. Increasing fractures often after menopause in affected women and in the sixth or eighth decades in affected men
vii. Healing rapidly with evidence of good callus formation and without deformity

b. Cranial features
i. Soft thin calvarium
ii. Wide fontanels
iii. Wormian bones
iv. Frontal and temporal bulging
v. Occipital flattening

c. Blue sclera (secondary to a thin sclera allowing partial visualization of the choroid)
i. Readily apparent at birth
ii. Gradually lightens to blue gray in the adulthood

d. Other ocular features
i. Occasional embryotoxon (opacity in the peripheral cornea)
ii. Occasional keratoconus or megalocornea

e. Teeth abnormalities
i. Rare dentinogenesis imperfecta
ii. Hypoplasia of pulp
iii. Yellow or gray teeth
iv. Susceptible to caries
v. Irregular placement
vi. Late eruption

f. Hearing loss
i. Early onset in about 50% of families beginning in late teens
ii. Gradually leading to profound hearing loss in the end of fourth or fifth decades secondary to otosclerosis
iii. Primarily conductive hearing loss in the early phase secondary to fractured and fused bones of the middle ear
iv. Early hearing loss typically of the high-frequency type resulting in a characteristic bifid compliance curve by tympanometry
v. Later hearing loss becoming mixed in type and surgical intervention may be less successful

g. Skin and joint abnormalities
i. Mild joint hypermobility
ii. Easy bruising
iii. Thinner translucent skin
iv. Capillary fragility
v. Inguinal or umbilical hernia
vi. Flat feet
vii. Joint dislocation
viii. Poorly developed muscles
ix. Decreased thrombocyte function leading to increased bleeding

h. Cardiovascular abnormalities
i. Mitral valve prolapse
ii. Aortic valvular insufficiency
iii. Slightly larger than normal aortic root diameter without significant risk of progression to dissection, identified in a small number of patients
iv. Increased bleeding tendency secondary to increased capillary fragility

i. Prognosis
i. Usually normal stature but may lose some height in later decades due to spine involvement
ii. In general, with good orthopedic cares, fractures heal quickly without deformities.
iii. No decrease in fertility or longevity in affected individuals

2. OI type II (perinatal lethal type)
a. Lethality during perinatal period resulting from:
i. Pulmonary insufficiency
ii. Congestive heart failure
iii. Infection

b. Prenatal history
i. Intrauterine growth retardation (dwarfism, low birth weight)
ii. Prematurity
iii. Nonimmune hydrops

c. Short-limbed dwarf
d. Characteristic craniofacial features
i. Extremely soft calvarium
ii. Dark-blue sclerae
iii. Beaked nose
iv. Micrognathia

e. Chest
i. Very small
ii. Beaded ribs
iii. Lung hypoplasia

f. Extremities
   i. Short and deformed limbs
   ii. Bowed legs
g. Hip: flexed and abducted (frog position)
h. Prognosis: death resulting from pulmonary insufficiency, congestive heart failure, or infection
   i. Usually during the first few hours of life
   ii. More than 60% of infants with OI type II during the first day
   iii. Eighty percent within the first month
   iv. Rare survival beyond a year

3. OI type III (progressively deforming type)
   a. Dwarfism and moderate deformities resulting from in utero fractures
   b. Craniofacial features
      i. Typical triangular faces
      ii. Relatively large cranium
   c. Fractures
      i. Very common
      ii. Progressive long bone deformities with growth
      iii. Marked deformities of most bones
   d. Significant kyphoscoliosis leading to cardiopulmonary insufficiency, a major cause of early death in these individuals
   e. Sclerae
      i. Often pale blue at birth
      ii. Generally becomes normal hue by puberty
   f. Abnormal dentinogenesis involving both primary and permanent teeth: common
   g. Hearing loss: common
   h. Prognosis
      i. Death resulting from cardiac decompensation, pulmonary insufficiency, or basilar impression with compression of the brain stem
      ii. Long-term survival possible with multiple fractures and deformities
      iii. Primary objective to lead a satisfying and productive life
      iv. Major limitations (severe bone fragility and deformity, muscle weakness, joint contractures that develop from inactivity, progressive scoliosis resulting in life-threatening cardiopulmonary decompensation, marked short stature)
4. OI type IV (moderately severe type)
   a. Significant intrafamilial and interfamilial phenotypic variation
   b. Fractures
      i. Occurring in utero, during labor and delivery, or in the newborn period
      ii. Fractures at birth, not observed in all affected infants
      iii. Some affected infants with only mild femoral bowing
      iv. Early recognition of these fractures is essential to prevent accusation of child abuse when the first fractures occur, and the previous, now healed, fracture(s) is/are detected by routine skeletal survey.
   c. Variable short stature
   d. Normal white or grayish sclera
   e. Occasional hearing loss
   f. Common dentinogenesis imperfecta
   g. Mild to moderate bone deformity
   h. Severe kyphoscoliosis may compromise cardiopulmonary function.
   i. Prognosis
      i. Life span near normal in the absence of severe cardiopulmonary complications
      ii. Treatment objectives (to minimize the long-term complications of kyphoscoliosis and to assure independence and mobility)
5. OI type V
   a. Represents 4–5% of the OI population seen in hospitals (Rauch and Glorieux 2004)
   b. Moderate to severe bone fragility (Glorieux et al. 2000)
   c. Does not have blue sclera or dentinogenesis imperfecta
   d. Distinctive clinical features
      i. Common occurrence of radial head dislocation/subluxation and calcification of the interosseous membrane between the radius and ulna (Lee et al. 2006; Fassier et al. 2007)
      ii. Frequent development of hypertrophic calluses at fracture sites
      iii. Calcification of the interosseous membranes between the bones of the forearm
      iv. Presence of a radio-opaque metaphyseal band immediately adjacent to the growth plates on x ray
      v. Upon histological examination, the bone organization has an irregular mesh-like appearance, clearly distinct from the normal lamellar pattern

e. The calcified interosseous membrane often severely limits the pronation/supination of the hand and may lead to secondary dislocation of the radial head.
f. The hyperplastic callus that may develop after fractures or surgical interventions may mimic osteosarcoma.

6. OI type VI
   a. Moderate to severe skeletal deformities: may represent in approximately 4% of moderately to severely affected OI patients (Rauch and Glorieux 2004)
   b. Clinically indistinguishable from OI type IV
   c. Does not have blue sclera or dentinogenesis imperfecta (Glorieux et al. 2002)
   d. Inheritance: autosomal recessive
   e. Distinctive histological features: The hallmark is abnormal bone mineralization on histological examination.
      i. The fish-scale-like appearance of the bone lamellae
      ii. The presence of excessive osteoid accumulation on bone-forming surfaces, suggesting a mineralization defect reminiscent of osteomalacia, but there is no abnormality in mineral homeostasis, and growth plate mineralization proceeds normally.
7. OI type VII
   a. Moderate to severe skeletal deformities and bone fragility
   b. Lacks blue sclera and dentinogenesis imperfecta
   c. Coxa vara may be present even in infancy.
   d. Distinctive clinical feature: rhizomelic shortening of the humerus and femur
   e. "Popcorn" epiphyses often seen in severe forms
   f. To date, only been observed in a community of Native Americans in northern Quebec, where it exhibits autosomal recessive inheritance
8. OI type VIII (Shapiro and Sponsellor 2009)
   a. Severe, lethal form
   b. Seen in South African blacks
   c. "Popcorn" epiphyses often seen in severe forms
9. Establishing a diagnosis (Basel and Steiner 2009): The following list of features would be typical in an individual presenting with OI:
   a. Family history of OI or recurrent fractures
   b. Fractures with minimal or no trauma in the absence of other factors, such as inflicted physical abuse or other known disorders of bone
   c. Short stature or stature shorter than predicted based on stature of unaffected family members, often with bone deformity
   d. Blue sclera
   e. Dentinogenesis imperfecta
   f. Progressive, postpubertal hearing loss
   g. Ligamentous laxity and other signs of connective tissue abnormality
   h. Family history of OI, usually consistent with autosomal dominant inheritance
   i. Fractures of varying ages and stages of healing, often of the long bones but may also involve ribs and skull. The metaphyseal chip fractures characteristic of child physical abuse can be seen in a small number of children with OI.
   j. "Codfish" vertebrae, which are the consequence of spinal compression fractures, seen primarily in the adult
   k. Wormian bones, defined as "sutural bones that are 6 mm by 4 mm (in diameter) or larger, in excess of 10 in number, with a tendency to arrangement in a mosaic pattern." Wormian bones are suggestive of, but not pathognomic, for OI. They are present in up to 60% of affected children.
   l. Protrusio acetabuli, in which the socket of the hip joint is too deep and the acetabulum bulges into the cavity of the pelvis causing intrapelvic protrusion of the acetabulum
   m. Low bone density detected by dual energy X-ray absorptiometry. There seems to be a correlation between bone mineral density and fracture risk in OI (Huang et al. 2006; Bachrach 2007).
10. Differential diagnosis (Basel and Steiner 2009)
    a. In utero: Prenatal ultrasound examination of severe OI may lead to following skeletal dysplasias which all present with relative macrocephaly and rhizomelic shortening of the limbs (OI type II with ultrasound findings of crumpled long bones and beaded ribs):
       i. Hypophosphatasia
       ii. Thanatophoric dysplasia
       iii. Campomelic dysplasia
       iv. Achondrogenesis

b. Infancy and childhood
   i. Nonaccidental trauma (child abuse)
   ii. Infantile hypophosphatasia: See the chapter on hypophosphatasia.
   iii. Bruck syndrome
      a) An autosomal recessive condition
      b) Bone fragility
      c) Congenital joint contractures
      d) Clubfeet
      e) Normal or blue sclera
      f) Wormian bones
      g) It results from defects in the lysyl hydroxylase (PLOD2) that hydroxylates the amino-terminal lysyl residues involved in crosslink formation.
   iv. Osteoporosis pseudoglioma syndrome
      a) Bone fragility and fractures
      b) Other skeletal deformities
      c) Pseudoglioma with blindness in infancy
      d) Other anomalies
      e) Caused by mutations in the gene encoding the lipoprotein receptor-related protein
   v. Cole-Carpenter syndrome
      a) Bone deformities
      b) Multiple fractures
      c) Ocular proptosis
      d) Shallow orbits
      e) Orbital craniosynostosis
      f) Frontal bossing
      g) Hydrocephalus
   vi. Hadju-Cheney syndrome
      a) Short stature
      b) Failure to thrive
      c) Conductive hearing loss
      d) Dysmorphic features
      e) Early tooth loss
      f) Genitourinary anomalies
      g) Osteopenia
      h) Pathologic fractures
      i) Wormian bones
      j) Failure of suture ossification
      k) Basilar impression
      l) Vertebral abnormalities
      m) Kyphoscoliosis
      n) Cervical instability
      o) Joint laxity
      p) Dislocation of the radial head
      q) Long-bowed fibulae
      r) Pseudoclubbing
      s) Short distal digits
      t) Acroosteolysis
      u) Hirsutism
   vii. Gerodermia osteodysplastica
      a) Dwarfism
      b) Lax skin
      c) Osteoporosis
      d) Wormian bones
      e) Fractures
      f) Vertebral compression
      g) Wizened facial appearance because of facial skin laxity
   viii. Idiopathic juvenile osteoporosis
      a) Typically presents in preadolescents with fractures and osteoporosis
      b) The fracture susceptibility and osteoporosis usually resolve spontaneously with puberty.
      c) The etiology is unknown.
   ix. Dentinogenesis imperfecta: can occur separately from OI as an isolated familial condition as a result of mutations in the DSPP gene on chromosome 4

11. Importance of diagnosis in the newly affected infant for whom there is no family history
   a. To facilitate genetic counseling
   b. To reassure the family about prognosis
   c. To remove the concern of child abuse in some families (Steiner et al. 1996)
      i. Fractures considered “highly specific” for child abuse: present in 33% (2/6) of cases with OI
         a) Metaphyseal fractures
         b) Posterior rib fractures
         c) Scapular spinous process
         d) Sternal fractures
      ii. Fractures considered “moderately specific” for abuse: present in 50% (3/6) of cases with OI
         a) Multiple fractures, especially bilateral
         b) Fractures of different ages
         c) Epiphyseal separations
         d) Digital fractures
         e) Complex skull fractures

iii. Fractures considered "low specificity" for child abuse: present in 17% (1/6) cases of OI
  a) Clavicular fractures
  b) Long bone shaft
  c) Linear skull fractures

d. General signs of child abuse
  i. Multiple fractures as described
  ii. Clinical findings highly indicative of child abuse
    a) Retinal hemorrhage
    b) Cephalohematoma
    c) Subdural hemorrhage
    d) Evidence of bodily abuse (bruises, lacerations, burns)
    e) Evidence of sexual abuse
  iii. Incompatible history with physical examination
  iv. History of domestic violence, corporal punishment, and child maltreatment

e. Useful for families to have a letter from the child's physician stating the diagnosis of the osteogenesis imperfecta

Diagnostic Investigations

1. Radiography
  a. OI type I
    i. None to multiple fractures with little bone deformities
    ii. Fractures primarily in long bones (may occur with minimal trauma, decreased dramatically in puberty, increase at later ages, normal healing with callus formation)
    iii. Osteopenia (generalized demineralization) which can be documented by densitometry
    iv. Thin bones (cortices)
    v. Little trabeculae with fragility
    vi. Bowing
    vii. Platyspondyly
    viii. Retarded ossification of the cranial vault with multiple Wormian bones
    ix. Flattening of vertical axis
    x. Widening in the transverse axis of the skull
    xi. Small facial bones
    xii. Susceptible to osteoporosis and compression fractures of the vertebrae
    xiii. Pectus carinatum/excavatum

  b. OI type II
    i. Short-limbed dwarfism
    ii. Rhizomelic limb shortening
    iii. Severely retarded (virtual absence) calvarial mineralization
    iv. Generalized osteoporosis
    v. Multiple fractures with callus formation
    vi. Small chest
    vii. Beaded and broad ribs
    viii. Shortened crumpled long bones especially compressed ("telescoped" or "accordion-like") femurs and/or humeri
    ix. Externally rotated and abducted femurs
    x. Bowed lower legs
    xi. Angulated tibiae
    xii. Usually flexed and abducted hip (frog-leg position)
    xiii. Flattened acetabulae and iliac wings
    xiv. Platyspondyly
    xv. Type IIA: short and squared tubular bones, continuous beading of the ribs
    xvi. Type IIB/III: thicker tubular bones, compressed vertebrae, better ossification of the cranial bones, more normally appearing ribs and scapulae
    xvii. Type IIC: thin, deformed tubular bones, severely twisted long tubular bones

  c. OI type III
    i. Undermineralized calvarium with a large fontanel and Wormian bones
    ii. Initially normal or mildly shortening long bones
    iii. Fractures present at birth or during the first year of life with evidence of deformity
    iv. Thin gracile ribs prone to fracture
    v. Gracile long bones showing evidence of intrauterine fractures with callus formation
    vi. Marked angulation or bowing of long bones (especially tibias and femurs, reducing the efficiency of weight bearing and increasing the likelihood of fracture)
    vii. "Accordion-like" short and deformed femurs
    viii. Later metaphyseal and diaphyseal widening with "popcorn" calcification appearance of cystic metaphyses
    ix. Codfish appearance of vertebrae

x. Fractures with minimal trauma and progressive deformities
xi. Severe and generalized osteopenia

d. OI type IV
i. Bowed femurs in the newborn period but tend to straighten with time
ii. Osteopenia/osteoporosis
iii. Thin bones
iv. Fractures with deformities
v. Scoliosis

2. Bone density analysis
a. Still experimental
b. Dual energy X-ray absorptiometry (DEXA)
3. Bone histology
a. Thin cortices
b. Decreased trabecular bone volume
c. Smaller apatite crystals
d. Defective microvascular system
e. Defective collagen fibril diameter
4. Collagen synthesis analyses by cultured fibroblasts from skin biopsy. In OI type I, about half the normal amount of type I procollagen is synthesized.
5. Gene sequence analysis (Basel and Steiner 2009): Genomic DNA can be isolated from peripheral leukocytes in blood or from any other tissue samples.
a. Sequence analysis of *COL1A1* and *COL1A2* cDNA to detect mutations in the coding sequence and sequence analysis of *COL1A1* and *COL1A2* genomic DNA to detect mutations that alter either sequence or stability of mRNA identify between 80% and 85% of mutations in the type I collagen genes.
b. The mutations in most families are unique; only a few recurrent mutations (mostly CpG dinucleotides) are seen in more than one family.
c. Mutation detection rate varies by COLA1-related OI type; a comprehensive database of all 850 known mutations has been published along with a genotype-phenotype correlation.
d. For patients in whom no collagen type I mutation is identified, sequencing of *CRTAP* and *LEPRE1* is available commercially and is a reasonable next step in sequential sequencing to identify a mutation.
e. The importance of identifying these mutations is to establish a genetic risk for future offspring as the parents of an affected individual would be at a 25% risk of conceiving another child with the disorder, and it would be imperative for them to be counseled accurately, and adequately, of antenatal services available to them.

Genetic Counseling

1. Recurrence risk for OI I
a. Patient's sib: not increased unless a parent is affected or with gonadal mosaicism
b. Patient's offspring
i. Fifty percent affected if an affected parent marrying a normal spouse
ii. Twenty-five homozygously affected infant (likely to be perinatally lethal or severely affected) if both parents are affected with OI type I
2. Recurrence risk for OI II
a. Patient's sib: an empiric recurrence risk of 2–3% to 6–7% among siblings resulting from parental mosaicism for the mutation that is lethal in the infant who is heterozygous for the same mutation or due to the rare recessive form
b. Patient's offspring: none surviving beyond infancy
3. Recurrence risk for OI III (also called type IIB)
a. Patient's sib
i. Autosomal dominant form: not increased unless a parent is affected or with gonadal mosaicism
ii. Autosomal recessive form: 25%
iii. An empiric recurrence risk of 7–8% (germinal mosaicism, homozygosity of *COL1A2* mutations, and autosomal recessive inheritance)
b. Patient's offspring
i. Autosomal dominant form: 50%
ii. Autosomal recessive form: not increased unless a spouse is a carrier or affected
4. Recurrence risk for OI IV
a. Striking intrafamilial variability making clinical classification difficult for OI IV, OI III, or OI I
b. Patient's sib: not increased unless a parent carries gonadal mosaicism
c. Patient's offspring
i. Fifty percent when an affected parent marrying a normal spouse
ii. Rare possibility of having children with lethal OI phenotype by a parent with OI IV as a consequence of parental mosaicism for the lethal mutations

5. Prenatal diagnosis
   a. OI type I
      i. Identification of the mutant allele including segregation studies with an appropriate family structure (CVS at 11–12 weeks gestation)
      ii. Identification of the nonexpressed allele in mRNA from the fetus
      iii. Direct identification of the mutation (CVS at 11–12 weeks gestation)
      iv. Recognition of fracture or bowing of long bones by ultrasound
   b. Type II
      i. Diagnosis by prenatal ultrasonography accomplished between 14 and 18 weeks gestation (short femurs, fractures, small thoracic cage, minimal calvarial mineralization, or polyhydramnios)
      ii. Analysis of chorionic villi for the presence of abnormal collagens
      iii. Analysis of collagens synthesized by cells grown from chorionic villi
      iv. Direct mutation analysis in families of an identified DNA mutation in a previously affected infant
   c. Type III
      i. Diagnosis by prenatal ultrasonography not feasible until 20–22 weeks gestation
      ii. Direct mutation analysis of collagens synthesized by chorionic villus cells or DNA isolated directly from the tissue
   d. Type IV
      i. Linkage analysis with *COL1A2* polymorphisms in the dominant families
      ii. Direct mutation analysis
      iii. Analysis of proteins produced by cells grown from CVS biopsies
      iv. Little value of ultrasound analysis because of the late appearance of short or deformed bones
   e. *CRTAP*-related OI and *LEPRE1*-related OI: Prenatal diagnosis is available provided the mutations are previously identified in the family member.
6. Management
   a. Improving bone mass
      i. Use of bisphosphonates (cyclic intravenous pamidronate) to decrease the resorption of bone and to increase the formation of bone. Hopefully, early commencement of bisphosphonate treatment will prevent serious deformities.
      ii. Bisphosphonate therapy does not constitute a cure of OI, but is an adjunct to physiotherapy, rehabilitation, and orthopedic care. These drugs have brought clear improvement to the lives of patients suffering from moderate to severe OI. In contrast, children and adolescents with OI who have few fractures and no functional limitations have less to gain from treatment. It therefore appears advisable not to treat such patients unless clinical benefit can be demonstrated in placebo-controlled studies (Glorieux 2008).
      iii. Use of bone marrow transplantation as means of introducing normal mesenchymal stromal cells that have the capacity to differentiate into normal osteoblasts
   b. Fractures
      i. Meticulous orthopedic care
      ii. Corrective osteotomies
      iii. Intramedullary roddings to improve mobility, prevent fractures, and correct and prevent progressive deformity
      iv. Avoid unnecessary immobilization.
      v. Avoid malunions.
   c. Progressive scoliosis in adolescence requires spinal fusion with instrumentation.
   d. Orthotics
      i. To stabilize lax joints such as the ankle and subtalar joints
      ii. To prevent progressive deformities and fractures
      iii. Commonly used devices include ankle-foot, knee-ankle-foot, and forearm orthoses.
   e. Recognition and management of hearing loss
   f. Care of dentinogenesis imperfecta

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Fig. 1 A boy with osteogenesis imperfecta type I showing blue sclera

Fig. 2 (**a**–**c**) Familial osteogenesis imperfecta type I in two sibs. Radiographs show fracture of a femur in the boy and that of humerus in the girl. Their father is also affected. Molecular testing revealed c.578^579insC of COL1A1 gene mutation in this family

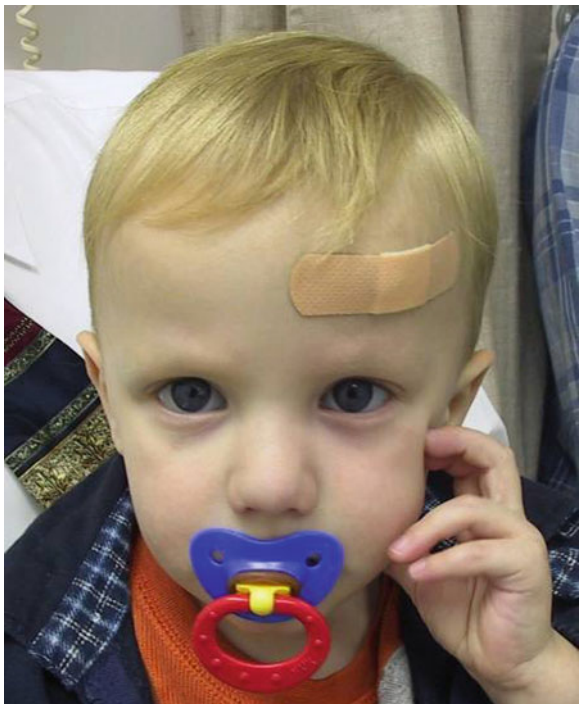

Fig. 3 A 22-month-old boy with osteogenesis imperfecta type I showing blue sclera. He has heterozygous mutation Arg75Stop of the COL1A1 gene by molecular genetic analysis

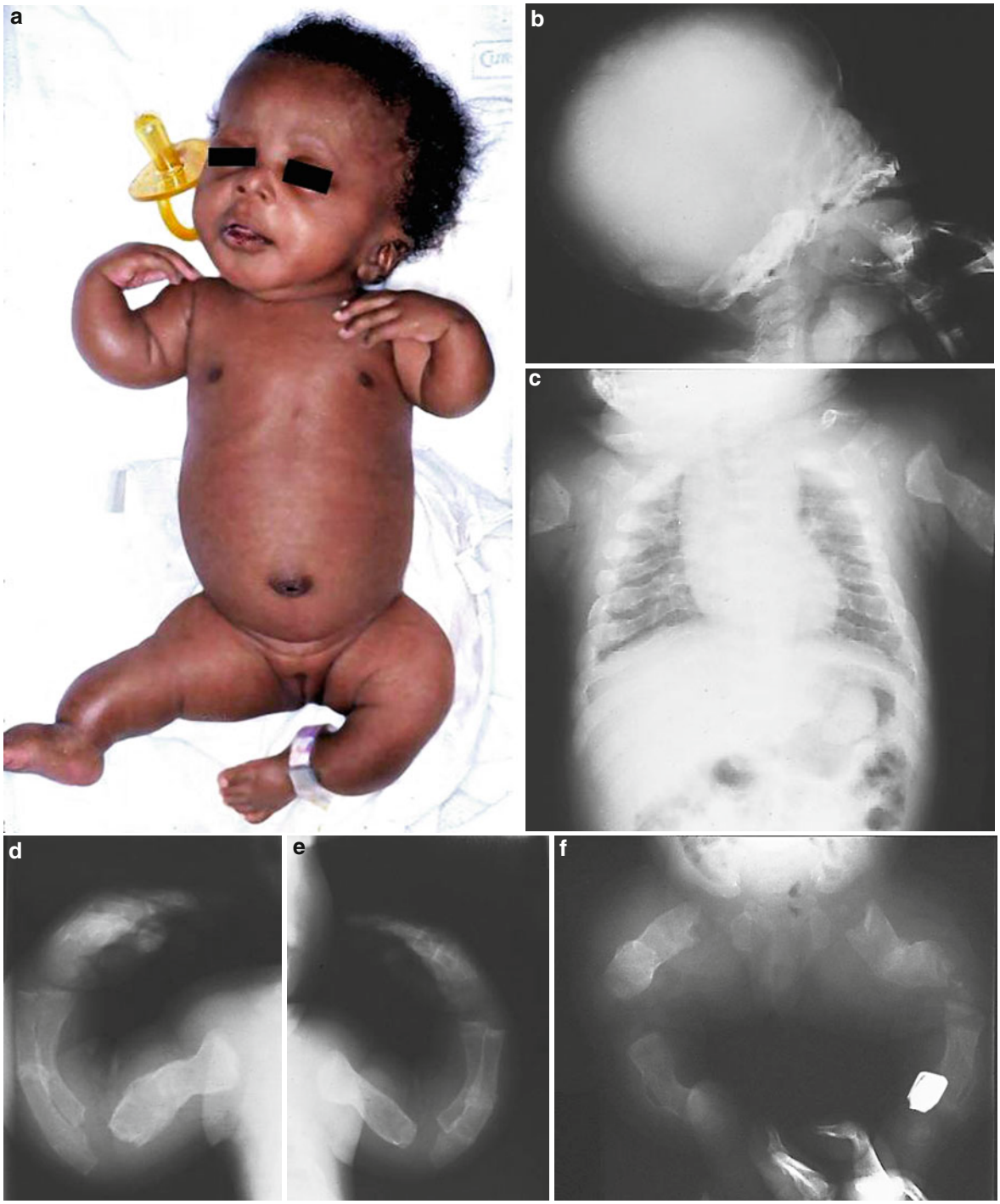

Fig. 4 (**a**–**f**) An infant with osteogenesis imperfecta type II showing severe dwarfism, characteristic craniofacial features, short and deformed limbs, and bowed legs. Radiographs showed short-limb dwarfism, rhizomelic limb shortening, severely retarded calvarial mineralization, multiple fractures with callus formation, beaded and broad ribs, and "telescoped" femurs and humeri

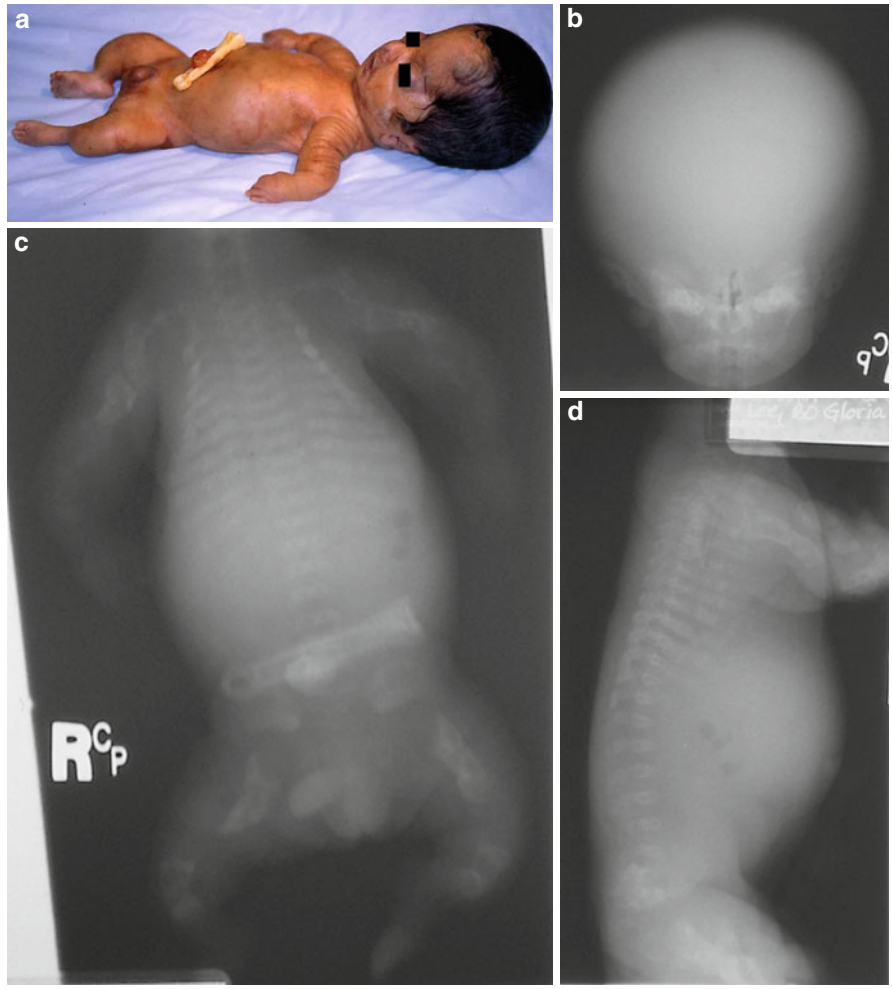

Fig. 5 (**a**–**d**) Another case of osteogenesis imperfecta type II showing the similar features

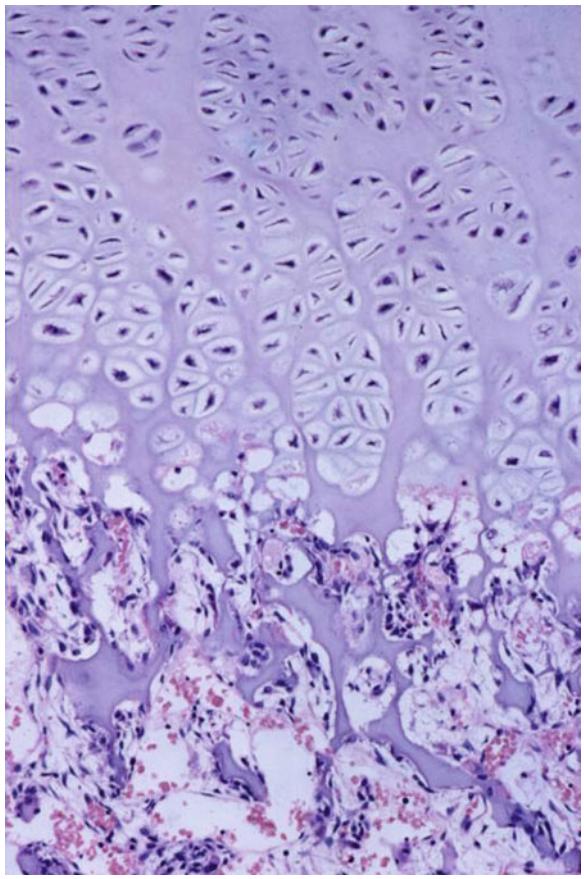

Fig. 6 Photomicrograph of rib of another case with type II osteogenesis imperfecta. The columns of cartilage in the metaphysis are covered by minimal amounts of basophilic primitive woven bone. Normal ossification is absent The physeal growth zone is moderately disorganized

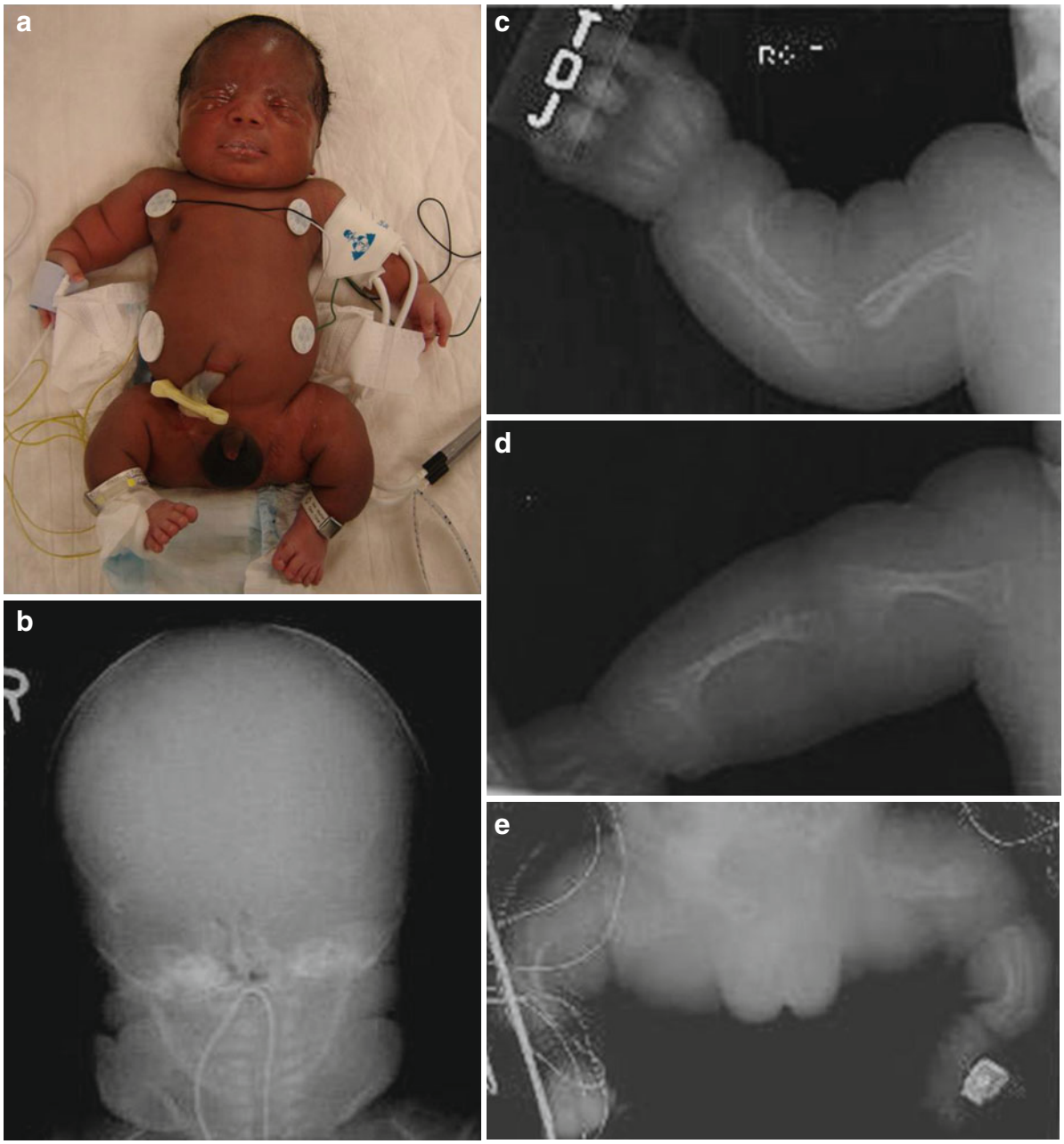

Fig. 7 (**a**–**e**) A neonate with osteogenesis type III showing short-limbed dwarfism, large head, short neck, short thigh, and curbed lower legs. Radiographs showed generalized osteopenia; poor mineralization of the skull; thin ribs with sixth, seventh, and eighth rib fractures with callus formation; short limbs; and bowed femurs with multiple fractures with callus formation. Molecular study showed heterozygous mutation of COL1A2 gene (del of three base pairs [GTT] at cDNA position c.763–765). This mutation has been reported in patients with osteogenesis imperfecta type III

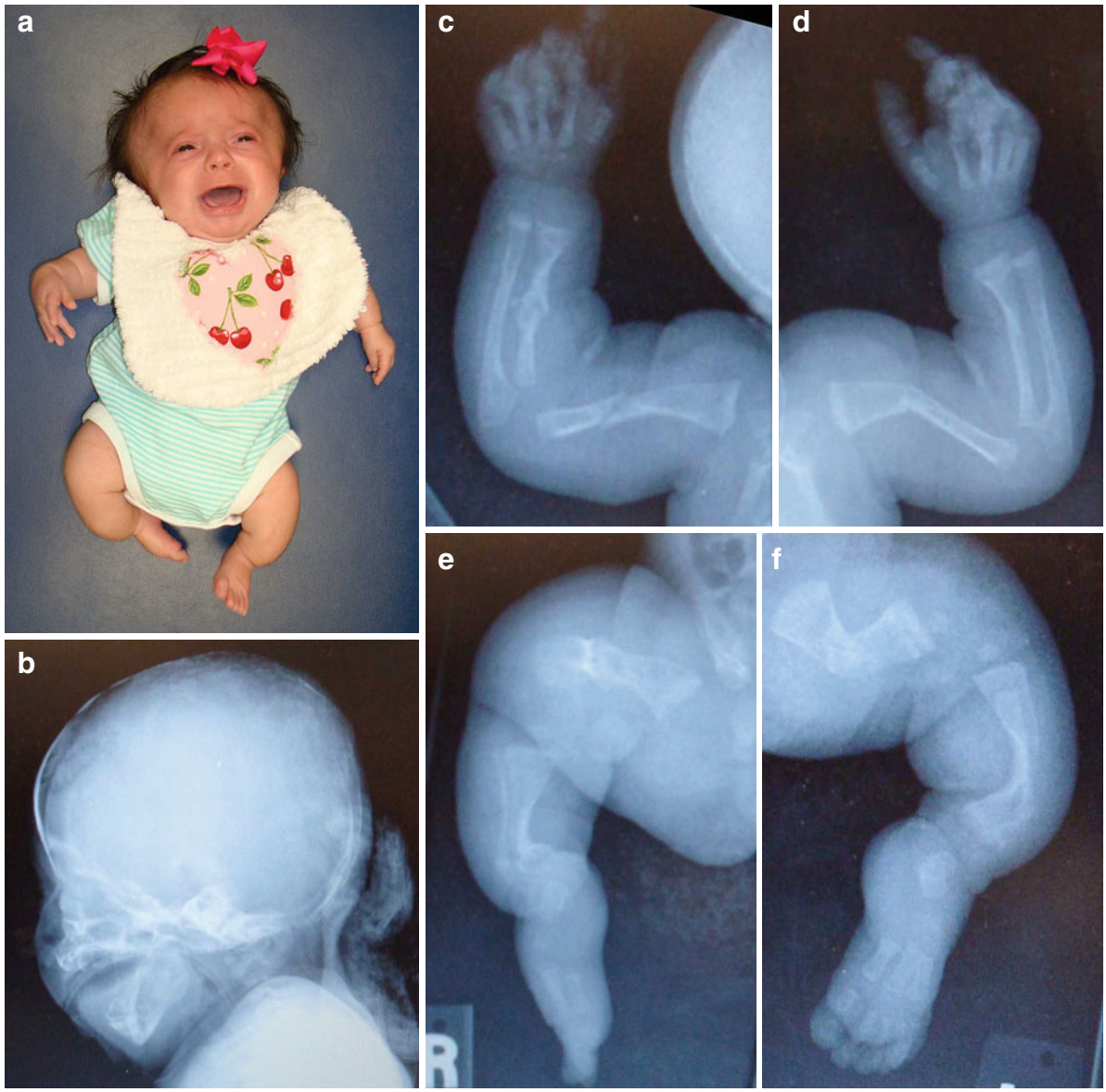

Fig. 8 (**a**–**f**) A neonate with osteogenesis type III showing short-limbed dwarfism, large head, short neck, and short and curbed upper and lower extremities. Radiographs showed generalized osteopenia, poor mineralization of the skull, and short and bowed limbs with multiple fractures with callus formation. Molecular study by sequence analysis indicated a variation in the fragment containing exon 21 and the flanking sequences of the *COL1A2* gene. Sequencing revealed a nucleotide G to A substitution that converted a codon for Glycine-289 (GGA) to a codon for glutamic acid (GAA) at cDNA position c.866. The patient thus showed a heterozygous mutation of *COL1A2* gene (Gly289Glu). This mutation has not been reported previously

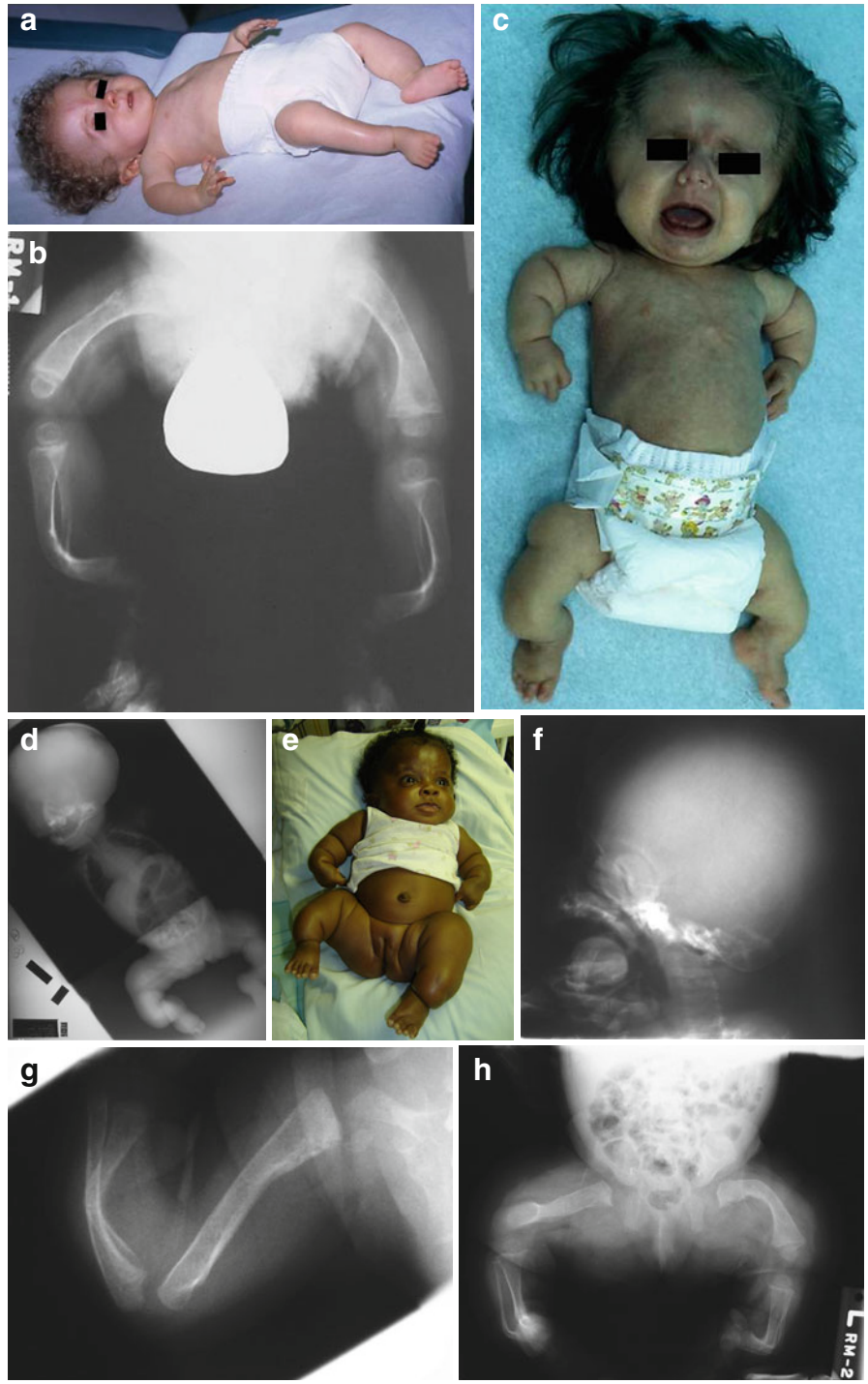

Fig. 9 (**a**–**h**) Three other infants with osteogenesis imperfecta type III showing dwarfism, moderate deformities resulting from in utero fractures, and typical triangular face with relatively large cranium. Radiographs showed undermineralized calvarium with a large fontanel and marked angulation or bowing of long bones, especially tibias and femurs

Fig. 10 An infant girl with osteogenesis imperfecta type IV

Fig. 11 (**a**–**d**) A girl with Cole-Carpenter syndrome showing ocular proptosis, craniosynostosis, and bone fragility with fractures

Osteopetrosis

Osteopetrosis is a heterogeneous group of sclerosing bone diseases due to impaired bone and cartilage resorption, resulting from absence or defective function of osteoclasts (Steward 2003). The overall incidence of these conditions is difficult to estimate, but autosomal recessive osteopetrosis has an incidence of 1 in 250,000 births, and autosomal dominant osteopetrosis has an incidence of 1 in 20,000 births (Stark and Savarirayan 2009).

Synonyms and Related Disorders

Albers-Schonberg disease; Infantile malignant osteopetrosis; Ostoclast-poor osteopetrosis

Genetics/Basic Defects

1. Inheritance of recognized subtypes of human osteopetrosis (Stark and Savarirayan 2009; Steward 2003, 2010)
   a. Autosomal recessive osteopetrosis
      i. Classic (infantile malignant osteopetrosis): Vacuolar proton pump deficiency (*ATP6i/TCIRG1*) (locus 11q13.3-q13.5)
      ii. Neuropathic (osteopetrosis and infantile neuroaxonal dystrophy): CLC-7 chloride pump deficiency (loss of function *CLCN7* mutations) (locus 16p13.3) and *OSTM1* mutations (cause an extremely severe form of autosomal recessive osteopetrosis with frequent CNS involvement (Pangrazio et al. 2006)
      iii. Autosomal recessive osteopetrosis with renal tubular acidosis (Jacquemin et al. 1998)
         a) Caused by mutations in *CA2*, the gene encoding carbonic anhydrase II
         b) Generalized osteosclerosis
         c) Cerebral calcifications
         d) Associated with intellectual disability
      iv. Autosomal recessive osteopetrosis secondary to *PLEKHM1* mutations: mild phenotype and can regress with increasing age (van Wesenbeeck et al. 2007)
   b. More benign osteopetrosis primarily affecting adults: two subtypes based on radiographic features
      i. Autosomal dominant osteopetrosis type I (locus 11q12-13)
      ii. Autosomal dominant osteopetrosis type II (Albers-Schőnberg disease): dominant negative *CLCN7* mutations (Most patients have this type.)
   c. Intermediate forms: Children presenting beyond 2 years of age often have a slower progressive disease.
      i. An autosomal recessive disease with milder mutations: carbonic anhydrase isoenzyme type II deficiency (CAII) and *CLCN7* mutations
      ii. Early diagnoses of the more severe end of the autosomal dominant spectrum
   d. RANKL deficiency (Askmyr et al. 2008)
      i. Recently discovered in a screen of 40 patients with recessive osteopetrosis with unknown genetic defects (Sobacchi et al. 2007)

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ii. Characterized by a decrease in osteoclast numbers
iii. Less severe with a slower progression than the classical malignant forms of osteopetrosis
iv. The gene that is mutated encodes RANKL, one of the osteoclast-promoting cytokines produced by stromal cells in the bone marrow.

e. Osteopetrosis associated with ectodermal dysplasia, lymphedema, and immunodeficiency
i. X-linked (Smahi et al. 2002)
ii. Resulting from a hypomorphic mutation in IKBKG [also known as NEMO (NF-kB essential modulator)]
iii. Most hypomorphic mutations do not cause osteopetrosis but mild ectodermal dysplasia and immunodeficiency in males.

f. Osteopetrosis with agenesis of corpus callosum: autosomal recessive

g. Dysosteosclerosis
i. Autosomal recessive
ii. X-linked also reported

2. Basic defects: Absence or defective function of osteoclasts results in defective remodeling of bone with partial or complete obliteration of marrow cavities, producing bone which is dense but has an increased tendency to fracture.

3. Potential clinical consequences of aberrant resorption and remodeling of bones caused by defective osteoclast function (Steward 2010)

a. Fractures
i. Undertubulated bones break easily.
ii. Common fracture sites (Cheow et al. 2001)
a) Long bones of the arms and leg
b) Posterior ribs
c) Acromial processes

b. CNS and eye involvements (Abinun et al. 1999; Steward 2003)
i. Bony overgrowth, or lack of remodeling, results in compression of nerves or blood vessels that pass through bones, especially the optic nerve (resulting in partial or complete visual loss) and, more rarely, the auditory and facial nerves.
ii. Arteries or venous sinuses within the skull can also be constricted, as can the foramen magnum.
iii. Early fusion of bones may result in craniosynostosis.
iv. Some patients have primary neurometabolic (neuronopathic) forms of osteopetrosis and may have abnormal retinal pigmentation and cerebral atrophy.

c. Cytopenia/pancytopenia (Steward et al. 2005)
i. Bony encroachment on medullary cavities results in extramedullary hemopoiesis with hepatosplenomegaly and the potential for hypersplenism.
ii. Anemia and thrombocytopenia result and blood films often show a markedly leukoerythroblastic picture, with a high white blood cell count and high numbers of circulating stem cells.

d. Growth: Most children with osteopetrosis fall below the tenth percentile on growth charts, and some have severe dwarfism (Gerritsen et al. 1994; Driessen et al. 2003).

e. Hypocalcemia: Defective osteoclast function can disturb calcium homeostasis, which may manifest as symptomatic hypocalcemia in the first few months of life, despite high total body calcium reserves (Gerritsen et al. 1994; Srinivasan et al. 2000).

f. Respiratory compromise (Wong et al. 1978)
i. The skull base, choanal bones, and jaw are often severely affected, which produces persistent snuffling, noisy breathing, and upper airway obstruction, and may predispose patients to pulmonary arterial hypertension.
ii. Patients often suffer increased ear, nose, and throat infections and respiratory infections.

g. Dentition (Luzzi et al. 2006)
i. Tooth eruption often delayed
ii. Poor tooth quality
iii. Osteomyelitis of the jaw can occur.

h. Other organ system involvement: The genes involved may have roles in other organs. For example, a small proportion of children have a severe neurometabolic disease and abnormalities of lymphocytes and immunoglobulin production are now recognized in some variants (Villa et al. 2009; Mazzolari et al. 2009).

Clinical Features

1. Malignant infantile osteopetrosis (Steward 2003)
   a. Usually diagnosed during the first year of life
   b. Signs and symptoms
      i. Presenting signs
         a) Blindness
         b) Failure to thrive
         c) Seizures due to hypocalcemia
         d) Infections
         e) Pathologic fractures
      ii. Neurovascular involvement: The most serious consequences of the osteopetrosis are cranial nerves, blood vessels, and the spinal cord compression by either gradual occlusion or lack of growth of skull foramina.
      iii. Visual impairment
         a) Optic atrophy: Some degrees of optic atrophy are present in most patients. Blindness is observed in many children with severe forms of autosomal recessive osteopetrosis.
         b) Nystagmus
         c) Strabismus
         d) Proptosis
         e) Limited extraocular movement
      iv. Compression of facial and trigeminal nerves
         a) Produce paralysis, spasm, or neuralgia
         b) Involvement of the trigeminal nerve tends to occur in type I autosomal dominant osteopetrosis.
         c) Involvement of the facial nerve predominant in type II disease
      v. Hearing loss
         a) Poor drainage of the middle ear
         b) Narrowing of the internal acoustic meatus
         c) Osteosclerosis
      vi. Blood vessel compression
         a) Stenosis of arterial supply (internal carotid artery, vertebral artery)
         b) Stenosis of venous supply
      vii. Craniofacial features
         a) Macrocephaly
         b) Frontal bossing
         c) Hypertelorism
         d) Exophthalmos
         e) Flat nasal bridge
         f) Chronic rhinitis
         g) Jaw: a frequent site of osteomyelitis
         h) Obligate mouth breathing in most children secondary to obstruction of the upper airway
      viii. Compromised nutritional state due to difficulty in eating and breathing resulting from limited posterior nasophrynx from bony overgrowth
      ix. Psychomotor retardation
         a) Secondary to hydrocephalus
         b) Secondary to apnea due to upper airway obstruction
         c) Common in carbonic anhydrase isoenzyme type II deficiency
      x. Bone marrow failure
         a) Results from bone marrow encroachment
         b) Leads to extramedullary hematopoiesis and hepatosplenomegaly (abdominal protuberance)
         c) Frequently progresses to hypersplenism and pancytopenia
         d) Signs secondary to thrombocytopenia (petechiae, ecchymoses, epistaxis, melena, gingival bleeding, intracerebral hemorrhages)
         e) Carries a high mortality
2. Autosomal dominant osteopetrosis type I
   a. Chronic bone pain
   b. Cranial nerve palsies
   c. Hearing loss
   d. Not associated with increased fracture rate
3. Autosomal dominant osteopetrosis type II (Albers-Schőnberg disease)
   a. Originally described by Albers-Schőnberg in 1904
   b. The most common form of osteopetrosis
   c. The prevalence: 5.5 in 100,000
   d. The term "benign osteopetrosis": a misnomer for autosomal dominant osteopetrosis type II because of the possibility of severe clinical complications
   e. Most prominent symptoms
      i. Bone pain

   ii. Multiple fractures: frequent (78%), perhaps due to the reduced elasticity of the brittle bone
   iii. Mandibular osteomyelitis
  f. Other signs
   i. Hip osteoarthritis
   ii. Thoracic or lumbar scoliosis
   iii. Hearing loss
   iv. Visual loss
   v. Optic atrophy
   vi. Facial palsy
   vii. Multiple dental abscesses
4. "Intermediate" form of osteopetrosis
  a. Usually diagnosed during the first decade and survive into adulthood
  b. Short stature
  c. Frontal bossing
  d. Mild hepatosplenomegaly
5. Carbonic anhydrase isoenzyme type II deficiency
  a. Most cases have been reported from Middle East or the Mediterranean region.
  b. Osteopetrosis with renal tubular acidosis (usually distal type)
  c. Short stature
  d. Fractures
  e. Psychomotor retardation
  f. Cranial nerve compression (>50%)
  g. Optic atrophy and visual loss
  h. Cerebral calcifications
  i. Minor hematological impairment
  j. Craniofacial features
   i. Micrognathia
   ii. Narrow prominent nose
   iii. Poorly developed philtrum
  k. Abnormal dentition
   i. Peg-shaped carious teeth with malocclusion
   ii. Delayed eruption of the teeth
   iii. Retained primary dentition
  l. Visual failure
  m. Episodic hypokalemic paralysis in some patients
6. Vacuolar proton pump deficiency
  a. Visual failure
  b. Symptomatic hypocalcemia in the first month (50%)
   i. Early or late neonatal convulsions
   ii. Irritability
   iii. Jittering episodes
  c. Fractures
  d. Mild to severe hematological impairment
  e. Hepatosplenomegaly
  f. Failure to thrive
  g. Poor growth
  h. Reduced life span
7. ClC-7 chloride pump deficiency: severe osteopetrosis
8. Neuronopathic osteopetrosis
  a. Causing rapid neurodegeneration and death within the first year
  b. Widespread axonal spheroids and accumulation of ceroid lipofuscin
  c. Often accompanied by severe hematological impairment
  d. Gross hepatosplenomegaly
  e. Severe anemia/thrombocytopenia
  f. High arched palate
  g. Gum hypertrophy
  h. Hyperreflexia
  i. Clonus
  j. Opisthotonos
  k. Fisting
  l. Poor head control
  m. Irritability
  n. Early death
9. Autosomal recessive osteopetrosis with renal tubular acidosis (Whyte 1993)
  a. A milder course
  b. Renal tubular acidosis
  c. Cerebral calcifications
  d. Fractures
  e. Short stature
  f. Dental abnormalities
  g. Cranial nerve compression
  h. Developmental delay
10. X-linked osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency (OLEDAID)
  a. Common variable immune deficiency in association with a particular subtype of osteoclast-poor autosomal recessive osteopetrosis (Guerrini et al. 2008)
  b. Leukocyte adhesion deficiency syndrome (Kilic and Etzioni 2008; Mory et al. 2008)
11. Osteopetrosis with agenesis of corpus callosum: possible variant to neuronopathic osteopetrosis
12. Dysosteosclerosis
  a. Bone fractures
  b. Developmental delay with occasional mental retardation

c. Cranial nerve impingement
   i. Visual loss (optic atrophy)
   ii. Hearing loss
   iii. Facial nerve paralysis
d. Osteomyelitis of the mandible
e. Macular atrophy of the skin
f. Flattened fingernails

13. Differential diagnosis (Manusov et al. 1993)
a. Hyperostosis corticalis generalisata (van Buchem syndrome)
   i. Diffuse/widespread sclerosis of the cortex, usually sparing spine
   ii. Hyperphosphatasemia
b. Oculo-dento-osseous dysplasia
   i. An autosomal dominant disorder
   ii. Enlarged mandible
   iii. Focal osteosclerosis in the pelvis
   iv. Other findings
      a) Microphthalmia
      b) Large jaw
      c) Hypoplasia of tooth enamel
c. Osteitis deformans (Paget disease)
   i. Localized osteosclerosis in one or a few regions of the skeleton
   ii. Local pain
   iii. Bone marrow biopsy finding
d. Progressive diaphyseal dysplasia (Camurati-Engelmann disease)
   i. An autosomal dominant disorder with variable expression
   ii. Caused by domain-specific mutations of the TGFB gene located on chromosome 19q13 encoding transforming growth factor β-1
   iii. Major clinical features
      a) Leg pain
      b) Muscular weakness
      c) Waddling gait
      d) Failure to thrive
   iv. Major radiographic features
      a) Fusiform sclerosis of cortical surfaces and subendosteum
      b) Sclerosis of the skull base
e. Pyknodysostosis
   i. An autosomal recessive disorder
   ii. Generalized osteosclerosis
   iii. Open fontanel
   iv. Associated with mental retardation and dwarfism
f. Heavy metals (lead, bismuth)
   i. Presence of radiodense lines (Harris lines)
   ii. Elevated levels of heavy metals
g. Mastocytosis
   i. Poorly demarcated sclerosis in the pelvis, ribs, vertebrae, skull, and proximal long bones
   ii. Not uniformly symmetric
   iii. Elevated histamine level
h. Renal osteodystrophy
   i. Widespread sclerosis of the skeleton
   ii. Increased density less clear
   iii. Elevated serum parathyroid hormone
   iv. Elevated renal function test
i. Metastatic carcinomas (breast, prostate, lung, kidney, and thyroid)
   i. Dispersed in random fashion
   ii. Bone marrow biopsy often diagnostic
j. Osteosclerosis or myelofibrosis
   i. Diffuse increased bone density with a smooth and even density
   ii. Bone marrow biopsy finding

Diagnostic Investigations

1. Laboratory work-up for infantile malignant osteopetrosis (Lam et al. 2007)
a. Anemia
b. Leukopenia
c. Thrombocytopenia
d. Reticulocytosis
e. Pancytopenia
f. Hypocalcemia
g. Inconsistent hypophosphatemia
h. Defective superoxide generation in peripheral leukocytes
i. Secondary hyperparathyroidism with elevated serum calcitriol: common (Key et al. 1984; Cournot et al. 1992)
j. Increased serum acylphosphatase (ACP)
k. Presence of the brain isoenzyme of creatine kinase (BB-CK) in the serum is a biochemical marker for osteopetrosis
l. ACP and BB-CK originate from osteoclasts (Whyte et al. 1996)

2. Radiographic features
a. Pathognomonic radiographic findings of osteopetrosis (Landa et al. 2007)
   i. Generalized sclerosis

ii. Endobone (bone within bone) formation
iii. Vertebral end plate thickening

b. Malignant infantile osteopetrosis
i. Increased density of the entire skeleton
ii. Complete absence of the medullary canal in severe cases
iii. Lack of remodeling gives rise to metaphyseal widening or a "club-shaped" appearance of the long bones
iv. "Bone within a bone" phenomena or "endobones" seen especially in the pelvis, vertebrae, hands, and feet
v. Transverse radiolucent bands within the metaphyseal regions of the long bones: attributed to periodic variations in the ability to resorb bone
vi. Longitudinal striations in the long bones: attributed to periosteal elevation by trauma or microfractures
vii. Increasingly thickened skull with a "hair-on-end" appearance
viii. Common occurrence of fractures
a) Especially epiphyseal separations and femur fractures
b) Diaphyseal and metaphyseal fractures: usually transverse or short oblique pattern

c. Various subtypes of osteopetrosis
i. Vacuolar proton pump deficiency
a) Generalized increased bone density
b) Bone-within-bone appearance due to periosteal new bone formation
c) Modeling deformities
d) Pseudorickets (widened and irregular metaphyses)
e) Metaphyseal lucencies in some children
f) Fractures: common particularly affecting acromial processes, long bones, posterior ribs, and pubic bones
ii. Carbonic anhydrase isoenzyme type II deficiency
a) Thick sclerotic skull base
b) Generalized osteopetrosis
c) Faulty modeling of metaphyses
d) Transverse striations in metaphyses
e) Arcuate striations in iliac bones
f) Bone-within-bone appearance
g) Sandwich vertebrae
h) Intracranial calcifications
iii. Neuronopathic osteopetrosis
a) Typical findings of severe malignant infantile osteopetrosis
b) Mild to severe cerebral atrophy
iv. Osteopetrosis with agenesis of the corpus callosum
a) As with neuronopathic osteopetrosis
b) Absence of the corpus callosum
v. Dysosteosclerosis
a) Thickening and sclerosis of cranial vault, base of skull, ribs, and clavicle
b) Sclerotic long bones with splayed submetaphyseal clear zones
c) Platyspondyly
d) Retarded white matter myelination
e) Intracerebral calcifications

d. Autosomal dominant osteopetrosis type I
i. Generalized/diffuse osteosclerosis affects especially the cranial vault
ii. Sclerotic skull base
iii. Vertebral bodies comparatively normal but the vertebral arches appearing dense

e. Autosomal dominant osteopetrosis type II (Albers-Schőnberg disease)
i. A spectacular radiological appearance with the segmental distribution of dense bone
ii. Characterized by diffuse osteosclerosis, predominantly involving spine, pelvis, and skull base
a) Thickened vertebral end plates ("sandwich vertebrae," Rugger-Jersey spine)
b) Classic "bone-within-bone" appearance/endobone structures (especially in pelvis)
c) Thickened (dense) skull base
iii. Common sclerotic bands in the metaphyses
iv. Fractures
a) Common (78%)
b) Heal slowly
v. Mandibular osteomyelitis
vi. Hip osteoarthritis (27%)
vii. Thoracic or lumbar scoliosis (24%)
viii. Cranial nerve encroachment leading to hearing loss, bilateral optic atrophy, and/or facial palsy (16%)

3. Major pathologic features
   a. General features for malignant infantile osteopetrosis
      i. Obliteration of the marrow spaces by unresorbed primary trabecular bone and calcified cartilage
      ii. The cartilage cores not remodeled despite an increased number of osteoclasts
      iii. Absent or diminished ruffled border of the osteoclast by electron microscopy
   b. Vacuolar proton pump deficiency: increased osteoclasts
   c. ClC-7 chloride pump deficiency: normal numbers of osteoclasts (in mice)
   d. Neuronopathic osteopetrosis
      i. Autofluorescent neuronal ceroid lipofuscin
      ii. Widespread eosinophilic neuroaxonal spheroids
   e. Autosomal dominant osteopetrosis type I: normal appearance of trabecular bone remodeling
   f. Autosomal dominant osteopetrosis type II (Albers-Schőnberg disease)
      i. Defective trabecular bone remodeling.
      ii. Increased number of osteoclasts.
      iii. Frequent delayed healing of fractures.
      iv. Increased total acid phosphatase probably reflects the increased number of osteoclasts that are unable to resorb bone.
      v. Observation of large multinucleated osteoclasts suggests a defect in osteoclast function rather than differentiation, as in infantile osteopetrosis.
   g. Intermediate form
      i. Mild to marked increased bone density of the axial skeleton and long bones
      ii. Defects of modeling seen especially at the distal femurs which may have "Erlenmeyer flask" deformity
      iii. Frequent coxa vara and pathologic long bone fractures
      iv. Problematic dental malocclusion and caries

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal recessive disorder: 25%
      ii. Autosomal dominant disorder: low unless one of the parent is affected or has gonadal mosaicism
      iii. X-Linked recessive
         a) Carrier mother: 50% of male sibs affected; 50% of female sibs carriers
         b) Noncarrier mother: still with a small risk of having further affected offspring due to gonadal mosaicism
   b. Patient's offspring
      i. Autosomal recessive disorder: low unless the spouse is a carrier
      ii. Autosomal dominant disorder: 50%
      iii. X-linked recessive
         a) No sons will inherit the mutant allele and therefore will not be affected with osteopetrosis.
         b) All daughters will be carriers for osteopetrosis.
2. Prenatal diagnosis
   a. Prenatal radiography (Oğur et al. 1995; Stark and Savarirayan 2009): possible for families with severe autosomal recessive osteopetrosis and unknown mutations (66)
      i. Made at the 25th week of pregnancy at risk for autosomal recessive osteopetrosis
      ii. Fetal radiographic findings
         a) Marked sclerosis of osteopetrotic bone
         b) Metaphyseal splaying and clubbing of both femurs
   b. Prenatal diagnosis available for pregnancies with a 25% risk for fetuses affected with malignant osteopetrosis by amniocentesis or CVS
      i. Using linked microsatellite markers in the region of chromosome 11q12-13
      ii. DNA mutation analysis of fetal DNA for the pregnancy at risk for malignant autosomal recessive osteopetrosis by amniocentesis or CVS when the mutation is previously characterized in the family
   c. Preimplantation diagnosis is theoretically possible in families, in whom the genetic mutation has been identified.
   d. If a family decides to continue with an affected pregnancy, hematopoietic stem cell transplantation before the age of 3 months can be planned with the aim of improving neurological outcomes (Stark and Savarirayan 2009).

3. Management (Wilson and Vellodi 2000)
   a. Supportive care
   b. Blood transfusion for anemia secondary to a failure of bone marrow development
   c. Risk of recurrent infections viewed as an indication for bone marrow transplantation
   d. Optical nerve decompression successful only in mildly affected older children
   e. Early insertion of ventilatory "grommet" tube for hearing impairment secondary to a combination of bony compression of the nerve, sclerosis of the middle ear ossicles, and/or chronic middle ear effusion
   f. Nasal gastric feeding for children with chronic anemia and feeding problems caused by bulbar nerve involvement, nasal congestion, and recurrent infections
   g. A high risk of anesthetic morbidity and mortality in patients with malignant osteopetrosis primarily related to airway and respiratory factors
   h. Manage osteomyelitis
      i. Pus drainage
      ii. Appropriate antibiotic therapy
      iii. Surgical debridement
      iv. Reconstruction if indicated
   i. Orthopedic cares: complicated by the difficulty of working with extremely hard, brittle, marble bone (Landa et al. 2007)
      i. Fracture fixation
         a) Difficulty inserting pins and screws
         b) Failure of load-bearing plate devices
         c) Increased time to union
      ii. Arthroplasty
         a) Iatrogenic fracture during implant placement
         b) Increased risk of osteomyelitis
         c) Obliteration of medullary canal by cortical bone
      iii. General considerations
         a) Overheating and breakage of drill bits
         b) Longer surgical time
   j. Corticosteroids and calcitriol (1,25-hydroxyvitamin D) with some short-term initial benefit but with debatable long-term benefit
   k. Recombinant human gamma interferon (Eapen et al. 1998)
      i. Enhances bone resorption and leukocyte function
      ii. Effects on morbidity and survival remain unclear.
   l. Bone marrow or peripheral blood stem cell transplantation
      i. Rational: Osteoclasts are derived from hematopoietic stem cells.
      ii. Long-term disease-free survival has been achieved in approximately 70% of infants receiving transplants from matched sibling donors (Cheow et al. 2001).
         a) Repopulating the bones with functioning osteoclasts by successful infusion of donor marrow
         b) Beginning the process of remodeling and restoration of normal calcium homeostasis
         c) Radiographic changes of osteopetrosis expected to gradually returning to normal 4 months to 2 years following bone marrow transfusion
         d) Improvement and resolution of the rachitic changes: the first observation after bone marrow transplantation
         e) Immune recovery
         f) Improved growth
   m. Improving results with the use of high-dose peripheral blood stem cell grafts for infantile osteopetrosis from alternative donors, including those from parents mismatched for up to one half of their HLA-type (haploidentical)
   n. Hematopoietic stem cell transplantation in patients with osteopetrosis: associated with disease-specific problems that require careful management, including the potential for life-threatening posttransplant hypercalcemia, a high prevalence of pulmonary arterial hypertension and, in at least one subtype of disease, failure to reverse osteosclerosis despite successful donor cell engraftment (Steward 2010)

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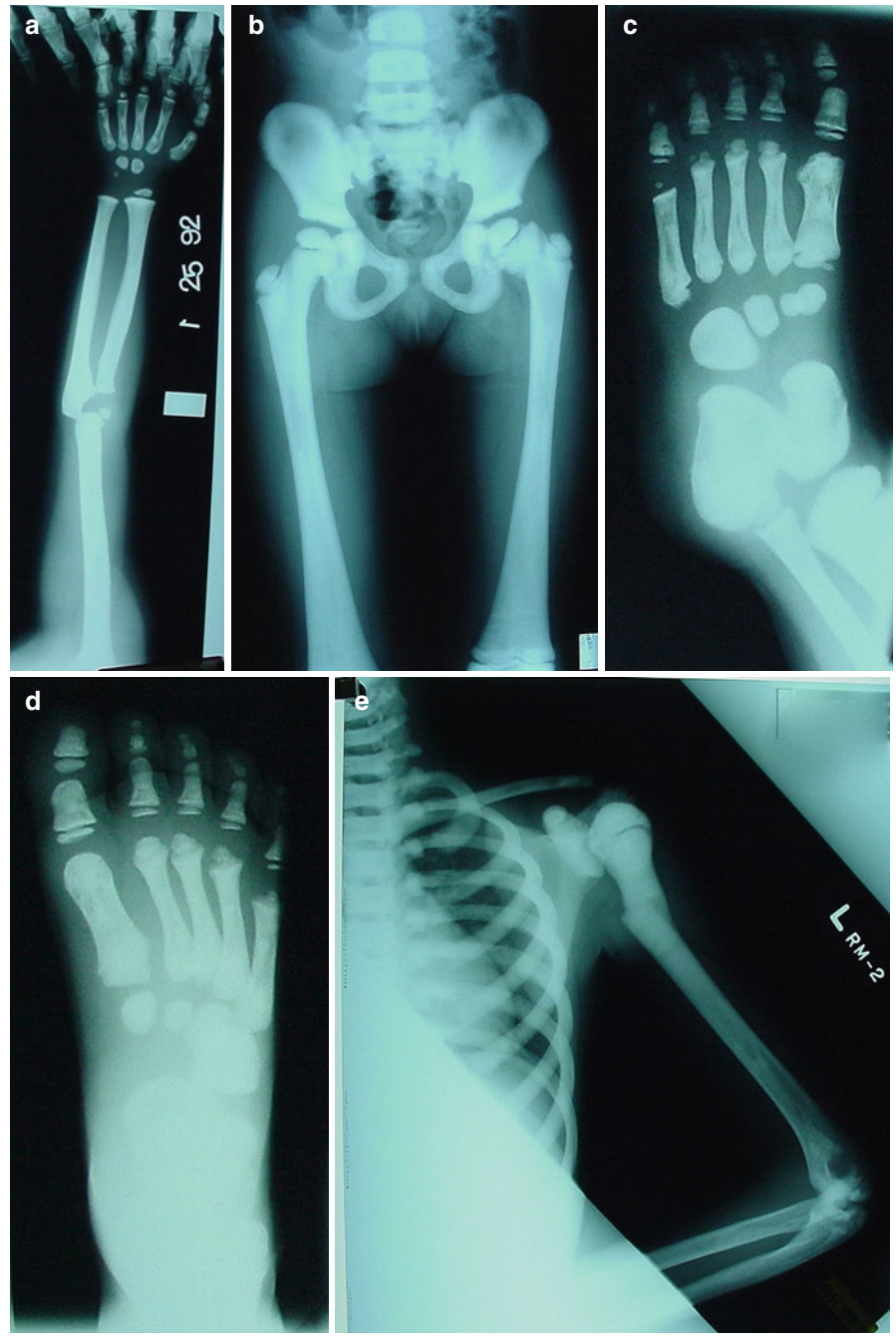

Fig. 1 (**a**–**e**) Radiographs of a girl with Albers-Schőnberg syndrome at 3 years (arm, pelvis, and foot) and at 10 years (arm and chest) showing sclerotic bones with loss of corticomedullary differentiation, fracture at the left humerus, and endobone appearance of phalanges of the hands and feet

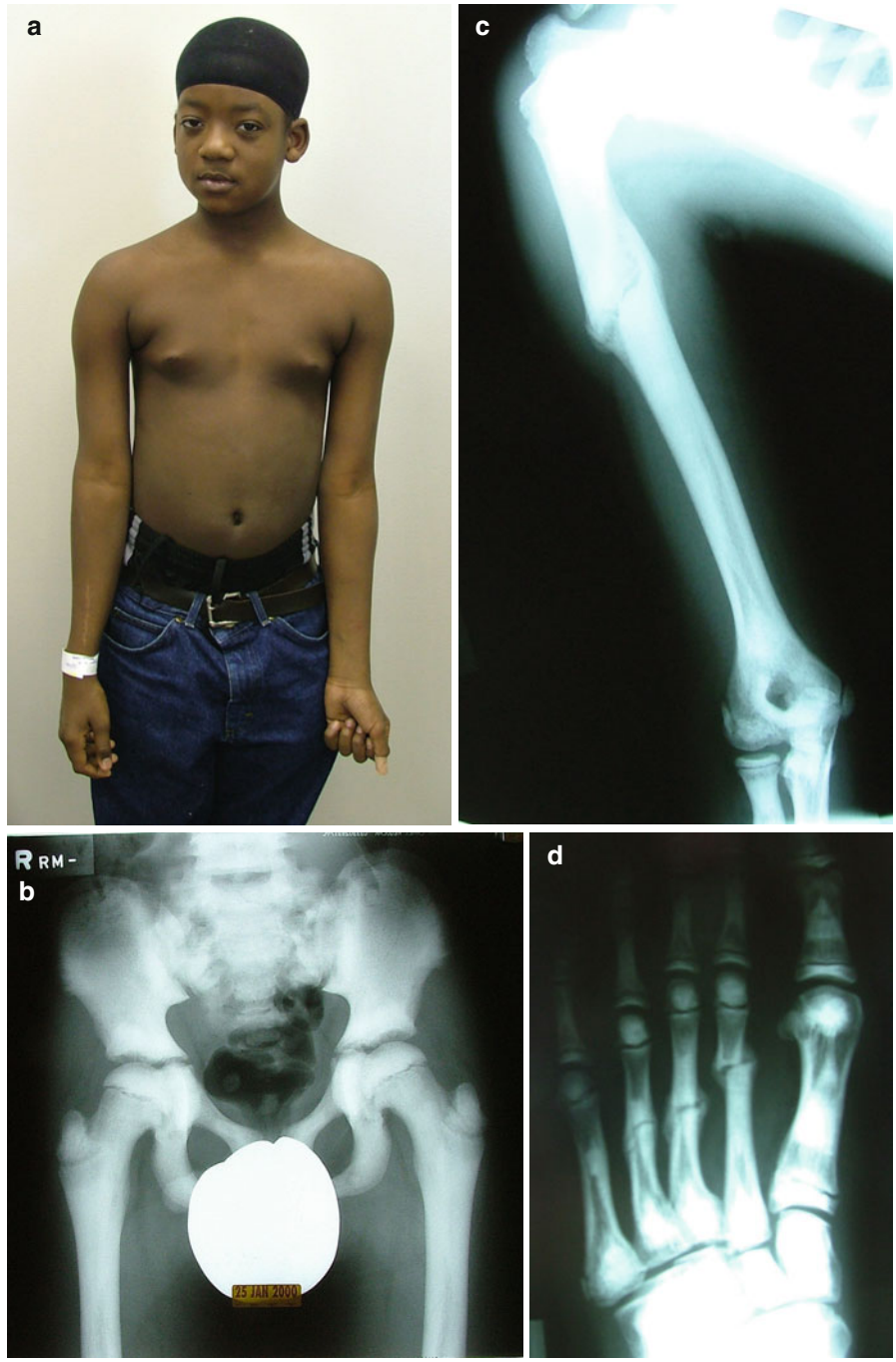

Fig. 2 (**a**–**d**) A 14-year-old boy with osteopetrosis showing sclerotic bones with loss of corticomedullary differentiation and multiple fractures, illustrated by a series of radiographs

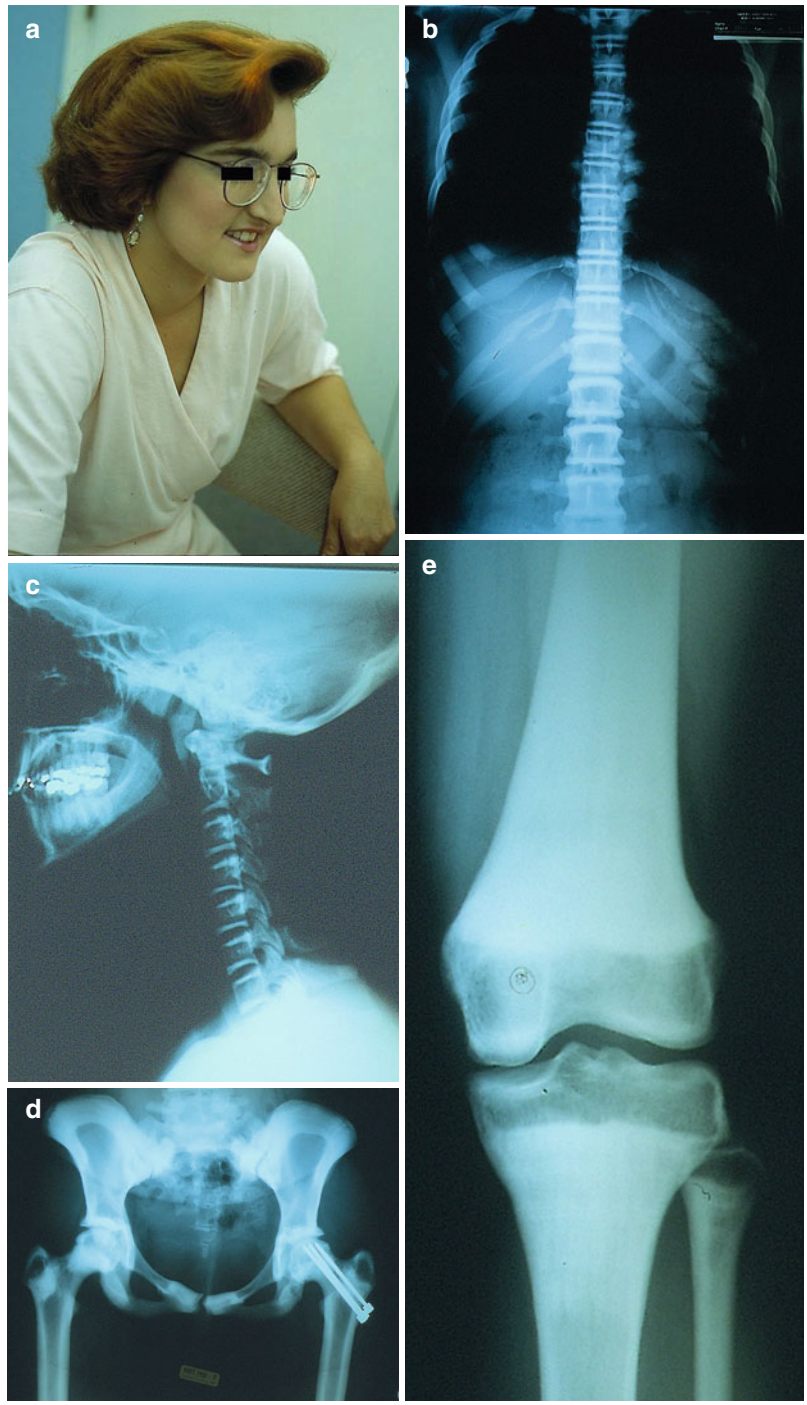

Fig. 3 (**a**–**e**) An adult female with osteopetrosis showing generalized sclerotic bones with loss of corticomedullary differentiation including sandwich cervical vertebrae, illustrated by radiographs

Osteopoikilosis

Osteopoikilosis was first described by Albers-Schonberg in 1915. It is a benign, usually asymptomatic condition diagnosed radiographically by the presence of multiple symmetrical circular/ovoid sclerotic opacities of the ischia, pubic bones, and the epimetaphysial regions of the short tubular bones. The incidence is estimated as 1/50,000 (Cazzola et al. 1989).

Synonyms and Related Disorders

Buschke–Ollendorff syndrome; Melorheostosis; Osteopathia striata

Genetics/Basic Defects

1. Inherited in an autosomal dominant pattern
2. Caused by loss of function mutation of LEM domain-containing three gene (*LEMD3*)
3. Usually occurs in isolation
4. Osteopoikilosis in association with elastic or collagen connective tissue nevi of the skin, known as Buschke–Ollendorff syndrome (dermatofibrosis lenticularis disseminate)
5. In some families and individuals, osteopoikilosis can occur with other osteosclerotic skeletal disorders, such as melorheostosis and osteopathia striata.

Clinical Features

1. Osteopoikilosis
   a. Presence of multiple osteosclerotic lesions in different parts of the skeleton (Lagier et al. 1984; Chigira et al. 1991)
      i. Epiphyses and metaphyses of long tubular bones
      ii. Hands and wrists
         a) Phalanges
         b) Carpal bones
         c) Metacarpals
      iii. Feet/ankles
         a) Phalanges
         b) Metatarsals
         c) Calcaneus
         d) Navicular bones
      iv. Pelvis
      v. Scapulae
   b. An uncommon disorder
   c. Evident at any age (uncommon before the age of 3 years) and persists for life
   d. Symmetric distribution
   e. Generally asymptomatic
   f. Joint inflammation and pain in about 15–20% of cases (Borman et al. 2002)
   g. Osteopoikilosis reported to coexist with other rheumatologic pathologies:
      i. Rheumatoid arthritis (Cazzola et al. 1989; Ureten 2007)

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   ii. Reactive arthritis (Mesci 2006)
   iii. Discoid lupus erythematosus (Bicer et al. 2002)
   iv. Familial Mediterranean fever (Kavukcu et al. 2003)
2. Melorheostosis
   a. A sporadic sclerosing bone condition
   b. Manifesting in a sclerotomal distribution
   c. Frequently affecting one limb
   d. Usually asymptomatic
   e. Pain, stiffness, leg-length discrepancy, and deformity in severe case
   f. Radiographically, presence of cortical hyperostosis with thickening, resembling dripping candle wax
3. Osteopathia striata
   a. Occurs in isolation or with cranial sclerosis
   b. A key radiographic feature: longitudinal striation of the metaphyses of the long bones
   c. Clinical features ranging from mild skeletal manifestation to multisystem organ involvement, even with the same family
      i. Typical features
         a) Macrocephaly
         b) Cleft palate
         c) Hearing loss
      ii. Additional features
         a) Cardiac malformations
         b) Developmental delay
         c) Cranial nerve palsies
         d) Anal malformations
         e) Cataracts
         f) Nervous system malformations
4. Buschke–Ollendorff syndrome
   a. A rare, autosomal dominant disorder
   b. Typically a benign disorder that combines osteopoikilosis together with skin lesions consisting of connective tissue nevi (Buschke and Ollendorff 1928) or juvenile elastomas (Uitto et al. 1981)

Diagnostic Investigations

1. Radiographic features
   a. Often detected incidentally at radiographic examination
   b. Numerous, small, well-defined circular or ovoid sclerotic foci in a symmetric distribution
      i. Usually seen in (Amezcua-Guerra et al. 2005):
         a) Epiphyses of short tubular bones
         b) Metaphyseal regions of long tubular bones
         c) Carpal bones
         d) Metacarpals
         e) Metatarsals
         f) Tarsal bones
         g) Sacrum
         h) Scapulae
         i) Iliac bones
      ii. Rarely involved in (Mesci 2006):
         a) Skull
         b) Spine
         c) Ribs
         d) Clavicles
2. CT scan and MRI: used to support the diagnosis
3. Radionuclide bone scans
   a. Typically normal
   b. Occasionally abnormal (Appenzeller et al. 2007), especially in younger patients (Borman et al. 2002; An et al. 2004)
4. Bone biopsy: focal condensations of compact lamellar bone within spongiosa (Benli et al. 1992)
5. Molecular genetic diagnosis of *LEMD3* gene mutation is not currently available clinically.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: a low recurrence risk if parents are not affected
   b. Patient's offspring: a 50% of risk of having an affected offspring if the spouse is normal
2. Prenatal diagnosis: has not been reported
3. Management
   a. Usually no treatment is required for the condition
   b. Supportive treatment for joint inflammation or joint pain

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Fig. 1 A 12-year-old boy with osteopoikilosis which was noticed incidentally from pelvic radiographic examination

Fig. 2 Pelvic radiograph showed small, oval osteosclerotic bone lesions at femoral head and neck and around the acetabulum of the pelvis and symphysis pubis

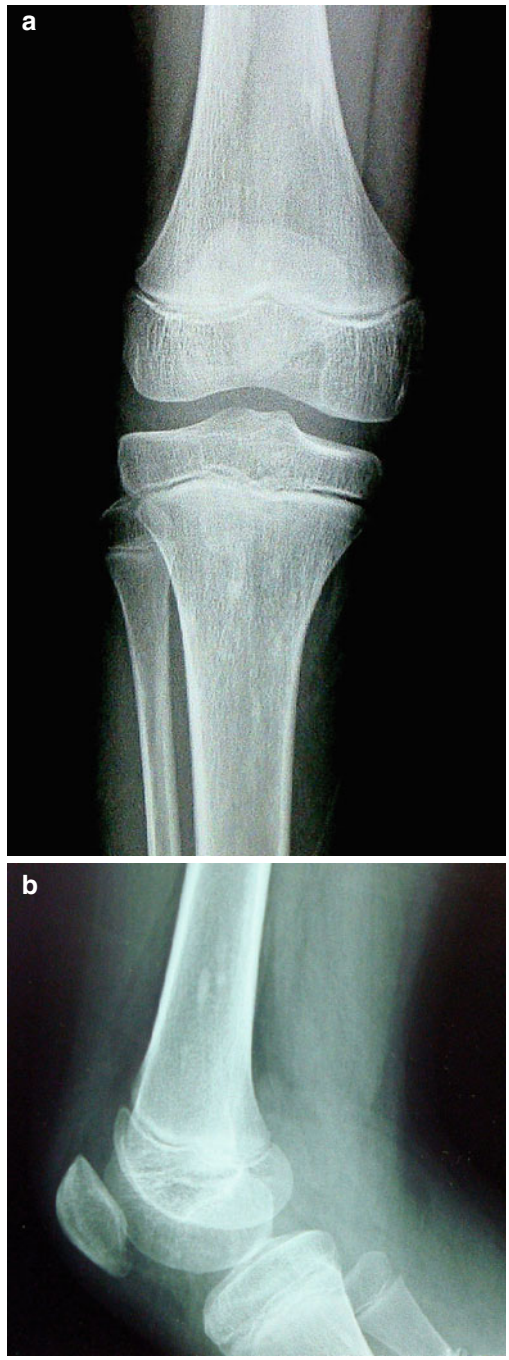

Fig. 3 (**a**, **b**) Oval osteosclerotic bone lesions on proximal tibia and distal femur

Fig. 4 A 9-year-old boy complained pain on both ankles and feet. He was diagnosed to have osteopoikilosis from radiographic findings

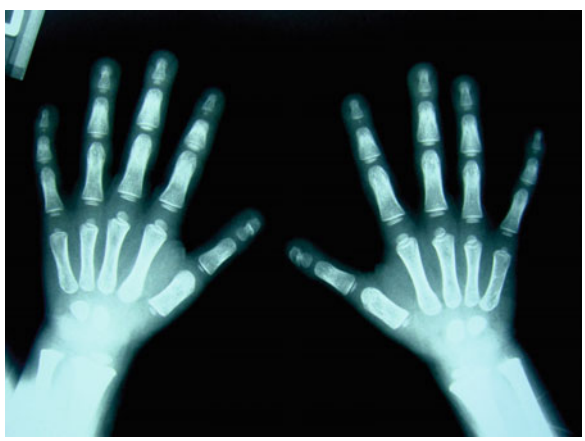

Fig. 5 Hand radiograph at age of 4 showing multiple sclerotic lesions along axis of phalanges and metacarpals

Fig. 6 Feet radiograph at age of 9 showing multiple sclerotic lesions along the axis of several phalanges

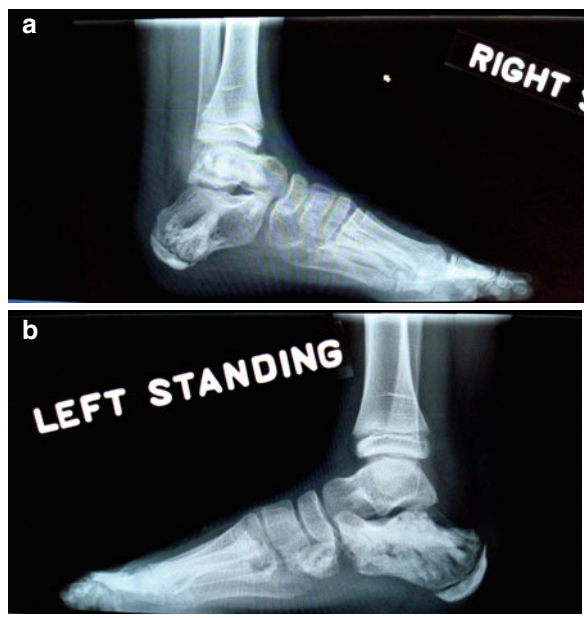

Fig. 7 (**a**–**b**) Lateral view of feet at age of 9 showing multiple sclerotic lesions at calcaneus and talus bones

Otopalatodigital Spectrum Disorders

Otopalatodigital spectrum disorders, a heterogeneous group of disorders characterized primarily by a skeletal dysplasia of variable severity, include otopalatodigital syndrome type I (OPD I), otopalatodigital syndrome type II (OPD II), frontometaphyseal dysplasia (FMD), and Melnick-Needles syndrome (MNS).

Dudding et al. in 1967 described three male sibs with conduction deafness, cleft palate, characteristic facies, and a generalized bone dysplasia. In retrospect, the male patient described by Taybi (1962) may have the same condition. The syndrome is now known as OPD I.

Fitch et al. in 1976 described a familial syndrome of cranial, facial, oral, and limb anomalies in which two male infants have microcephaly, abnormal ears, antimongoloid slant, small mouth, cleft palate, flexed overlapping fingers with syndactyly of the second to the fifth toes, and normal karyotype. The name OPD II was proposed for this syndrome by Fitch et al. (1983).

Gorlin and Cohen in 1969 described a male patient with extraordinarily marked frontal hyperostosis giving great prominence to the supraciliary ridges, underdeveloped mandible, cryptorchidism, subluxated radial heads, and metaphyseal dysplasia resembling that in Pyle disease (metaphyseal dysplasia).

Melnick and Needles in 1966 described families having multiple cases in multiple generations of a severe congenital bone disorder characterized by typical facies (exophthalmos, full cheeks, micrognathia, and malalignment of teeth), flaring of the metaphyses of long bones, S-like curvature of bones of legs, irregular constrictions in the ribs, and sclerosis of base of skull.

In 2000, Verloes et al. presented clinical evidence for a single entity encompassing FMD, MNS, and OPD I and II. Later, mutations in *FLNA*, a gene encoding the cytoskeletal protein filamin A, were found to be associated with otopalatodigital spectrum disorders.

Synonyms and Related Disorders

Frontometaphyseal dysplasia; Melnick-needles syndrome; Otopalatodigital syndromes type I and type II

Genetics/Basic Defects

1. Inherited as X-linked disorders (Robertson 2009)
2. Mutations in *FLNA*, a gene encoding the cytoskeletal protein filamin A, mapped on Xq28, were found to be associated with otopalatodigital spectrum disorders.
3. Different mechanisms contribute to the pathogenesis of these conditions based on the contrast in phenotypic consequences between loss-of-function mutation (leading to periventricular nodular heterotopia) and clustered missense mutations (leading to otopalatodigital spectrum disorders).
4. The four otopalatodigital spectrum disorders are likely allelic based on previous clinical observations, despite remarkably diverse phenotypic presentations.
   a. Mild end of the spectrum: Affected males with OPD I have cleft palate and mild skeletal anomalies with conductive deafness caused by ossicular anomalies.
   b. Intermediate end of the spectrum: Affected males with FMD have a propensity to develop

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stenosis of the subglottic region, ureters, and urethra in addition to skeletal anomalies.

c. Severe end of the spectrum: Affected males with OPD II have more marked skeletal anomalies, CNS anomalies, and other congenital malformations.

d. Most severe end of the spectrum: Affected males with MNS also have severe skeletal anomalies and other congenital malformations similar to OPD II leading to prenatal and perinatal lethality.

5. Genetically related (allelic) disorders
   a. X-linked periventricular nodular heterotopia
      i. Presence of uncalcified nodules of neurons ectopically situated along the surface of the lateral ventricles
      ii. Affected individuals: predominantly heterozygous females; males show early lethality.
      iii. Affected females
         a) Seizures on average at age 14–15 years
         b) Intelligence ranging from normal to borderline functioning
         c) Increased risk for stroke and other vascular problems or coagulopathies
      iv. Germline mutations of *FLNA* leading to null alleles are found almost exclusively in females, whereas missense mutations or mosaicism for truncating mutations can account for affected males or a mild phenotype in females.
   b. A variant of X-linked periventricular nodular heterotopia with marked connective tissue dysfunction (skin fragility, vascular dilatation) described in females has been associated with mutations in *FLNA*, predicted to lead to loss of function.
   c. Gastrointestinal dysmotility associated with periventricular nodular heterotopia associated with *FLNA* mutations
   d. A dual phenotype of periventricular nodular heterotopia and FMD in a female caused by a mutation variably leading to either a substitution or a small deletion as a result of aberrant splicing
   e. Myxomatous cardiac valvular dystrophy associated with X-linked periventricular nodular heterotopia: caused by *FLNA* mutations

Clinical Features

1. Males with OPD I
   a. Skeletal anomalies
      i. Digital anomalies
         a) Thumbs: short, often proximally placed
         b) Distal phalanges of other digits: hypoplastic with a squared (or "spatulate") disposition to the finger tips
         c) Characteristic toes: hypoplasia of the great toe, a long second toe, and a prominent sandal gap
   b. Limitation of joint movement (elbow extension, wrist abduction) in almost all affected individuals
   c. Mild limb bowing
   d. Characteristic facial features
      i. Prominent supraorbital ridges
      ii. Downslanting palpebral fissures
      iii. Ocular hypertelorism
      iv. Broad nasal bridge and nasal tip
   e. Deafness: secondary either to ossicular malformation, neurosensory deficit, or a combination of both
   f. Cleft palate
   g. Oligohypodontia
   h. Normal intelligence
2. Females with OPD I
   a. Exhibit variable expressivity
   b. Some females can be affected to a similar degree as affected, related males.
3. Males with OPD II
   a. Skeletal anomalies
      i. Thoracic hypoplasia
      ii. Limb bowing
      iii. Digital anomalies
         a) Most commonly hypoplasia of the first digit of the hands and feet
         b) Camptodactyly
      iv. Delayed closure of the fontanels
   b. Characteristic craniofacial features
      i. More pronounced than those in OPD I
      ii. Pierre Robin sequence commonly observed
   c. Cardiac septal defects and obstructive lesions to the right ventricular outflow tract in some affected individuals

   d. Associated anomalies
      i. Omphalocele
      ii. Hydronephrosis secondary to ureteric obstruction
      iii. Hypospadias
   e. Central nervous system anomalies
      i. Hydrocephalus
      ii. Cerebellar hypoplasia
      iii. Rare encephalocele and meningomyelocele
   f. Developmental delay: common
   g. Death commonly in the neonatal period secondary to respiratory insufficiency
   h. Survival into the third year of life has been described with intensive medical treatment.
4. Females with OPD II
   a. Usually present with a subclinical phenotype
   b. Characteristic craniofacial features
      i. Prominent supraorbital ridges and a broad nasal root and tip: most common findings
      ii. Occasional conductive hearing loss
   c. Occasional females manifest a phenotype similar in severity to that of males (craniofacial dysmorphism, cleft palate, conductive hearing loss, skeletal and digital anomalies)
5. Males with FMD
   a. Skeletal anomalies
      i. Digital anomalies
         a) Distal phalangeal hypoplasia
         b) Progressive contractures of the hand over the first two decades resulting in marked limitation of movement at the interphalangeal and metacarpophalangeal joints
      ii. Joint limitation at the wrists, elbows, knees, and ankles
      iii. Scoliosis
      iv. Limb bowing
   b. Characteristic craniofacial features
      i. Pronounced supraorbital hyperostosis
      ii. Ocular hypertelorism
      iii. Downslanting palpebral fissures
      iv. Rare cleft palate
   c. Frequent oligohypodontia
   d. Conductive and sensorineural hearing loss in almost all affected individuals
   e. Common underdevelopment of the musculature, most notably around the shoulder girdle and in the intrinsic muscles of the hands
   f. Extraskeletal anomalies
      i. Subglottic stenosis presenting as congenital stridor
      ii. Hydronephrosis
   g. Normal intelligence
6. Females with FMD
   a. Characteristic craniofacial features similar to those of affected males
   b. Digital, subglottic, and urologic anomalies observed in males with FMD either do not occur in females or are observed in markedly attenuated form.
7. Males with MNS
   a. Usually present with a phenotype indistinguishable from, or more severe than, that associated with OPD II
   b. Affected male fetuses born to several women with classic MNS have presented with a lethal phenotype reminiscent of a severe form of OPD II.
   c. Some mildly affected males have been born to clinically unaffected parents.
8. Females with MNS
   a. Skeletal anomalies
      i. Short stature
      ii. Digital anomalies
         a) Typically long phalanges of both hands and feet
         b) Mild distal phalangeal hypoplasia
      iii. Thoracic hypoplasia
      iv. Limb bowing
      v. Joint subluxation
      vi. Scoliosis
   b. Characteristic craniofacial features
      i. Prominent lateral margins of the supraorbital ridges
      ii. Exorbitism
      iii. Micrognathia
   c. Frequent oligohypodontia
   d. Common sensorineural and conductive deafness
   e. Common hydronephrosis secondary to ureteric obstruction
   f. Normal intelligence
   g. Normal pubertal development

Diagnostic Investigations

1. Diagnosis of the OPD spectrum disorders is made by a combination of clinical examination, radiologic studies, family history consistent with X-linked inheritance, and molecular genetic testing (Robertson 2009).
2. Audiometry for hearing loss
3. Renal ultrasound for renal tract anomalies
4. Radiographic studies
   a. Males with OPD I
      i. Skull
         a) Sclerosis of the skull base
         b) Thickening of the calvaria
         c) Underdevelopment of the frontal sinuses
         d) Typically underpneumatized mastoids
         e) Increased mandibular angle
      ii. Spine: Failure of fusion of posterior vertebral or neural arches, particularly in the cervical spine
      iii. Long bones
         a) Mildly bowed upper and lower limbs
         b) Common dislocation of the radial heads
      iv. Hands and feet
         a) Characteristic accessory proximal ossification center of the second metacarpal
         b) Characteristic short, broad first metacarpal and distal phalangeal hypoplasia most marked in the thumb
         c) Presence of accessory carpal bones and fusion of carpal and tarsal bones
      v. Pelvis: typically contracted with a lack of normal flaring of the ilia
   b. Males with OPD II
      i. Skull: findings similar to those in OPD I but delayed in ossification pattern, manifesting as large fontanels in infancy
      ii. Cervical spine
         a) Failure of fusion of the posterior neural or vertebral arches
         b) Segmentation anomalies
      iii. Long bones: bowed upper and lower limbs with splaying of the metaphyses
      iv. Hands and feet
         a) Abnormal modeling of the metacarpals and phalanges, more prominently on the radial side
         b) Hypoplastic or absent great toe
         c) Broad and poorly modeled phalanges and metatarsals
         d) Pelvis: hypoplastic, with lack of normal flaring of the ilia
   c. Females with OPD II
      i. Characteristic sclerosis of the skull base and odontoid process
      ii. Flared metaphyses of the long bones
      iii. Digital anomalies: either absent or presence of hypoplasia of the first metacarpal or metatarsal
   d. Males with FMD
      i. Skull
         a) Sclerosis of the skull base
         b) Marked thickened calvarium
         c) Craniosynostosis
         d) Underpneumatization of the mastoids
         e) Hypoplasia or aplasia of the paranasal sinuses
         f) A spur arising from the anteroinferior tip of the mandible
      ii. Spine
         a) Fusion of vertebral bodies (especially C2-3-4)
         b) Deficiency of the posterior vertebral arches
      iii. Thorax: Ribs can adopt a distorted shape (coat-hanger configuration) even though the thoracic cage is not hypoplastic.
      iv. Long bones: undermodeled and frequently mildly bowed
      v. Hands and feet
         a) Carpal and tarsal fusions: common
         b) Erosion of the carpal bones: observed in adolescence and adulthood
         c) Metacarpals, metatarsals, and phalanges: elongated and poorly modeled
         d) Distal phalanges of the thumb and great toes: hypoplastic
   e. Females with FMD: exhibit the same cranial and long bone features as males, but to a lesser degree
   f. Females with MNS
      i. Skull
         a) Sclerotic skull base
         b) Delayed closure of the fontanels
      ii. Spine
         a) Vertebral bodies: increased in height, especially in the lumbar region
         b) Scoliosis: common

iii. Thorax
  a) Ribs: irregular in contour and form
  b) Clavicle: similarly wavy and irregular, with some expansion of its proximal end
iv. Long bones: bowed both limbs with marked cortical irregularity
v. Hands and feet: elongated and undermodeled phalanges, metacarpals, and metatarsals
vi. Pelvis: exhibits a supra-acetabular constriction with flaring of the ilia

5. Molecular genetic testing
  a. *FLNA* is the only gene currently known to be associated with the otopalatodigital (OPD) spectrum disorders.
  b. Sequence analysis of entire coding region and of select exons: available clinically for confirmation of the diagnosis in the proband and carrier testing of the relatives
  c. Both somatic and germline mosaicism in FLNA leading to periventricular nodular heterotopia (PVNH) have been observed and have been associated with modulation of the severity of the phenotype and survivorship in males (Guerrini et al. 2004; Parrini et al. 2004; Robertson 2007).
    i. Germline mosaicism has been observed in association with OPD I.
    ii. Somatic mutation has been shown to have led to MNS, suggesting similar processes may modulate the expression of OPD spectrum phenotypes (Robertson et al. 2006).

Genetic Counseling

1. Recurrence risk (Robertson 2009)
  a. Sibs of a male proband with OPD I, OPD II, or FMD: Risk depends on the genetic status of the parents.
    i. Mother is a carrier.
      a) A 50% risk to her son to receive the disease gene and express the disease
      b) A 50% risk to her daughter to receive the disease gene and become a carrier with a range of possible phenotypic expression
      c) Mother of an affected child, regardless of proven carrier status, has an increased risk of having an affected male fetus due to presence of maternal germinal mosaicism.
    ii. Father has an *FLNA* mutation.
      a) All female sibs will inherit the mutation.
      b) Male sibs will not inherit the mutation.
  b. Sibs of a proband with MNS: Risk depends upon the genetic status of the mother.
    i. Mother has the gene mutation.
      a) A 50% chance of transmitting the *FLNA* mutation to each child
      b) Male sibs who inherit the mutation will be affected and generally dies prenatally or perinatally.
      c) Female sibs who inherit the mutation will have a range of phenotypic expression.
    ii. Mother is clinically unaffected: Risk to sibs appears to be low but greater than that of the general population due to possible parental germline mosaicism.
  c. Patient's offspring
    i. Males with OPD II do not reproduce.
    ii. Males with OPD I or FMD transmit the disease-causing mutation to all of their daughters and none of their sons.
    iii. Females with OPD I, OPD II, or FMD
      a) A 50% chance of transmitting the disease-causing mutation to each child
      b) Sons who inherit the mutation will be affected.
      c) Daughters will have a range of possible phenotypic expression.
    iv. Males with MNS usually die prenatally or perinatally and do not reproduce.
    v. Females with MNS
      a) A 50% chance of transmitting the disease-causing mutation to each child
      b) Sons who inherit the mutation will be affected and generally die prenatally.
      c) Daughters will have a range of possible phenotypic expression.
2. Prenatal diagnosis
  a. Prenatal ultrasound diagnoses of OPD II in a fetus of an affected mother and in a fetus of a normal mother have been reported.
  b. Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

3. Management
   a. Hearing aids for deafness
   b. Stridor in the neonatal period due to laryngeal stenosis rarely requires surgical intervention and is nonprogressive.
   c. Cosmetic surgery to correct the fronto-orbital deformity attempted in some individuals with good results. Regrowth postsurgery does not seem to occur (Kung and Sloan 1998).
   d. Surgery to correct hand and foot malformations and scoliosis
   e. Chest expansion surgery attempted in several individuals with Melnick-Needles syndrome, with only marginal clinical benefit
   f. Continuous positive airway pressure (CPAP) for prevention of airway collapse and sleep apnea secondary to micrognathia and tracheobronchomalacia in severely affected individuals
   g. Anesthetists should be aware of the associated laryngeal stenosis, if intubation and ventilation are required (Leggett 1988; Mehta and Schou 1988).

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Fig. 1 (**a**–**d**) A 2-month-old premature (33-week gestation) male infant has multiple congenital anomalies, consisting of marked brachycephaly, widely opened anterior fontanel, short neck with redundant nuchal skin, severe downslanting palpebral fissures, arched eyebrows, a small and flat nose, an extremely small mouth with posterior inverted U-shaped cleft palate, a groove present at philtrum site and lower lip areas, low-set, posteriorly rotated malformed ears, a short sternum, a large umbilical hernia, and hypoplastic scrotum with undescended testicles. Marked limb anomalies are noted: mildly bowed upper arms and forearms, flexed hands with ulnar deviation and overlapping fingers, and duplicated fifth fingers with clinodactyly, bowing of upper and lower legs, and dorsiflexed feet with four toes each with medially deviated great toes and laterally deviated second through fourth toes. Clinical, postmortem, and radiological findings are consistent with otopalatodigital type II syndrome. DNA testing identified two hemizygous missense mutations: c.613 T > C (p.Cys-205-Arg) and c.5290 G > A (p.Ala-1764-Thr) in the *FLNA* gene. The first sequence variation is previously reported to be associated with periventricular heterotropia. The significance of the second sequence variant is unknown. *FLNA* mutations with presumed gain of function are previously reported in association with four other disorders: otopalatodigital syndrome type I and II, frontometaphyseal dysplasia, and Melnick-Needles syndrome

Fig. 2 (**a**–**l**) Radiographs show hypoplastic scapulae, curved humeri, radii, and ulnae, duplicated fourth fingers with four unusually shaped metacarpals and phalanges, markedly bent femora, bent tibiae, unossified fibulae, and four toes in each foot with unusually shaped metatarsals and phalanges

Pachyonychia Congenita

Pachyonychia congenita is a group of rare genetically inherited diseases characterized by nail dystrophy and by varying features of ectodermal dysplasias. There are two major clinical subtypes recognized: type I with oral leukokeratosis and type II with multiple pilosebaceous cysts (Çelebi et al. 1999).

Synonyms and Related Disorders

Jadassohn-Lewandowsky syndrome; Pachyonychia congenita, Jadassohn-Lewandowsky type; Pachyonychia congenita, Jackson-Lawler type

Genetics/Birth Defects

1. Inheritance (Çelebi et al. 1999; Conners et al. 2001)
   a. Type I pachyonychia congenita (Jadassohn–Lewandowsky type)
      i. Autosomal dominant inheritance
      ii. Possible autosomal recessive inheritance
   b. Type II pachyonychia congenita (Jackson–Lawler type): autosomal dominant
2. Etiology
   a. Type I: caused by mutations in genes encoding one of the paired keratins of specialized epidermis, KRT6a or KRT16, resulting in
      i. Fragility of specific epithelia
      ii. Phenotypes of pachyonychia congenita I or focal nonepidermolytic palmoplantar keratoderma with insignificant nail changes
   b. Type II: caused by mutations in genes encoding one of the paired keratins of specialized epidermis, KRT6b or KRT17
      i. Linkage analysis mapped pachyonychia congenita type II phenotype within the type I keratin gene cluster on chromosome 17q12-21
      ii. A germline mutation has been identified in keratin 17 gene (K17).
      iii. Colocalization of K17 with keratin 6b
3. Genotype-phenotype correlation
   a. Differences in type I and type II phenotypes: largely explainable by the difference in expression patterns between the K6a/K16 and K6b/K17 expression pairs
   b. K6b/K17 expresses at higher levels in the pilosebaceous unit than K6a/K16: responsible for the pilosebaceous cysts in type II
   c. Conversely, K6a/K16 more widely expressed in oral epithelia: responsible for the greater predominance of oral leukokeratosis in type I

Clinical Features

1. Presence of intra- and interfamilial phenotypic variation (Feinstein et al. 1988)
2. Pachyonychia congenita type I (56.2% of cases)
   a. The most common subtype
   b. Onset in infancy
   c. Severe nail dystrophy affecting all the nails symmetrically (Dogra et al. 2002)
      i. The best hallmark of the disease

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ii. Thickened wedge-shaped nails
iii. Proximal portions of the nails: smooth and normally attached to the lateral nail folds
iv. Distal portions of the nails: may increase to many times the normal thickness, producing a subungual keratinous mass that pushes the nail plate upward, arching it transversally, folding it longitudinally, and elevating it distally
v. Nails commonly shed and regrow with similar but more severe changes.
vi. Projections from the nail beds make the nails susceptible to trauma with consequent chronic paronychial infections.

d. With or without following associated anomalies
i. Focal nonepidermolytic palmoplantar keratoderma (predominantly a feature of type I)
ii. Follicular keratoses observed on
a) Temple
b) Eyebrows
c) Extensor aspect of the proximal parts of the extremities
iii. Hyperkeratosis of palms, soles, knees, and elbows
iv. Localized foot blistering
v. Oral leukokeratosis: a prominent sign
vi. Neonatal teeth
vii. Blister formation on palms and soles
viii. Hoarse voice due to laryngeal involvement (leukokeratosis)
ix. Palmar and plantar hyperhidrosis

3. Pachyonychia congenita type II (24.9% of cases)
a. Nail dystrophy
b. Less pronounced or absent palmoplantar keratoderma and oral changes
c. Follicular keratoses
d. Oral leukokeratosis
e. Multiple pilosebaceous cysts (most useful distinguishing feature for type II but usually occurring at puberty)
i. Epidermoid or infundibular cysts (arising from the hair follicle infundibulum)
ii. Eruptive vellus hair cysts and multiple steatocystomas (characteristic of type II) (arising from the sebaceous duct epithelium)
f. Bullae of palms and soles
g. Palmar and plantar hyperhidrosis
h. Natal or neonatal teeth
i. Pili torti in children
j. Bushy eyebrows
k. Hidradenitis suppurativa

4. Pachyonychia congenita type III (Schafer–Brunauer type) (11.7%)
a. Features of type I and type II
b. Angular cheilosis
c. Leukokeratosis of the cornea
d. Cataracts

5. Pachyonychia congenita tarda (type IV) (7.2%)
a. A rare form of pachyonychia congenita
b. Features of type I, type II, and type III
c. Laryngeal lesions
d. Hoarseness
e. Mental retardation
f. Hair anomalies
g. Alopecia
h. Nail changes occurring in the second or third decade
i. Abnormal painful nails
j. Palmoplantar keratoderma

6. Pachyonychia congenita with early onset nail changes in the absence of other associated features

Diagnostic Investigations

1. Histology and ultrastructure of cutaneous and oral lesions: suggest a keratin disorder (Munro 2001)
2. Molecular analyses of mutations in genes encoding one of the paired keratins of specialized epidermis, K6a/K16 and K6b/K17

Genetic Counseling

1. Recurrence risk
a. Patient's sib
i. Autosomal dominant inheritance: not increased unless a parent is affected
ii. Autosomal recessive inheritance: 25%
b. Patient's offspring
i. Autosomal dominant inheritance: 50%
ii. Autosomal recessive inheritance: not increased unless the spouse is a carrier

2. Prenatal diagnosis: genomic mutation detection possible in prenatal diagnosis of pachyonychia congenita type I (KRT6a/KRT16) or type II (KRT6b/KRT17) by CVS or amniocentesis

3. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation) has been identified.
4. Management (Dahl et al. 1995)
   a. No ideal treatment for the thickened nail plate available
   b. Vigorous use of topical lubricants and keratolytics
   c. Antiseptic wet dressings for secondarily infected areas
   d. Systemic treatment with acitretin producing variable and inconsistent results with caution of side effects (teratogenicity and hyperostosis)
   e. Custom-fitted footwear for protective support of painful fissures and blisters on the soles
   f. Simple avulsion of the distorted nails is inadequate because the dystrophic nail regrows.
   g. Curettage and electrofulguration or surgical excision of the nail matrix and bed can improve function and appearance.
   h. Surgical excision of focal, hyperplastic epithelial mass results in improvement of hoarseness due to laryngeal obstruction by laryngeal lesions. Additional microsurgery may be necessary for the recurrence of the laryngeal lesions.
   i. Therapeutic small interfering RNAs (siRNAs) for pachyonychia congenita (Leachman et al. 2008)
      i. A new siRNA entering clinical trials in PC patients with the *KRT6A* N171K mutation, with a gene-specific *KRT6A* siRNA study possibly to follow
      ii. This is the first-in-man siRNA therapeutic trial for a skin indication and the first siRNA to target a gene mutation.

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Fig. 1 (**a**–**d**) Characteristic nail changes in an 8-month-old girl with pachyonychia congenita type I showing smooth proximal ends and thick distal ends of the nails, producing a subungual keratinous mass that pushes the nail bed upward, arching it transversally, folding it longitudinally, and elevating it distally. The patient also has oral leukokeratosis

Pallister–Killian Syndrome

Pallister–Killian syndrome is a rare sporadic cytogenetic abnormality, caused by a tissue-specific mosaic distribution of an additional isochromosome 12p, first described in three adults by Pallister et al. in 1977 and followed by report of a child by Teschler-Nicola and Killian in 1981 (Pallister et al. 1977; Teschler-Nicola and Killian 1981). The syndrome is also known as Teschler-Nicola/Killian syndrome, Pallister mosaic aneuploidy syndrome, or isochromosome 12p mosaicism. It is the most frequent autosomal tetrasomy in humans (Bresson et al. 1991).

Synonyms and Related Disorders

Isochromosome 12p syndrome; Mosaic tetrasomy 12p syndrome

Genetics/Basic Defects

1. Genetics
   a. Always reported as sporadic
   b. Appears to be associated with increased maternal age
2. Basic cytogenetic defect (Bresson et al. 1991; Yeung et al. 2009).
   a. Caused by tetrasomy 12p
   b. Generally a mosaic
   c. Frequently undetectable by standard cytogenetic analysis of peripheral blood
   d. In the great majority of patients, the i(12p) is maternal in origin, with the underlying mechanism thought to involve a combination of centromere misdivision and nondisjunction at meiosis.
   e. As a result, the i(12p) is present at conception, and mosaicism results from postzygotic mitotic loss (Peltomaki et al. 1987).
   f. There is no apparent correlation between the proportion of tetrasomic cells and the severity of clinical presentation (Schinzel 1991).

Clinical Features

1. Normal or large birth weight (Mathieu et al. 1997)
2. Craniofacial dysmorphism
   a. Brachycephaly
   b. High and broad forehead with frontal bossing
   c. Temporal alopecia
   d. Sparse eyebrows and eyelashes
   e. Hypertelorism
   f. Short nose with anteverted nares
   g. A thick philtrum
   h. A large mouth with down-slanting corners
   i. Full cheeks
   j. Cleft lip/palate
   k. High-arched palate
   l. Micrognathia
   m. Macroglossia
   n. Oral frenula
   o. Delayed dental eruption
   p. Dental anomalies
   q. Low-set and posteriorly rotated ears
   r. Hypertrophy of anthelix crux
   s. Thick earlobes
3. Short neck
4. Diaphragmatic hernia with or without lung hypoplasia

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5. Imperforate anus
6. CNS/neurologic abnormalities
   a. Severe hypotonia
   b. Mental retardation
   c. Dilated ventricles
   d. Bifrontal cortical atrophy
   e. Absent speech
   f. Poor vision
   g. Epilepsy
7. Congenital heart defects
   a. Ventricular septal defect: the most frequent single malformation
   b. Coarctation of the aorta
   c. Patent ductus arteriosus
   d. Atrial septal defect
   e. Aortic stenosis
8. Limb defects
   a. Talipes
   b. Broad and short hands and fingers
   c. Hypoplastic nails
   d. Abnormal palmar creases
   e. Lymphedema
9. Skin anomalies
   a. Loose/excess skin
   b. Pigmentary dysplasia
   c. Mild hyperkeratosis
   d. Dry skin
   e. Sweating abnormalities
10. Occasional internal organ malformations
    a. Umbilical hernia
    b. Malrotation of the gut
    c. Omphalocele
    d. Abnormalities of urogenital tract including cystic or dysplastic kidneys
    e. Genital anomalies in males
       i. Cryptorchidism
       ii. Small scrotum
    f. Occasional genital anomalies in females
       i. Ambiguous external genitalia
       ii. Hypoplasia of the labia majora
       iii. Absence of the upper vagina and uterus
11. Majority of patients die prenatally, perinatally, or early postnatally, and may die even after 10 or 15 years.
12. Phenotype in older children and young adults: marked phenotypic changes occurring during childhood and adolescence (Horneff et al. 1993)
    a. Coarse and flat facies
    b. Macroglossia
    c. Prognathia
    d. Everted lower lip
    e. Muscular hypertonia
    f. Contractures
    g. Severe psychomotor retardation

Diagnostic Investigations

1. Cytogenetic studies
   a. Demonstration of a supernumerary isochromosome of 12p
   b. Confirmation of 12p tetrasomy by FISH techniques
      i. Using centromere probe on chromosome 12
      ii. Using whole chromosome 12 painting probe
   c. Cytogenetic studies of several tissues because of mosaicism (Mathieu et al. 1997): the mosaicism is usually detected in cultured skin fibroblasts or amniotic cells and rarely in phytohemagglutinin-stimulated lymphocytes, which suggests stimulation of T lymphocytes may distort the percentage of abnormal cells.
      i. Circulating lymphocytes: mosaicism as low as 1–3%
      ii. Amniocytes, chorionic cells and skin fibroblasts: mosaicism ranging from 6% to 100%
2. aCGH (comparative genomic hybridization) can detect partial tetrasomy of 12p in blood without invasive skin biopsy (Theisen et al. 2009).
3. Radiography
   a. Asymmetry of diaphyseal length
   b. Short humerus or femur
   c. Radial notch
   d. Diaphyseal irregularities
   e. Costovertebral defect
4. Echocardiography for congenital heart defect
5. EEG for seizure activities
6. MRI of the brain (Saito et al. 2006)
   a. Normal MRI findings
   b. Abnormal MRI findings
      i. Cortical atrophy with frontal predominance
      ii. Ventricular dilatation
      iii. Hydrocephalus
      iv. Reduced white matter
      v. Thickened cortex
      vi. Micropolygyria

vii. Heterotopic neurons
viii. Agenesis of corpus callosum
ix. Pineal gland tumor
x. Multiple T2-high lesions
xi. T2-elongation in the white matter

7. Postmortem pathologic examinations (Mathieu et al. 1997).
   a. Malpositioned feet
   b. Diaphragmatic defect
   c. Hypoplastic nails
   d. Genital malformation
   e. Imperforate or anteriorly placed anus
   f. Supernumerary spleen
   g. Heart valvular dysplasia
   h. Hypoplasia of the fibula

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: low recurrence risk (All cases are sporadic with only one preliminary case report of recurrence.) (Mathieu et al. 1997)
   b. Patient's offspring: not surviving to reproductive age or severely handicapped by profound mental retardation
2. Prenatal diagnosis (Doray et al. 2002)
   a. Ultrasound anomalies
      i. Hydramnios (84%)
      ii. Diaphragmatic hernia (16%)
      iii. Short limbs, predominantly rhizomelic type of micromelia (10%)
      iv. Hydrops fetalis (6%)
      v. Cystic hygroma (3%)
      vi. Increased nuchal translucency (3%)
      vii. Fetal overgrowth (3%)
      viii. Flat fetal facial profile with a small nose and protruding lips (Liberati et al. 2008)
      ix. Ventriculomegaly (3%)
      x. Dilatation of cavum pellucidum (3%)
      xi. Absence of visualization of the stomach (3%)
      xii. Presence of a sacral appendix (3%)
      xiii. Cardiac malformation
      xiv. Hypertelorism
      xv. Short neck
      xvi. Other congenital anomalies
   b. Cytogenetic studies on amniocytes, cells from CVS, or fetal blood cells from cordocentesis
      i. Conventional karyotyping
      ii. FISH using chromosome 12 centromeric and whole chromosome painting probes
         a) Interphase cells
         b) Metaphase cells
3. Management
   a. Supportive treatment
   b. Surgical repair of diaphragmatic hernia or other congenital anomalies in nonlethal cases

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Fig. 1 Postmortem picture of a neonate with prenatally diagnosed mosaic i(12p). Amniocentesis was performed because of ultrasonographic finding of diaphragmatic hernia

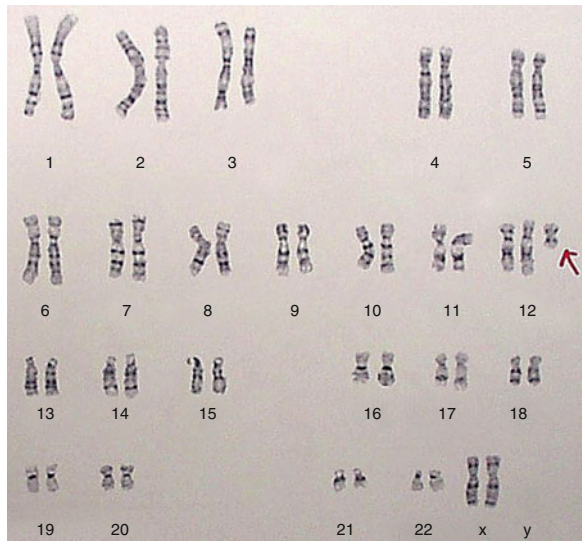

Fig. 2 A G-banded karyotype showing a supernumerary i(12p) (*arrow*)

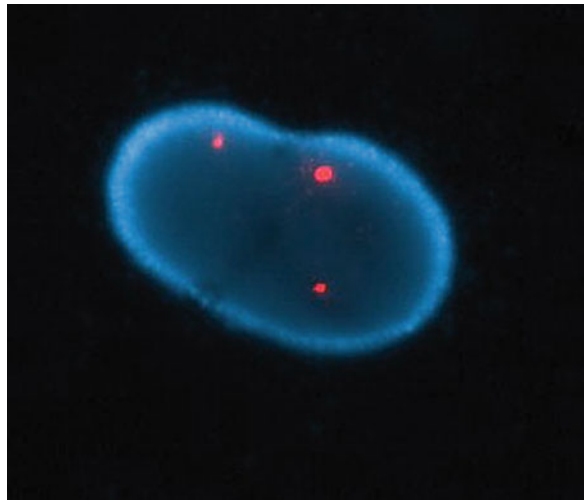

Fig. 3 FISH of an interphase cell with centromere specific probe for chromosome 12 showing three signals

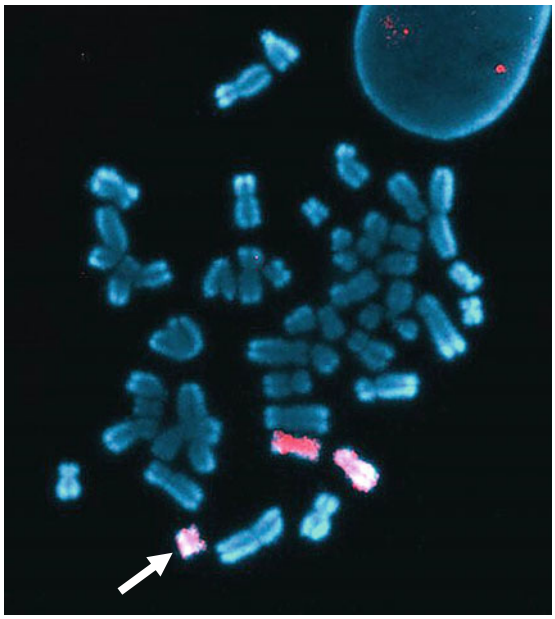

Fig. 4 FISH of a metaphase chromosome spread with a whole chromosome probe specific for chromosome 12 showing two chromosome 12s and the i(12p) (*arrow*)

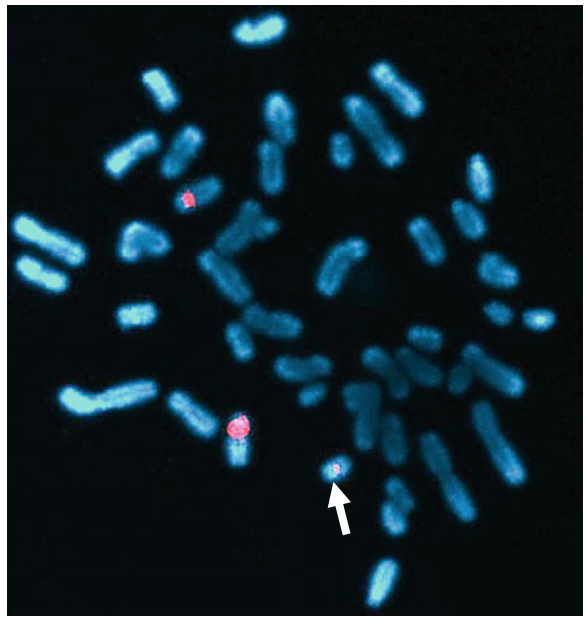

Fig. 5 FISH of a metaphase chromosome spread with a centromere probe specific for chromosome 12 showing two chromosome 12s and the i(12p) (*arrow*)

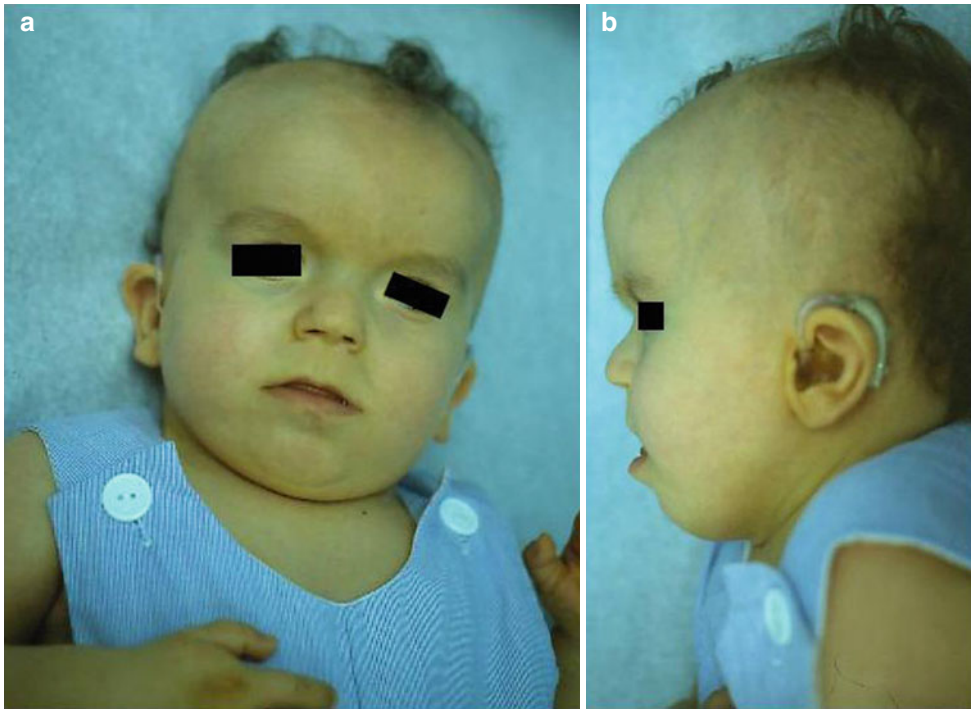

Fig. 6 (**a**, **b**) Another child with Pallister–Killian syndrome confirmed by cytogenetic studies showing prominent forehead, flat nasal bridge, sparse eyebrows, bitemporal alopecia, and everted lower lip

Phenylketonuria

Classical phenylketonuria (PKU) is a rare metabolic disorder, resulting from a deficiency of a liver enzyme, phenylalanine hydroxylase. The deficiency of the enzyme leads to elevated phenylalanine (Phe) levels in the blood and various tissues including the brain. The incidence in Caucasians is approximately one in 10,000, giving a heterozygote frequency of one in 50 to one in 70. About one in 15,000 infants is born with PKU in the United States.

Synonyms and Related Disorders

Hyperphenylalaninemia; Phenylalanine hydroxylase deficiency; PKU

Genetics/Basic Defects

1. Inheritance
   a. Autosomal recessive
   b. Parents: obligatory carriers
2. Basic defect
   a. Deficient activity of the enzyme phenylalanine hydroxylase (PAH), resulting in hyperphenylalaninemia. PAH, a liver-specific enzyme, catalyzes the conversion of phenylalanine to tyrosine, using tetrahydrobiopterin as a cofactor. Chromosomal locus of the *PAH* gene is on 12q24.1.
   b. Identification of more than 400 different mutations in the *PAH* gene (National Institutes of Health Consensus Development Conference Statement 2001)
      i. Deletions
      ii. Insertions
      iii. Missense mutations
      iv. Splicing defects
      v. Nonsense mutations
   c. Compound heterozygotes in most PKU patients, contributing to the clinical heterogeneity and biochemical heterogeneity
   d. Consequences of accumulation of phenylalanine (Phe) and other amino acids in the CNS
      i. Irreversible brain damage from the first few weeks of life
      ii. Severe learning disabilities and associated behavioral and psychological problems

Clinical Features

1. Treated patients
   a. Symptom-free on strict metabolic control using a low-phenylalanine diet for the infants detected by newborn screenings
   b. Normal development with a normal life span when diagnosed early in the newborn period and treated effectively with lifelong dietary control
2. Untreated patients
   a. Profound mental retardation
   b. Psychomotor handicaps
   c. Microcephaly
   d. Delayed speech
   e. Seizures
   f. Light hair and eyes and fair skin secondary to decreased formation of melanin pigment because of compromised tyrosine formation
   g. Musty body or urine odor secondary to excretion of phenylacetic acid into the sweat and the urine

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h. Vomiting
i. Irritability
j. Eczema
k. Subtle neurologic findings, sometimes noted even in treated individuals
   i. Hypertonic reflexes
   ii. Intention tremor
l. Behavior problems
   i. Autistic-like behaviors
   ii. Hyperactivity
   iii. Agitation
   iv. Aggression

3. Maternal PKU
   a. Background information
      i. Loss of dietary compliance frequently starting during midchildhood
      ii. Noncompliance on special diet by many affected adolescent females, capable of reproduction, with blood phenylalanine levels above the current recommended therapeutic range
      iii. Loss of follow-up of such females despite effort to identify them
      iv. Teratogenic effect of elevated phenylalanine levels during pregnancy
      v. Fetal anomalies preventable by dietary therapy starting before conception and throughout pregnancy on women with PKU
   b. Abnormalities in the children of women with uncontrolled PKU during pregnancy
      i. Psychomotor retardation (92%)
      ii. Intrauterine growth retardation (40%)
      iii. Microcephaly
      iv. Congenital heart defects (10%)
      v. Postnatal growth retardation
      vi. Neurologic deficits
      vii. Mild craniofacial dysmorphic features
      viii. The frequency of abnormalities directly related to the degree of elevation of maternal phenylalanine levels during pregnancy
      ix. Abnormalities more likely to occur if maternal phenylalanine levels are not controlled during critical periods of embryogenesis and organogenesis early in pregnancy
   c. Currently, the control of phenylalanine levels during pregnancy is recommended at 2–6 mg/dL or 1–4 mg/dL: at least as strict, if not more strict, as that currently recommended for PKU treatment during early childhood.
   d. Women with mild forms of PKU having relatively mild elevations of the phenylalanine are at risk of adversely affecting the fetuses if the mothers are unmonitored and untreated during pregnancies. Because placental gradient favors the fetus, the levels of Phe are higher in the fetus than in the mother.
   e. Effects of uncontrolled maternal PKU occur regardless of the genetic PKU status of the fetus.

Diagnostic Investigations

1. Universal newborn screening from a heel stick bloodspot for PKU (since the 1960s) for early detection and treatment of the disorder (National Institutes of Health Consensus Development Conference Statement 2001)
   a. Guthrie bacterial inhibition assay
      i. Inexpensive
      ii. Simple
      iii. Reliable
   b. Fluorometric analysis
      i. Quantitative and automated test
      ii. Fewer false positive
   c. Tandem mass spectrometry
      i. Quantitative and automated test
      ii. Fewer false positive
      iii. Measurements of tyrosine
      iv. Identification of other metabolic disorders on a single sample
2. Plasma quantitative amino acid analysis especially phenylalanine and tyrosine levels (National Institutes of Health Consensus Development Conference Statement 2001)
   a. Phe concentrations persistently >2 mg/dL in the untreated state
   b. Recommended blood Phe levels in US clinics
      i. 2–6 mg/dL for age <12 years
      ii. 2–10 mg/dL for age >12 years
   c. Frequent monitoring of blood Phe levels
      i. During first year: once a week to once a month
      ii. After first year: once a month to once every 3 months
   d. Recommended blood Phe levels in pregnant maternal PKU
      i. <6 mg/dL achieved at least 3 months before conception
      ii. 2–6 mg/dL during pregnancy

3. MRI of the brain
   a. Hypoplasia of the corpus callosum: a marker for adverse brain development in maternal PKU
   b. Areas of demyelination
4. Molecular genetic testing
   a. Primary purpose
      i. Confirmatory diagnostic testing
      ii. Determine carrier status of at-risk relatives
      iii. For prenatal diagnosis
   b. Methodology
      i. Targeted mutation analysis
      ii. Mutation scanning
      iii. Sequence analysis
      iv. Duplication/deletion analysis
      v. Linkage analysis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Twenty-five percent affected
      ii. Fifty percent carrier
      iii. Twenty-five percent normal
   b. Patient's offspring
      i. Not increased unless the spouse is also a carrier in which case there will be a 50% risk of having an affected offspring and a 50% of having a carrier offspring
      ii. All offspring of PKU mothers
         a) Carry at least one abnormal gene at the PAH locus inherited from their homozygous affected mothers (obligatory heterozygotes)
         b) Approximately one in 120 (1/4 × 1/30) offspring will be affected by inheriting two abnormal *PAH* genes from both parents depending on the PKU carrier status of the father
2. Prenatal diagnosis
   a. Fetal ultrasonography in noncompliant maternal PKU
      i. Intrauterine growth retardation
      ii. Microcephaly
      iii. Congenital heart disease
   b. DNA mutation analysis on fetal cells by amniocentesis or CVS
      i. Provided the disease-causing mutations in the *PAH* gene identified in an affected family members
      ii. Informative markers available for linkage analysis
   c. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified in an affected family member
3. Management
   a. Dietary phenylalanine restriction: the only known strategy of preventing neurological impairment and mental retardation in patients with PKU
      i. Natural history of the disease modified by a low-phenylalanine diet
      ii. Early strict restriction of phenylalanine intake resulting in normal intelligence
      iii. Phenylalanine-restricted diet required for life
      iv. Special medical foods devoid of or low in phenylalanine supplemented with tyrosine
      v. Restricted diet worth trying in most individuals with previously untreated PKU with possible benefits in the areas of concentration, alertness, mood, irritability, and adaptive behavior (Fitzgerald et al. 2000)
   b. Late-treated PKU: although the severe cognitive impairment associated with untreated PKU can in many cases be partially reversed with dietary treatment, prompt initiation of treatment following newborn metabolic screening is essential for optimal development and the prevention of disability (Grosse 2010).
   c. Adult complications in PKU (Hoeks et al. 2009): consisting of two components, namely high Phe levels (e.g., neurological and neuropsychological problems) and complications occur as a cause of dietary protein restriction (e.g., vitamin deficiencies and osteoporosis)
      i. Adults with PKU who were treated from early infancy have normal intelligence, but their neuropsychological test scores are somewhat lower than those of the general population, their parents, and their unaffected siblings (Weglage et al. 1993).
      ii. Adults with PKU who were continuously treated but relaxed the diet have displayed white matter abnormalities on structural magnetic resonance imaging (Cleary et al. 1994; Sener 2003), which are considered to be indicative of a reduction in myelin (Dyer et al. 1996; Joseph and Dyer 2003). These abnormalities disappear after reintroducing a strict diet.

iii. Neurological investigations in early-treated adults with PKU who discontinued the diet reveal a higher incidence of minor neurological signs including tremor, brisk deep tendon reflexes, or clumsy motor coordination (Thompson et al. 1990; Pietz et al. 1998). In rare cases, severe neurological deterioration may occur after cessation of dietary treatment.

iv. Severe behavior and psychiatric problems are seen in profoundly retarded (untreated) adults with PKU in the third and fourth decade of life (Paine 1957). With introduction of a Phe-restricted diet, these symptoms are sometimes reversible (Baumeister and Baumeister 1998).

v. Vitamin B12 deficiency
   a) Vitamin B12 is only found in animal protein, the sources being meat, fish, and poultry. Since the PKU diet is restricted in protein, vitamin B12 must be provided either combined with the amino acid supplement or from a separate supplement.
   b) Vitamin B12 deficiency can occur when PKU patients relax their diet in adolescence (Robinson et al. 2002). They tend to choose products that are low in animal protein, and amino acid supplements are not taken properly (Hvas et al. 2006).

vi. Osteoporosis: possibly due to long-standing dietary deficiency in protein, calcium, vitamin D, or trace elements, or a primary defect in bone turnover inherent to the disease itself (Modan-Moses et al. 2007)

d. Nutritional management of PKU (Feillet and Agostoni 2010)
   i. Becomes more complex with the multitude of amino acid substitutes available and with the different nutritional issues, such as polyunsaturated fatty acids, micronutrient deficiencies, bone disease, and antioxidant status, that have arisen
   ii. Long-term dietary guidance and monitoring of the nutritional status of patients with PKU should be part of a follow-up program that continues for life.

e. Counseling for maternal PKU
   i. Genetic and nutritional evaluation and counseling, optimally before contemplating pregnancy
   ii. Benefits of dietary phenylalanine restriction in pregnant women with hyperphenylalaninemia: decrease the incidence of following fetal effects (Hanley et al. 1999)
      a) Mental retardation
      b) Microcephaly
      c) Congenital heart disease
      d) Intrauterine growth retardation
   iii. Assistance of women with hyperphenylalaninemia, who are unable or unwilling to maintain blood phenylalanine levels in the range for optimum pregnancy outcome, to obtain adequate means for birth control, including tubal ligation if requested
   iv. Counseling of women with hyperphenylalaninemia who conceive with blood phenylalanine levels greater than 4–6 mg/dL concerning risks to the fetus: offer detailed ultrasonography to detect fetal abnormalities such as growth retardation and congenital heart defects
   v. Close monitoring of serum phenylalanine levels at 2–6 mg/dL during pregnancy of PKU mother and intake of vitamins (folic acid and vitamin B12, in particular) and other nutrients (National Institutes of Health Consensus Development Conference Statement 2001)
   vi. Blood testing for hyperphenylalaninemia indicated to children born to women with features of maternal PKU fetal effects without a known cause

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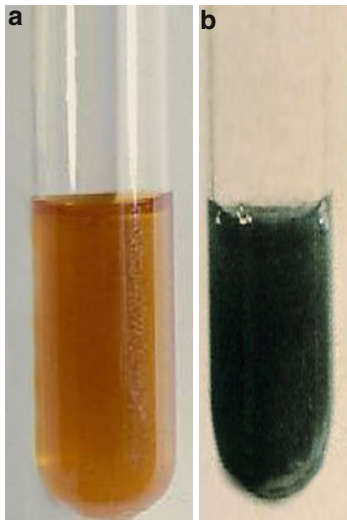

Fig. 1 (**a, b**) Normal-colored urine (*left*) and deep green color change after adding ferric chloride due to the presence of phenylpyruvic acid (*right*)

Fig. 2 (**a–c**) Two successfully treated girls: the first girl at age 3 years and 7 months, the second girl at age 6 years and at age16 years

Fig. 3 A successfully treated 25-year-old adult female with PKU

Fig. 4 (**a**–**f**) Six adults with untreated PKU showing varying degrees of mental retardation

Fig. 5 Noncompliant PKU mother and her infant with microcephaly and mental retardation

Pierre Robin Sequence

Pierre Robin described a group of patients with cleft palate, micrognathia, and glossoptosis in 1923. The meticulous documentation of the triad of findings led to the recognition of the sequence that bears his name. Pierre Robin sequence is estimated to affect approximately 1 in 8,500 births (Bush and Williams 1983).

Synonyms and Related Disorders

Glossoptosis, micrognathia, and cleft palate

Genetics/Basic Defects

1. Inheritance
   a. Sporadic in most instances
   b. May be familial with autosomal dominant mode of inheritance
   c. Syndromic form: etiologically heterogeneous (Cohen 1999; Taylor 2001)
      i. Monogenic
         a. Stickler syndrome (common cause)
         b. Beckwith-Wiedemann syndrome
         c. Camptomelic syndrome
         d. Cerebrocostomandibular syndrome
         e. Congenital myotonic dystrophy
         f. Distal arthrogryposis-Robin syndrome
         g. Mandibulofacial dysostosis
         h. Miller-Dieker syndrome
         i. Otopalatodigital syndrome II
         j. Robin-oligodactyly syndrome
      ii. Chromosomal
         a. Del(22q) velocardiofacial syndrome (common cause)
         b. Del(4q) syndrome
         c. Del(6q) syndrome
         d. Dup(11q) syndrome
      iii. Teratogenic
         a. Fetal alcohol syndrome
         b. Fetal hydantoin syndrome
         c. Fetal trimethadione syndrome
      iv. Deformation
         a. Oligohydramnios
         b. Uterine structural anomalies
         c. Amniotic band syndrome
      v. Disruption: amniotic band disruption
      vi. Unknown cause:
         a. CHARGE syndrome
         b. Femoral dysgenesis
         c. Moebius sequence
         d. Robin/amelia association
2. Pathogenetically and phenotypically variable (Robin sequences and complexes)
   a. Malformation sequence based on intrinsic mandibular hypoplasia that prevents the normal descent of the tongue interfering with palatal fusion, for example:
      i. Treacher-Collins syndrome
      ii. Del(22q) syndrome
   b. Deformation sequence based on extrinsic mandibular hypoplasia caused by intrauterine constraint
      i. Oligohydramnios (reduced amniotic fluid results in compression of the chin against the sternum restricting mandibular growth and impacting the tongue between the palatal shelves)

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ii. Mandibular catch-up growth expected after birth when intrauterine deforming forces are no longer acting since micrognathia is based upon intrauterine molding
c. Neurogenic hypotonia leading to lack of mandibular exercise
d. Connective tissue dysplasia: Stickler dysplasia complex
e. Spondyloepiphyseal dysplasia congenita complex
3. Genetic basis of the Pierre Robin sequence (Jakobsen et al. 2006)
a. A comparison among cases in the literature and cases in cytogenetic databases revealed consistency to a certain degree to loci 2q24.1–33.3, 4q32–qter, 11q21–23.1, and 17q21–24.3.
b. No particular candidate genes can be identified for certain from the present study, but GAD67 on 2q31, PVRL1 on 11q23–q24, and the SOX9 gene on 17q24.3–q25.1 are suggested to be important.
5. Developmental delay
a. Usually not present in isolated Robin sequence
b. May be present depending on the underlying syndrome
6. Middle ear diseases associated with cleft palate
a. Otitis media (80%)
b. Auricular anomalies (75%)
c. Hearing loss, mostly conductive (60%)
7. Cleft palate–associated problems
a. Speech defects
b. Velopharyngeal insufficiency
8. "Catch-up growth" of the mandible
a. Normal mandibular growth in patients with Robin sequence secondary to mechanical constraint
b. Deficient mandibular growth in patients with intrinsic mandibular anomalies
9. Other signs and symptoms and associated anomalies depending on the underlying conditions

Clinical Features

1. Classic triads
a. Posterior, U-shaped cleft palate
b. Micrognathia/retrognathia
c. Glossoptosis (observed tendency of the tongue to move posteriorly obstructing the oropharynx)
2. Pierre Robin sequence using different criteria
a. Mandibular deficiency
b. Cleft palate
c. Upper airway obstruction
3. Respiratory difficulty
a. Often the first sign causing concern relating to feeding
b. May not necessarily be present at birth
c. Upper airway obstruction and apnea
i. Glossoptosis associated with retrognathia
ii. Upper airway collapse secondary to:
a. Hypotonic pharynx
b. Laryngomalacia
c. Laryngeal cleft
d. Laryngeal web
d. Complications of continuing airway obstruction
i. Failure to thrive
ii. Pectus excavatum
iii. Decreased pulmonary function
iv. Sudden death
4. Failure to thrive

Diagnostic Investigations

1. Assess respiratory sounds with stethoscope during feeding and at rest.
2. Monitor developmental milestone achievement.
3. Pulse oximetry monitoring to document drops in oxygen saturation
4. Flexible fiber optic nasopharyngoscopy
a. To identify exact mechanism of upper airway obstruction
b. To assess pharyngeal, palatal, lingual, and laryngeal morphology and function during feeding and swallowing
5. Identify the underlying cause of the micrognathia.
6. Orthodontic assessment
7. Hearing assessment
8. Cephalometric radiographs
a. Deformation sequence
i. Mandible
a. Short body
b. Short ramus
c. Increased gonial angle
d. Incomplete catch-up growth
ii. Cranial base angle: decreased
b. Treacher-Collins syndrome
i. Mandible
a. Short body
b. Short ramus

c. Characteristic shape
d. Severely affected growth
ii. Cranial base angle: decreased
c. Del(22q11.2) syndrome
i. Mandible
a. Retrognathia
b. Essentially normal in shape
ii. Cranial base angle: increased
d. Stickler dysplasia complex
i. Mandible
a. Short ramus
b. Antegonial notching of body
ii. Cranial base angle: decreased
e. Spondyloepiphyseal dysplasia congenita complex: short body of mandible
9. Chromosome analysis: del(22q11.2)
10. Molecular diagnosis (Cohen 1999)
a. Treacher-Collins syndrome: mutations in *TCOF1*
b. Stickler dysplasia complex
i. Mutations in *COL2A1*
ii. Mutations in *COL11A1*
c. Spondyloepiphyseal dysplasia congenita complex: mutations in *COL2A1*

Genetic Counseling

1. Recurrence risk
a. Patient's sib: rare unless Pierre Robin sequence is a part of a syndrome
b. Patient's offspring: rare unless Pierre Robin sequence is a part of a syndrome
2. Prenatal diagnosis by ultrasonography demonstrating micrognathia/retrognathia and cleft palate
3. Management
a. Prone positioning of infants believed to help prevent the tongue and mandible from obstructing the airway, leading to generally improved oxygen saturation
b. Nasogastric tube placement for early feeding
c. Occupational therapy directed toward management of the palatal abnormality
d. Surgical intervention for airway obstruction
i. Glossopexy to bring tongue forward and attach it to an anterior structure to prevent the tongue from falling back into the airway
ii. Tracheotomy needed only in cases where conservative treatments fail
iii. Mandibular distraction involving surgical incision of the mandible followed by the application of traction to stimulate new bone growth
iv. Repair of cleft palate
e. Treat middle ear infections
i. Antibiotics
ii. Placement of tympanostomy tubes
f. Speech therapy

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Fig. 1 (**a**–**f**) Three infants with typical Pierre Robin sequence

Polycystic Kidney Disease, Autosomal Dominant Type

Autosomal dominant polycystic kidney disease (ADPKD) is the most common form of polycystic kidney disease with an estimated incidence of approximately 1/400–1/1,000 individuals worldwide. It roughly accounts for 10% of patients with chronic renal failure requiring hemodialysis or transplantation (Arnaout 2001).

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant with almost complete penetrance
   b. Negative family history in 40% of cases
2. Genetically heterogeneous with at least three different genes now known to cause ADPKD. All three types of ADPKD present with an identical profile of extrarenal manifestations (including liver cysts and aneurysms) (Wilson 2004).
   a. Type I (85–90% of cases): caused by mutations in *PKD1* gene, which is:
      i. Mapped on chromosome 16p13.3
      ii. The most severe form with a lower median survival and a higher risk of progressing to end-stage renal disease
      iii. Closely linked to TSC2, a gene responsible for a major form of tuberous sclerosis
   b. Type II (most of the remaining cases): caused by mutations in *PKD2* gene, which is:
      i. Mapped on chromosome 4q21–q23
      ii. Identified by positional cloning
      iii. Producing milder disease but otherwise phenotypically identical with the *PKD1* disease
   c. A small number of familial cases reported to be unlinked to both the *PKD1* and *PKD2* loci, suggesting the existence of at least one more proposed gene (*PKD3*) which has not been identified
   d. Patients with mutations in both the PKD1 and PKD2 genes (transheterozygotes) have a more severe clinical course than those with mutations in only one of the genes.
3. Mechanism of cyst formation: somatic second-hit model (Wilson 2004)
   a. A germline mutation in one PKD allele in all cells in ADPKD
   b. A random somatic mutation (second hit) occurring in the normal allele causing increased cell proliferation, leading to cyst formation
4. Molecular basis of ADPKD (Rossetti et al. 2002b)
   a. Protein products of the disease gene forming a macromolecular signaling structure, the polycystin complex, that regulates fundamental aspects of renal epithelial development and cell biology
   b. Protein products of PKD1 and PKD2 (polycystin-1 and polycystin-2, respectively
      i. Share sequence homology
      ii. May form components of a receptor/channel complex
   c. Polycstin-1
      i. Predicted to have a receptor-like structure
      ii. May be involved in cell-cell/matrix interactions

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iii. May have a regulatory role over a polycystin channel
d. Polycystin-2
i. Similar to and functioning as an ion channel subunit
ii. Causes nonselective cation permeability
e. Basic defect in ADPKD: could be in polycystin-regulated intracellular Ca^{++} levels
5. Disease characteristics.
a. Principal ductal organs with cyst formation
i. Kidneys
ii. Liver
b. Consequences of cyst enlargement
i. Progressive destruction of normal renal tissue
ii. End-stage renal failure in >50% of patients by age 60
c. Systemic involvement
i. Arterial hypertension developing early and observed in >50% of patients
ii. Vascular aneurysms
iii. Cardiac valve defects
iv. Colonic diverticula

Clinical Features

1. Intrafamilial and interfamilial variability in the onset, phenotype, and progression of the disease
a. Due to genetic heterogeneity
i. More common PKD1 (accounting for approximately 85% of cases associated with more severe disease)
ii. Evidence of significant intrafamilial phenotypic variation suggesting modifying factors (such as the angiotensin-converting enzyme insertion/deletion polymorphism) as well as environmental factors that influence the clinical course
iii. Association of the position of the *PKD1* mutation with earlier end-stage renal disease
b. Age of onset
i. Presenting at any age
ii. Generally presenting in the fourth and fifth decades of life
iii. Occasionally presenting in the fetal or neonatal period
2. Onset of disease in the childhood in children who carry *PKD1* gene
a. Frequency of children with renal cysts detectable by ultrasound
i. Sixty percent by 5 years of age
ii. Seventy-five to Eighty percent among children aged 5–18 years
b. Number of renal cysts at 11 years
i. One to ten in 60% of children
ii. More than ten cysts in 40% of children
3. Age at the time of diagnosis and progression of the disease
a. Diagnosis in utero or in the first year of life (intrauterine or infantile onset)
i. Manifesting unusually severe disease
ii. End-stage renal disease during childhood in 18% of cases
b. Diagnosis after the first year of life
i. Increase in the number of cysts over a mean interval of 3.7 years
ii. Systolic hypertension in 9% of cases
iii. None with decreased renal function
4. Renal manifestations (Fick et al. 1994)
a. Development of bilateral renal cysts
i. Primary renal manifestation
ii. Leading to functional changes (impaired renal concentrating capacity, hypertension)
iii. Leading to various clinical manifestations
b. Flank or back pain (about 60%)
c. Acute pain
i. Infected cyst
ii. Ruptured cyst (associated with gross hematuria)
iii. Nephrolithiasis (20–36%)
d. Urinary tract infection (40–68%)
e. Hematuria
f. Mild proteinuria
g. End-stage renal disease
5. Extrarenal manifestations
a. Liver involvement
i. Most common extrarenal manifestation
ii. Liver cysts uncommon before 16 years of age
iii. Liver cysts observed in about 75% of patients older than 60 years
iv. No liver symptoms in most patients with ADPKD
v. Occasionally encountered liver changes
a) Congenital hepatic fibrosis
b) Segmental dilation of the biliary tract

vi. Liver cysts responsible for most of the hepatic complications
vii. Acute complications (Chauvear et al. 2000)
a) Cyst infection
b) Cyst hemorrhage
c) Cyst rupture
d) Cyst torsion
viii. Chronic complications related to progressive increase of the polycystic liver (Chauvear et al. 2000)
a) Abdominal mass
b) Ascites
c) Hepatic venous outflow obstruction (Budd-Chiari syndrome)
d) Portal hypertension with variceal bleeding
e) Inferior vena cava compression
f) Bile duct compression
g) Jaundice
ix. Intrahepatic biliary cysts
a) More common in women
b) Exacerbated by pregnancy

b. Other rare cystic involvement (Fick et al. 1994)
i. Pancreatic cysts (10%)
ii. Arachnoid cysts (5%)
iii. Ovarian cysts

c. Cardiovascular manifestations not uncommon
i. Intracranial berry aneurysms (5–10%)
ii. Dolichoectatic arteries
iii. Aortic root dilatation
iv. Dissections of intracerebral, coronary, thoracic, iliac, aortic, and splenic arteries reported
v. Cardiac valve defects

d. Other noncystic involvement
i. Colonic diverticula (80% of patients with end-stage renal disease)
ii. Hernias (25%)

6. Clinical course in children
a. Clinical spectrum ranging from severe neonatal manifestations mimicking autosomal recessive polycystic kidney disease to renal cysts noted on ultrasound in asymptomatic children
b. Diagnosis made in utero by ultrasound: massively enlarged cystic kidneys
c. Newborn presenting with Potter phenotype and death from pulmonary hypoplasia
d. Newborn with large abdominal masses
e. After neonatal period
i. Hypertension
ii. Abdominal pain
iii. Palpable abdominal mass
iv. Hematuria
v. Renal insufficiency, only rarely
vi. Renal infections

f. Rare extrarenal manifestations
i. Liver cysts
ii. Cerebral vessel aneurysms

g. Prognosis
i. Severe symptoms in neonatal or infantile cases
ii. Milder symptoms in late childhood cases

7. Reproductive issues for adults with ADPKD (Vora et al. 2008)
a. Men with ADPKD
i. Necrospermia
ii. Immotile sperm
iii. Seminal vesicle cysts
iv. Ejaculatory duct cysts

b. Female fertility is not affected
i. Affected women with ADPKD and normal renal function have a high rate of successful uncomplicated pregnancies.
ii. Pregnant women with ADPKD with compromised kidney function should be monitored carefully for the development of hypertension and preeclampsia.

8. Risk factors precipitating faster progression of the disease
a. The *PKD-1* gene
b. Male gender
c. Earlier onset of symptoms
i. Renal enlargement
ii. Hematuria
iii. Proteinuria
iv. Incipient renal failure
v. Hypertension

d. Having >10 renal cysts before age 12 years
e. Having blood pressures above the 75th percentile for age, height, and gender
f. Polycystic liver disease
i. Frequently associated with autosomal dominant polycystic kidney disease
ii. Develops later than renal cysts
iii. Develops earlier and more severe in women than in men

9. End-stage renal disease
   a. The most feared renal complication of ADPKD
   b. Occurs in more than half of patients by the seventh decade of life
10. Differential diagnosis (Wolyniec et al. 2008)
   a. Autosomal recessive polycystic kidney disease: manifests advanced renal insufficiency present already in childhood or early youth (see the chapter on Autosomal Recessive Polycystic Kidney Disease)
   b. Tuberous sclerosis complex (see the chapter)
      i. Cysts in the kidneys observed in 20% of patients with tuberous sclerosis complex
      ii. Associated with characteristic skin and neurological symptoms
   c. Von Hippel-Lindau disease (see the chapter)
   d. Medullary cystic kidney disease
      i. Most commonly occurs as juvenile nephronophtisis
      ii. Associated with chronic renal failure in childhood
   e. Oral-facial-digital syndrome (see the chapter)
   f. Multicystic renal dysplasia in adults
      i. Usually a unilateral disorder
      ii. Frequent presence of calcification in the cyst walls and abnormal structure of parenchyma between the cysts visible on ultrasound
   g. Medullary sponge kidney: lithiasis and nephrocalcinosis commonly observed in the course of the disease
   h. Acquired cystic kidney disease

Diagnostic Investigations

1. Urinalysis
   a. Hematuria
   b. Mild proteinuria
   c. Evidence of infection
2. Sonography
   a. Prenatal presentation
      i. Large hyperechogenic kidneys
      ii. Variable size
      iii. Mixtures of small and large cysts
      iv. Exceptionally uncommon oligohydramnios
   b. Postnatal presentation: invariably large cysts
3. Renal ultrasound and IVP
   a. Enlarged kidneys
   b. Macrocysts and distortion of the collecting system
4. CT scan and/or MRI for renal, hepatic, pancreatic, and ovarian cysts
5. CT scan and/or MRI angiography for intracranial aneurysm
6. Renal function tests
7. Renal ultrasound to assess carrier status
   a. A painless and relatively noninvasive procedure
   b. Detection rate in asymptomatic subjects from families with known ADPKD
      i. Twenty-two percent of cases in the first decade
      ii. Sixty-six percent of cases by the second decade
      iii. Eighty-six percent by age 25
8. Molecular diagnosis (Harris and Rossetti 2010)
   a. Diagnosis of ADPKD before the onset of symptoms is usually performed using renal imaging by either ultrasonography, CT, or MRI. In general, these modalities are reliable for the diagnosis of ADPKD in older individuals.
   b. However, molecular testing can be valuable when a definite diagnosis is required in young individuals, in individuals with a negative family history of ADPKD, and to facilitate preimplantation genetic diagnosis.
   c. Although linkage-based diagnostic approaches are feasible in large families, direct mutation screening is generally more applicable.
   d. Identification and characterization of *PKD1* and *PKD2* provided an opportunity for mutation-based molecular diagnostics to be used for ADPKD. Mutations in *PKD1* account for ~85% of cases and cause more severe disease than mutations in *PKD2*.
   e. As ADPKD displays a high level of allelic heterogeneity, complete screening of both genes is required.
   f. Consequently, such screening approaches are expensive. Screening of individuals with ADPKD detects mutations in up to 91% of cases.
   g. However, only ~65% of patients have definite mutations, with ~26% having nondefinite changes that require further evaluation.
   h. Collation of known variants in the ADPKD mutation database and systematic scoring of nondefinite variants is increasing the diagnostic value of molecular screening.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Not increased in de novo case
      ii. Fifty percent if one of the parent is affected
   b. Patient's offspring
      i. Fifty percent risk of acquiring the disease
      ii. Both sexes of offspring affected equally
2. Carrier testing for family members at risk
   a. Ultrasound and radiography
   b. Molecular mutation analysis of *PKD1* and *PKD2* genes
3. Prenatal diagnosis
   a. Prenatal ultrasonography
      i. Enlarged kidneys (hyperechogenic) with or without cysts: the most common fetal findings
      ii. Absence of urine in the bladder
      iii. May not be evident until the third trimester
      iv. Evidence of uteroplacental insufficiency (Vora et al. 2008)
         a) Intrauterine growth restriction
         b) Oligohydramnios
   b. Molecular mutation analysis of *PKD1* and *PKD2* genes on fetal DNA obtained from amniocentesis or CVS, provided the mutation has been identified in the affected family members or linkage has been established in the family
   c. Preimplantation genetic diagnosis possible, provided the mutation has been identified previously
4. Management (Harris 2002)
   a. No treatment currently directed at the disease process
   b. Monitoring of presymptomatic patients with ADPKD
      i. Monitor blood pressure
      ii. Test renal function
      iii. Advantages
         a) Prevent or control hypertension
         b) Prevent or control infection
         c) Identify potential kidney donors from among the family
         d) Offer advice on reproduction
         e) Provide prenatal diagnosis
   c. Treatment of polycystic kidney disease
      i. Narcotic analgesics for pain
      ii. Antibiotics for infection
      iii. Treatment of nephrolithiasis
         a) Potassium citrate for uric acid lithiasis, hypocitric calcium oxalate nephrolithiasis, and distal acidification defects
         b) Extracorporeal shock wave lithotripsy
         c) Percutaneous nephrostolithotomy
      iv. Needle aspiration of dominant cysts
      v. Laparoscopic cyst decortication
      vi. Open renal cyst decortication
      vii. Therapeutic intervention aimed at slowing the progression of renal failure
         a) Control of hypertension
         b) Control of hyperlipidemia
         c) Dietary protein restriction
         d) Control of acidosis
         e) Prevention of hyperphosphatemia
      viii. Renal dialysis
      ix. Renal transplantation for end-stage renal disease
   i. Treatment of massive polycystic liver disease
      i. Aspiration of cyst fluid
      ii. Stenting
      iii. Cyst fenestration
      iv. Liver resection
      v. Liver transplantation
   j. Treatment of intracranial aneurysms
      i. Asymptomatic aneurysm
         a) Observation and yearly follow-up
         b) Surgery for enlarging aneurysm
      ii. Ruptured or symptomatic aneurysm: surgical clipping at its neck
   k. Management of aortic dissection
      i. Aortic root dilatation
         a) Yearly follow-up
         b) Strict blood pressure control with β-blockade
      ii. Surgery (replacement of the aorta) for aortic root greater than 55–60 mm

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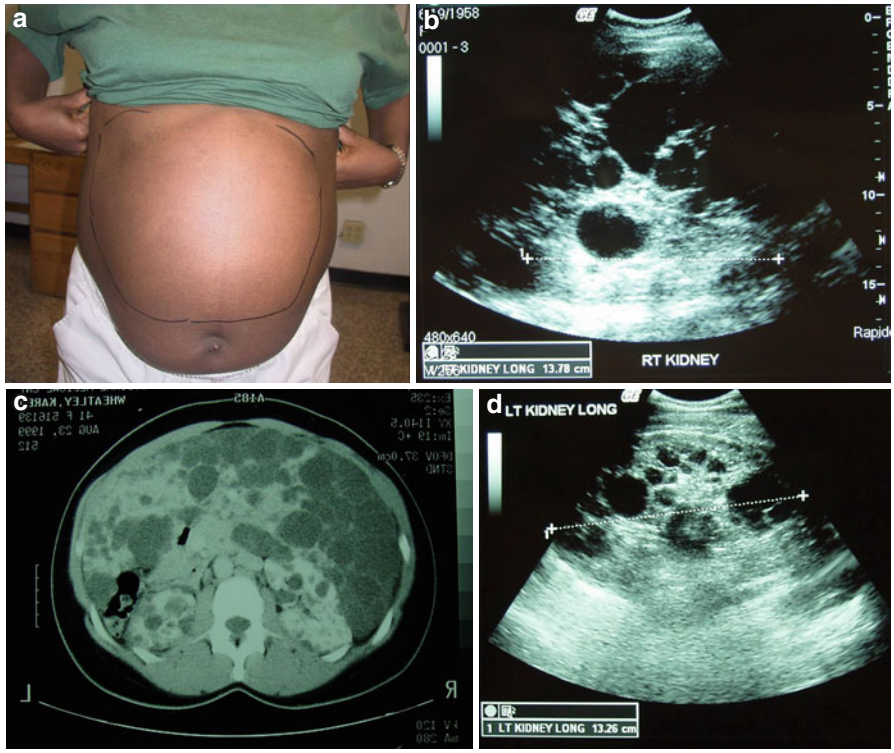

Fig. 1 A lady (**a**) with autosomal dominant polycystic kidney disease and with family history of multiple affected family members. Her liver was markedly enlarged as shown by a pencil mark on the patient's photo. The ultrasonography of the kidneys showed numerous cysts with minimal residual normal appearing cortex. The right kidney (**b**) measured 11 cm, with the largest cyst measuring 2.9 cm. The left kidney measured 13.3 cm in length, with the largest cyst measuring 3.8 cm (image not shown). The abdominal CT scan (**c**) showed marked hepatomegaly which occupies the entire abdomen. Numerous hepatic cysts and renal cysts were evident. Numerous cysts of different sizes were also detected in her brother's enlarged kidneys by ultrasonography (the *left* kidney is shown here on image **d**)

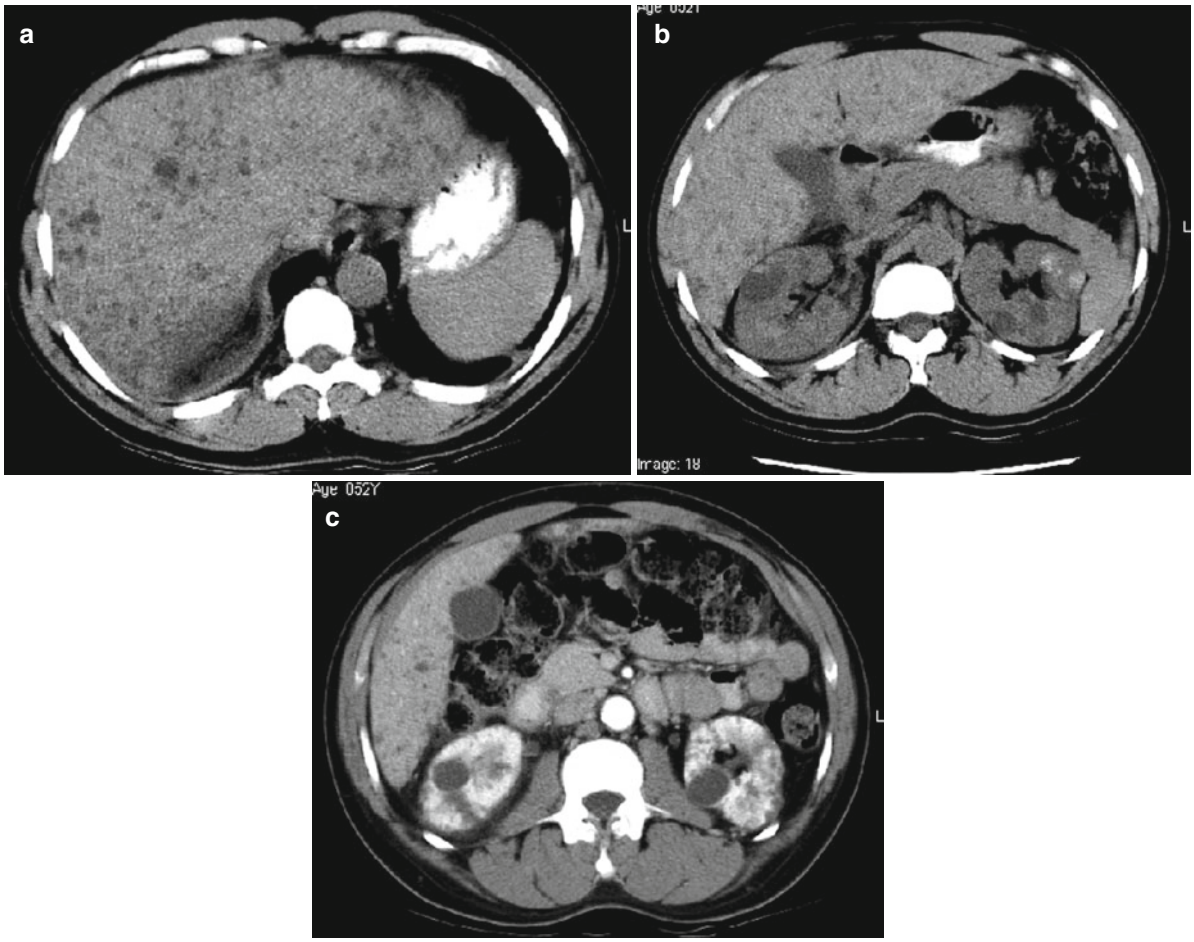

Fig. 2 (**a**–**c**) Three CT scans of an adult patient with polycystic kidney disease with and without contrast showing multiple cysts in the kidneys and liver

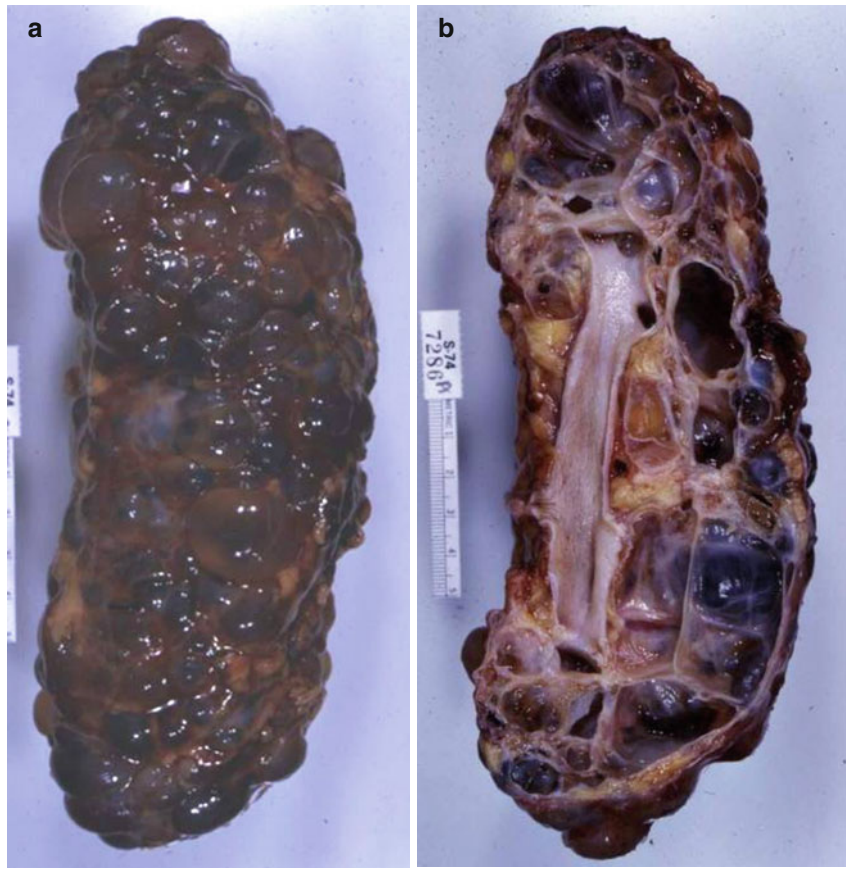

Fig. 3 (**a**, **b**) Appearance of the gross and cut section of a kidney (745 g) surgically removed from a 43-year-old female with autosomal dominant polycystic kidney disease

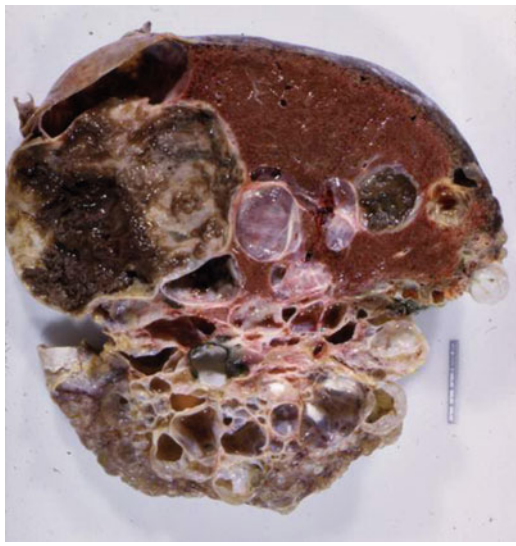

Fig. 4 Multiple hepatic cysts of a patient with autosomal dominant polycystic kidney disease

Polycystic Kidney Disease: Autosomal Recessive Type

Autosomal recessive polycystic kidney disease (ARPKD) or polycystic kidney and hepatic disease 1 (*PKHD1*) is an often devastating form of polycystic kidney disease. It is also known as infantile polycystic kidney disease. The incidence of ARPKD is estimated to be 1 in 20,000 live births, and the frequency of the heterozygous carrier state is 1 in 70 (Lonergan et al. 2000).

Synonyms and Related Disorders

Infantile polycystic kidney disease; Polycystic kidney and hepatic disease

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. No clear evidence of genetic heterogeneity
3. Molecular cause (Harris and Rossetti 2004)
   a. Mutations in the *PKHD1* gene on chromosome 6p21.1-p12, encoding a putative receptor protein, fibrocystin (or polyductin)
   b. The ARPKD protein, fibrocystin, is predicted to be an integral membrane, receptor-like protein containing multiple copies of an Ig-like domain (TIG).
   c. Fibrocystin is localized to the branching ureteric bud, collecting and biliary ducts, consistent with the disease phenotype, and often absent from ARPKD tissue.
   d. In common with other PKD-related proteins, fibrocystin is localized to the primary cilia of renal epithelial cells, reinforcing the link between ciliary dysfunction and cyst development.
   e. The majority of patients are compound heterozygotes, and preliminary genotype/phenotype studies associate two truncating mutations with severe disease.
   f. The complexities of *PKHD1*, marked allelic heterogeneity, and high level of missense changes complicate gene-based diagnostics.
4. Genotype-phenotype correlations (Denamur et al. 2010)
   a. All patients carrying two truncating mutations displayed a severe phenotype with perinatal or neonatal demise (Dell and Avner 2011).
   b. Patients who survive have at least one missense mutation.

Clinical Features

1. The most common heritable cystic renal disease manifesting in infancy and childhood (Lonergan et al. 2000)
2. A wide variable clinical spectrum, ranging from severe renal impairment, and a high mortality rate in infancy to older children and adolescents with minimal renal disease and complications of congenital hepatic fibrosis, cholangitis, and portal hypertension
3. Principal manifestations
   a. Fusiform dilatation of renal collecting ducts and distal tubuli
   b. Dysgenesis of the hepatic portal triad
4. Clinical characteristics at presentation
   a. Zero to 1 month
      i. Prenatal diagnosis made
      ii. Positive family history

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iii. Pneumothorax
iv. Flank mass
v. Hypertension
vi. Renal insufficiency

b. >1 month–1 year
i. Frank mass
ii. Hepatomegaly
iii. Hypertension
iv. Urinary tract infection

c. >1–5 years
i. Hepatomegaly
ii. Portal hypertension

d. >5 years
i. Hepatomegaly
ii. Hypertension
iii. Renal insufficiency
iv. Portal hypertension

e. Predominance of renal abnormalities in younger children

f. Predominance of hepatic disease in older children and adolescents

g. Tendency of inverse relative degrees of kidney and liver involvement
i. Children with severe renal disease usually with milder hepatic disease
ii. Children with severe hepatic disease with milder renal impairment

5. "Potter" phenotype developed in affected fetuses
a. Pulmonary hypoplasia, often incompatible with life
b. Characteristic face
i. Short and snubbed nose
ii. Deep eye creases
iii. Micrognathia
iv. Low-set flattened ears
c. Deformities of the spine and limbs (clubfoot)

6. Renal manifestations
a. Frequent loss of concentrating ability of the kidney
b. Common recurrent urinary tract infections
c. Proteinuria
d. Hematuria
e. Creatinine clearance improving early but declining progressively during adolescence
f. Hypertension early in life but usually regresses
g. Enlarged kidneys
h. End-stage renal disease

7. Hepatic manifestations
a. Congenital hepatic fibrosis
i. Invariably present but only occasionally do hepatic symptoms predominate
ii. Two predominant features characterizing the liver in ARPKD
a) Bile ducts: abnormally/irregularly formed, often increased in number, and dilated intrahepatic bile ducts
b) Portal tracts: enlarged and fibrotic
iii. Normal hepatic parenchyma
iv. Hepatocellular function almost always normal in affected patients, even when they have relatively severe portal tract disease.
v. Not by itself a diagnostic (not pathognomonic) sign. Congenital hepatic fibrosis has been observed in the following situations (Lonergan et al. 2000):
a) Meckel-Gruber syndrome
b) Vaginal atresia
c) Tuberous sclerosis
d) Juvenile nephronophthisis
e) Rarely autosomal dominant polycystic kidney disease

b. Caroli disease
i. Congenital hepatic fibrosis accompanied by a nonobstructive dilation of the intrahepatic bile ducts
ii. Clinical risk of secondary complications
a) Stone formation
b) Recurrent cholangitis: may result from ectatic bile ducts
c) Hepatic abscesses
d) Rare cholangiocarcinoma

c. Hepatomegaly

d. Portal hypertension (Lonergan et al. 2000)
i. The most common sequelae of congenital hepatic fibrosis
ii. Splenomegaly
iii. Variceal bleeding
iv. Hypersplenism
a) Leukopenia
b) Thrombocytopenia
c) Anemia
d) Increased susceptibility to infections resulting from leukopenia associated with splenic sequestration

e. Ascending cholangitis (Lonergan et al. 2000)
i. Presumably caused by entry of nonsterile gastrointestinal contents into the dilated intrahepatic bile ducts
ii. Common in patients with macroscopically dilated bile ducts

iii. Clinical features
a) Abdominal pain
b) Fever
c) Elevation in levels of hepatic enzymes
iv. Tends to recur
v. May lead to hepatic abscess formation, sepsis, and death

8. Cerebral aneurysm, a common feature of ADPKD, reported in an adult with ARPKD
9. Prognosis
a. Thirty to fifty percent of affected neonates die shortly after birth in respiratory insufficiency due to pulmonary hypoplasia.
b. Recent trend with improved prognosis
c. Sixty-seven percent of children who survive the newborn period with life-sustaining renal function at 15 years of age

Diagnostic Investigations

1. Radiography in neonates and infants with moderate to severe renal disease
a. Smoothly enlarged kidneys because of the numerous dilated collecting ducts
b. Abdominal distension
c. Gas-filled bowel loops often deviated centrally
d. Pulmonary hypoplasia and small thorax in the baby with severe kidney disease
e. Pneumothorax common at birth following assisted ventilation
2. Ultrasonography
a. Absence of renal cysts in both parents as demonstrated by ultrasound examination
b. Neonatal ultrasonography with more marked renal cystic disease
i. Massive enlarged kidneys
ii. Increased echogenicity of entire parenchyma
iii. Loss of corticomedullary differentiation
iv. Loss of central echo complex
v. Small macrocysts
vi. Usually small bladder
vii. Increased hepatic echogenicity, mainly in medulla
c. Ultrasonography in children with more prominent hepatic fibrosis
i. Massive kidney enlargement
ii. Increased hepatic echogenicity, mainly in medulla
iii. Macrocysts
a) Less than 2 cm in diameter
b) Tend to become larger and more numerous over time
iv. Enlarged echogenic liver
v. Hepatic cysts
vi. Pancreatic cysts
vii. Splenomegaly secondary to portal hypertension
viii. Hepatofugal-flow duplex and color-flow Doppler
3. CT scan
a. Nonenhanced CT: smooth, enlarged, and low-attenuating kidneys, likely the reflection of the large fluid volume in the dilated ducts
b. CT with contrast
i. Kidneys with a striated pattern representing accumulation of contrast material in the dilated tubules
ii. Linear opacifications representing retention of contrast medium in dilated medullary collecting ducts
iii. Macrocysts appearing as well-circumscribed rounded lucent defects
iv. Time of delay in visualizing the contrast medium in the kidneys, proportionate to the severity of renal impairment
4. Ultrasonography and magnetic resonance cholangiography to investigate the presence of an extent of Caroli disease in children with autosomal recessive polycystic kidney disease
5. MRI of affected children (perinatal, neonatal, and infantile course) (Kern et al. 1999)
a. Kidney appearance
i. Enlarged, humpy but still reniform in shape
ii. Homogeneously grainy parenchyma
b. Signal intensity
i. Hypointense on T1-W spin-echo sequences
ii. Hyperintense on T2-W turbo spin-echo sequences
c. RARE (rapid acquisition with relaxation enhancement)-MR-urography
i. Hyperintense, linear radial pattern seen in the cortex and medulla representing the characteristic microcystic dilatation of collecting ducts
ii. Possible few circumscribed small subcapsular cysts

6. Histopathology of the kidney
   a. Radially arranged cylindrical and fusiform ducts are present throughout renal medulla and cortex, due to a generalized dilatation of collecting ducts.
   b. The portal tracts of the liver are enlarged and contain abundant fibrous tissue and many cistern-like dilated bile ducts. The abnormal changes are the result of ductal plate malformation.
7. Molecular diagnosis
   a. Linkage analysis of the affected family using 6p21 markers demonstrating linkage to the *ARPKD1* gene with the affected proband
   b. 33 different mutations detected on 57 alleles (Rossetti et al. 2003)
      i. 51.1% in ARPKD
      ii. 32.1% in congenital hepatic fibrosis/(Caroli disease)
      iii. Two frequent truncating mutations
         a) 9689delA (9 alleles)
         b) 589insA (8 alleles)
      iv. Mutation detection rate
         a) High in severely affected patients (85%)
         b) Lower in moderate severe ARPKD (41.9%)
         c) Low, but significant, in adults with congenital hepatic fibrosis/Caroli disease (323.1%)
      v. Complications for the prospects for gene-based diagnostics
         a) Large gene size
         b) Marked allelic heterogeneity
         c) Clinical diversity of the ARPKD phenotype
   c. Direct DNA analysis: available clinically
      i. Mutation scanning
      ii. Sequence analysis
      iii. Targeted mutation analysis
      iv. Deletion/duplication analysis
      v. Linkage analysis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased (theoretical risk 0.7%)
2. Prenatal diagnosis
   a. Ultrasonography in most severely affected fetuses
      i. Enlarged, echogenic kidneys
      ii. Dilated collecting ducts
      iii. Characteristic hepatic ductal plate malformation
      iv. A small or nonvisualized bladder
      v. Oligohydramnios attributable to poor fetal renal output
      vi. Unreliable especially in early pregnancy
   b. Molecular genetic testing by mutation scanning of *PKHD1* is available clinically by analysis of fetal DNA obtained by amniocentesis or CVS. Both disease-causing alleles of an affected family member must be identified or linkage has been established in the family before prenatal testing can be performed. The ARPKD locus mapped to proximal chromosome 6p allowing haplotype-based prenatal diagnosis in "at-risk" family with a previously affected child in whom prior family studies have identified informative linked markers. An absolute prerequisite for these studies is an accurate diagnosis of ARPKD in the previously affected sib (Zerres et al. 1998b; Dell 2011).
   c. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified.
3. Management (Dell 2011)
   a. Initial management of affected infants to focus on stabilization of respiratory function. Mechanical ventilation may be necessary to treat both pulmonary hypoplasia and respiratory compromise from massively enlarged kidneys.
   b. Water and electrolyte balance
   c. Peritoneal dialysis may be required for neonates with oliguria or anuria within the first days of life.
   d. Vigorous treatment of systemic hypertension with antihypertensive agents
      i. ACE inhibitors
      ii. Calcium channel blockers
      iii. Beta blockers
      iv. Judicious use of diuretics (e.g., thiazides, loop diuretics)
   e. Antibiotics for treatment of urinary tract infections

f. Management of renal osteodystrophy in children with ARPKD and chronic renal insufficiency
   i. Calcium supplements
   ii. Phosphate binders
   iii. 1,25-dihydroxyvitamin D3 to suppress parathyroid hormone (PTH)
   iv. Erythropoietin (EPO)
      a) Increases hemoglobin levels
      b) Improves the overall well-being of the child
g. Potential use of recombinant human growth hormone therapy to improve the growth of children with uremia
h. Therapeutic options available for the treatment of portal hypertension in children (Lonergan et al. 2000)
   i. Conservative management
   ii. Control of variceal bleeding
      a) Sclerotherapy effective in controlling bleeding
      b) Banding of varices
      c) Placement of portosystemic shunts occasionally necessary to reduce bleeding and the formation of additional varices
   iii. Prompt management with antibiotics and, when indicated, surgical drainage to help reduce morbidity and mortality associated with ascending cholangitis
   iv. Splenectomy for hypersplenism
   v. Liver transplantation in patients with severe hepatic dysfunction or chronic cholangitis
i. Replacement therapy for renal failure
   i. Renal dialysis
   ii. Renal transplant
j. Combined liver/kidney transplantation

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Fig. 1 (**a**, **b**) A newborn with ARPKD showing Potter facies. The spongy appearing cut surface of a kidney from the same patient is due to generalized dilatation of the collecting ducts in both cortex and medulla

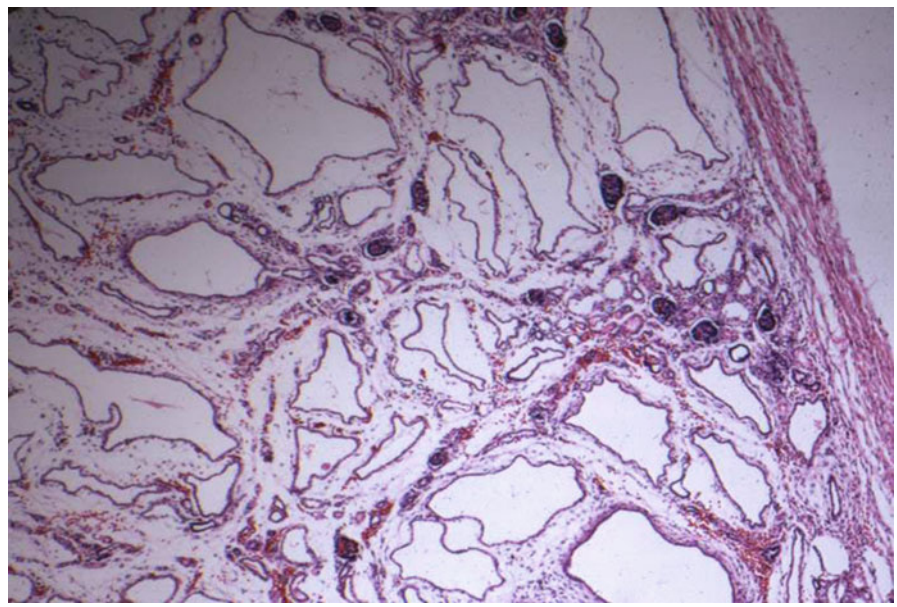

Fig. 2 Photomicrograph of a kidney of a neonate (37 weeks gestation) with ARPKD showing markedly dilated collecting ducts in the medulla (*top*) and the cortex (*bottom*). The infant also had intrahepatic bile duct proliferation and mild cystic changes, and pulmonary hypoplasia

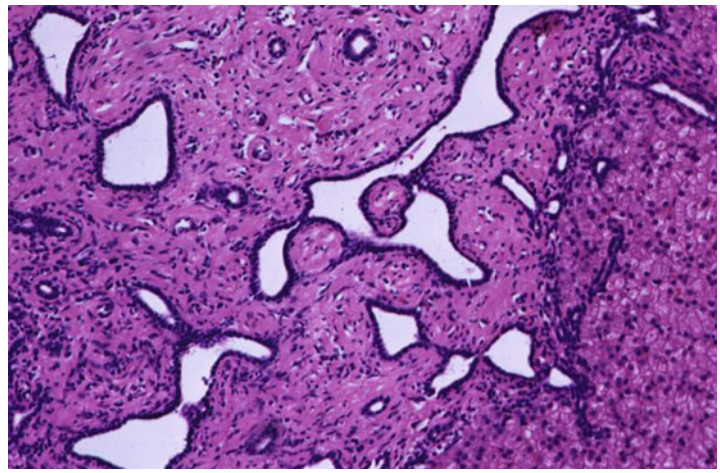

Fig. 3 Photomicrograph of the liver of a 2-year-old girl with congenital hepatic fibrosis, consistent with ARPKD. Note the irregularly dilated branching bile ducts. There is abundant fibrous connective tissue in this enlarged portal tract

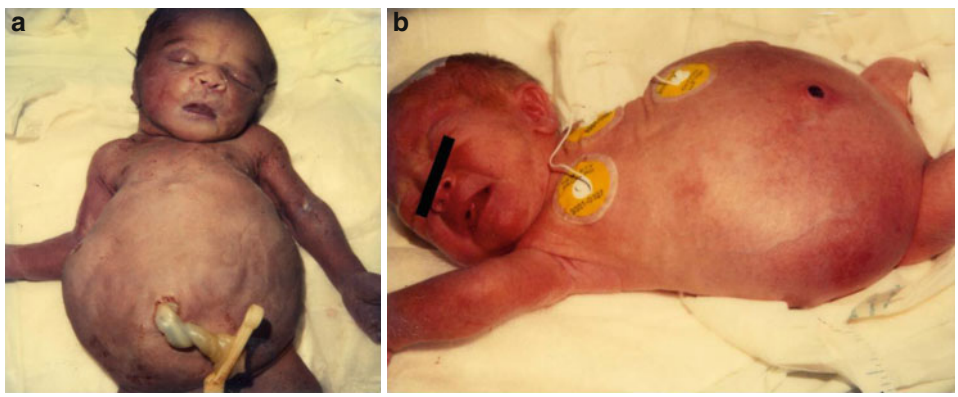

Fig. 4 (**a**, **b**) Two neonates with ARPKD showing markedly distended abdomen

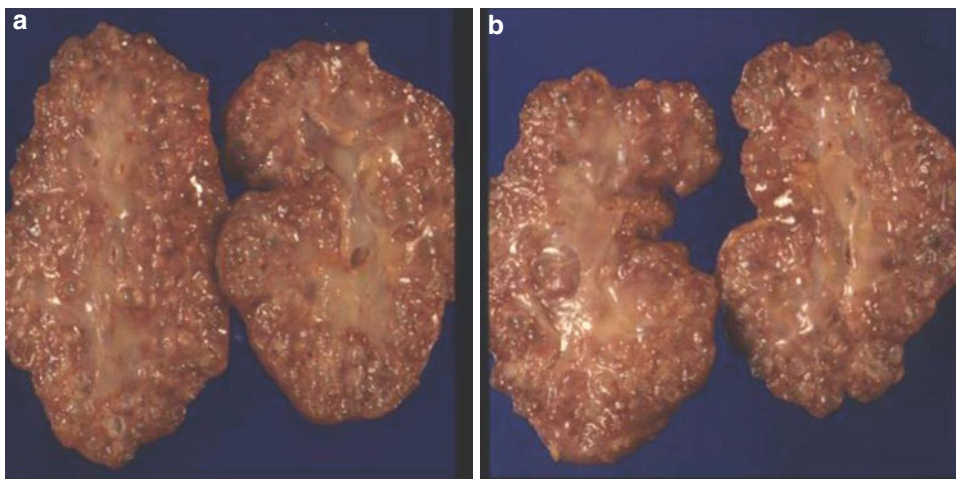

Fig. 5 (**a**, **b**) Kidneys in another neonate with ARPKD

Popliteal Pterygium Syndrome

In 1968, Gorlin et al. described an autosomal dominant form of popliteal pterygium syndrome (PPS), a syndrome comprising cleft lip and palate, popliteal and intercrural pterygia, and digital and genital anomalies. Van der Woude syndrome (VWS) is one of the most common oral cleft syndromes. It accounts for about 2% of all cleft lip and palate cases. Both syndromes are caused by *IRF6* mutations.

In 1972, Bartsocas and Papas reported on four sibs of third-cousin parents with a severe, presumably autosomal recessive form of popliteal pterygium syndrome.

Synonyms and Related Disorders

Bartsocas-Papas syndrome; *IRF6*-Related Disorders including Van der Woude syndrome

Genetics/Basic Defects

1. Interferon regulatory factor 6 (*IRF6*) encodes a member of the IRF family of transcription factors (de Lima et al. 2009)
2. Mutations in *IRF6* cause popliteal pterygium syndrome and Van der Woude syndrome.
3. Popliteal pterygium syndrome
   a. Inherited as an autosomal dominant trait
   b. Exonic mutations in *IRF6* are found in nearly all families with PPS (De Lima et al. 2009).
4. Van der Woude syndrome
   a. Inherited as an autosomal dominant trait with high penetrance (96.7%) but with variable expression
   b. A nonsense mutation in the interferon regulatory factor 6 (*IRF6*) gene in the affected sib of two monozygotic twins discordant for VWS, suggesting *IRF6* as a candidate for VWS (Kondo et al. 2002)
   c. This hypothesis was confirmed in the same study by the detection of *IRF6* mutations in 45 additional unrelated families with VWS. In addition, a unique set of mutations in *IRF6* was discovered in 13 families with PPS, demonstrating that VWS and PPS as allelic, as previously suggested (Lees et al. 1999).
   d. Subsequently, mutations in *IRF6* were identified in 56 additional families with VWS and three with PPS (de Lima et al. 2009).
   e. Exonic mutations in *IRF6* are found in 68% of families with VWS.
5. Bartsocas-Papas syndrome (BPS)
   a. Inherited as an autosomal recessive trait
   b. Early lethality
   c. *IRF6* mutation has not been studied in BPS.

Clinical Features

1. Autosomal dominant popliteal pterygium syndrome
   a. Cleft lip with or without cleft palate
   b. Fistula of the lower lip
   c. Filiform synechiae may connect the upper and lower jaws (syngnathia) or the upper and lower eyelids (ankyloblepharon).
   d. Webbing of the skin extending from the ischial tuberosities to the heels
   e. Bifid scrotum and cryptorchidism in males
   f. Hypoplasia of the labia majora in females

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g. Syndactyly of fingers and/or toes
h. Anomalies of the skin around the nails: A characteristic pyramidal fold of skin overlying the nail of the hallux is almost pathognomonic.
i. Normal growth and intelligence

2. Van der Woude syndrome (Gorlin et al. 2001)
   a. Congenital lower-lip fistulae (pits)
      i. Usually bilateral and paramedian
      ii. The phenotype of the lower lip varies from a single barely evident depression to bilateral fistulae of the lower lip.
      iii. Phenotypes of the orofacial cleft vary from a bifid uvula to a complete cleft lip and palate.
   b. Cleft lip with or without cleft palate and cleft palate only
   c. Hypodontia
   d. Less common features
      i. Syndactyly of the fingers
      ii. Syngnathia
      iii. Ankyloblepharon
   e. Normal growth and intelligence
3. Autosomal recessive Bartsocas-Papas syndrome
   a. Oral clefts
   b. Filiform bands between jaws
   c. Ankyloblepharon
   d. Popliteal pterygium
   e. Syndactyly of fingers and toes
   f. Phalangeal anomalies such as hypoplasia and/or synostosis
   g. Nail hypoplasia
   h. Genital anomalies in both sexes
   i. Early lethality is common
   j. Causes of death
      i. Bronchopneumonia
      ii. Respiratory distress
      iii. Sepsis

Diagnostic Investigations

1. Histology of popliteal pterygium (Gorlin et al. 1968)
   a. Bilateral pterygium extending from the heel to the ischial tuberosity
   b. Limiting extension and abduction as well as rotation of the leg
   c. A hard, inelastic subcutaneous cord or fibrous band runs along the free edge of the pterygium
   d. The sciatic nerve lies free within the pterygium deep to the fibrous band about halfway between the free edge and the apex being covered by fibromuscular septa.
   e. The popliteal vessels are normally situated deep in the popliteal space.
   f. Absence of muscle groups or abnormal muscle insertions in many cases
2. Molecular genetic testing by sequence analysis of the *IRF6* coding region (exons 1–9) (Durda et al. 2011)
   a. Detects mutations in approximately 70% of individuals with the Van der Woude syndrome phenotype
   b. Detects mutations in approximately 97% of individuals with the popliteal pterygium syndrome phenotype

Genetic Counseling

1. Recurrence risk for autosomal dominant *IRF6*-related disorders
   a. Patient's sib
      i. Appears to be low when parents are clinically unaffected, but the possibility of incomplete penetrance in a parent or of germline mosaicism need to be considered
      ii. Fifty percent if a parent of the proband is affected or has an *IRF6* mutations
   b. Patient's offspring
      i. Each child of an individual with an *IRF6* mutation has a 50% chance of inheriting the mutation.
      ii. The clinical manifestations of *IRF6*-related disorders are variable and cannot be predicted in the offspring.
2. Prenatal diagnosis
   a. Ultrasonography
      i. Oral cleft
      ii. Popliteal pterygium
   b. Molecular genetic testing
      i. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing allele of an affected family member is previously identified.
      ii. Preimplantation genetic diagnosis: may be available for families in which the disease-causing mutation has been identified in an affected family member

3. Management (Gahm et al. 2007)
   a. Early surgical treatment is of importance to enable and preserve oral feeding.
   b. Intranasal flexible fiber intubation with the patient awake is a possible anesthetic strategy to secure the airway prior to surgery in patients with multiple or extensive interalveolar syngnathia.
   c. Surgical removal for synechiae
   d. Cleft lip/cleft palate: surgical and orthodontic management
   e. Speech therapy and audiologic evaluation for cleft palate
   f. Surgery for lip pits for cosmetic purpose
   g. Syndactyly may require surgery.
   h. To accomplish knee extension (Gardetto and Piza-Katzer 2003)
      i. Resect fibrous bands
      ii. Free the sciatic nerve
      iii. Z-lengthening of the Achilles tendon and multiple Z-plasties
      iv. Surgery result: 1 year after surgery, the patient can put his heel on the ground and has almost complete range of motion in the knee and ankle joints.
   i. Orthopedic care and physical therapy may be needed.

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Fig. 1 (**a**–c) The newborn was evaluated for multiple congenital anomalies, consisting of ankyloblepharon connecting upper and lower eyelids by fimbria (thin thread-like connective tissue), unilateral cleft lip and palate, thin strings of connective tissue connecting the upper and lower alveolar ridge on both sides, absence of labia majora, hypoplastic labia minor, a clitoral hood, a sacral dimple, popliteal pterygium (webbing of the skin extending from the ischial tuberosities to the heels), skin over the nails of her great toes giving the nail a somewhat triangular shape with a flat base, and syndactyly over second to fifth toes bilaterally. The clinical diagnosis of popliteal pterygium syndrome was confirmed by molecular genetic analysis of *IRF6* gene which showed a missense mutation of exon 4 [c252G > A or p.Arg841His (R84H)]

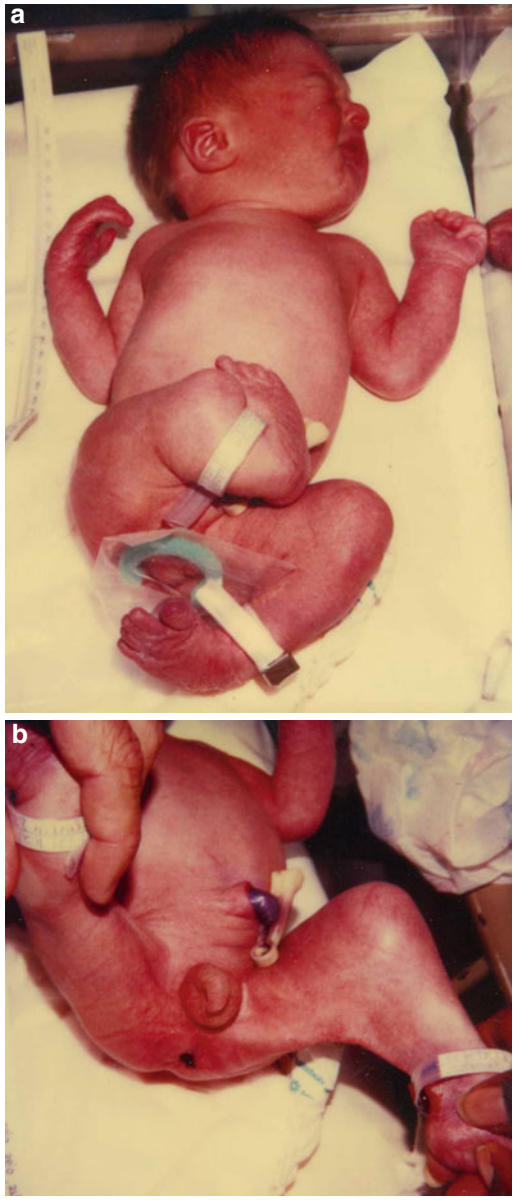

Fig. 2 (**a**, **b**) Another baby with popliteal pterygium syndrome

Prader–Willi Syndrome

Prader–Willi syndrome is a neurogenetic disorder characterized by hypotonia and feeding difficulties in infancy, followed by hyperphagia, hypogonadism, mental retardation, and short stature. It was the first recognized microdeletion syndrome identified with high-resolution chromosome analysis, the first recognized human genomic imprinting disorder, and the first recognized disorder resulting from uniparental disomy. The incidence of Prader–Willi syndrome is approximately 1/10,000–1/15,000 individuals.

Genetics/Basic Defects

1. Inheritance
   a. Usually sporadic events (de novo deletions of 15q11–q13)
   b. Rare familial transmission (balanced translocations involving 15q11–q13) (<1%)
2. A contiguous gene syndrome involving multiple paternally expressed genes
3. Caused by the lack of expression of normally active paternally inherited genes at chromosome 15q11–q13 because of a phenomenon called genomic imprinting
   a. The relevant region on chromosome 15q11–q13: normally expressed on the paternally derived chromosome and imprinted on maternally derived chromosome
   b. The imprinted maternal allele is unable to produce functional protein since the normally expressed paternal copy is often deleted in Prader–Willi syndrome.
4. Molecular subclassification of Prader–Willi syndrome: All involving loss of paternal gene expression from chromosome 15q11–q13 (Buiting 2010)
   a. Paternal deletion 15q11–q13 (de novo) (70% of cases: microdeletion of the actively transcribed segment on the paternally derived chromosome 15q11–q13
   b. Maternal uniparental disomy (UPD15) (25–30% of cases)
      i. Inheritance of two copies of the maternal chromosome without paternal contribution
      ii. In normal individuals, the paternally donated chromosome expresses multiple genes in the Prader–Willi syndrome region while the maternal chromosome is largely silent.
      iii. In case of maternal uniparental disomy, without the presence of a chromosome donated from the father, normal imprinting on the two maternally donated chromosomes leads to the absence of gene expression in this region.
   c. Mutation in the imprinting control center
      i. Deletion of the imprinting center (1% of the cases) of the *SNRPN* (*s*mall *n*uclear *r*ibonucleoprotein *p*olypeptide *N*) gene causing inability to establish the normal methylation status
      ii. Without imprinting center deletion (One percent of cases)

Clinical Features

1. Neonatal presentation
   a. Central hypotonia in infancy
   b. Poor feeding/sucking

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   c. Poor weight gain (failure to thrive)
   d. Genital hypoplasia/hypogonadism
   e. Diminished deep tendon reflexes
   f. Abnormal squeaky weak cry
   g. History of fetal inactivity (in utero hypotonia)
2. Developmental delay
3. Mild dysmorphic features
   a. Almond-shaped eyes
   b. Dolichocephaly
   c. Narrow bifrontal diameter
   d. Narrow nasal bridge
   e. Small mandible
   f. Small mouth
   g. High-arched palate
   h. Down-turned lips
   i. Thick viscous saliva
4. Hyperphagia after the 1st–2nd postnatal years
5. Severe obesity without significant intervention
6. Retinal hypopigmentation
7. Small hands and feet (acromicria)
8. Mild to moderate mental retardation
9. Hypothalamic insufficiency suggested by several autonomic dysfunctions that affect appetite regulation, growth, pubertal development, control of breathing, and alertness
10. Behavioral and psychiatric difficulties
    a. Excessive food-seeking behaviors
    b. Obsessions
    c. Compulsions
    d. Mood lability
    e. Depression
11. Other manifestations
    a. Infantile lethargy
    b. Sleep disturbance and/or sleep apnea
    c. Short stature
    d. Hypopigmentation
    e. Skin sores from constant picking
    f. Esotropia/myopia
    g. Speech articulation defects
    h. High pain threshold
    i. Ineffective thermoregulation
    j. Early adrenarche
    k. Osteoporosis
    l. Kyphoscoliosis
12. Prognosis
    a. Obesity: the major cause of morbidity and mortality
    b. Cardiopulmonary compromise (Pickwickian syndrome) resulting from excessive obesity
    c. Most common causes of death: respiratory insufficiency or infections (Tauber et al. 2008)
13. Diagnostic criteria (adapted from Holm et al. 1993): five points for children under 3 years (three from major criteria); eight points for children above 3 years (four from major criteria)
    a. Major Criteria (one point each)
       i. Infantile central hypotonia
       ii. Infantile feeding problems/failure to thrive
       iii. Rapid weight gain between 1 and 6 years
       iv. Characteristic facial features
       v. Hypogonadism (genital hypoplasia, pubertal deficiency)
       vi. Developmental delay/mental retardation
    b. Minor Criteria (1/2 point each)
       i. Decreased fetal movement and infantile lethargy
       ii. Typical behavioral problems
       iii. Sleep disturbance/sleep apnea
       iv. Short stature for the family by age 15 years
       v. Hypopigmentation
       vi. Small hands and feet for height age
       vii. Narrow hands with straight ulnar border
       viii. Esotropia/myopia
       ix. Thick viscous saliva
       x. Speech articulation defects
       xi. Skin picking
    c. Supportive Criteria (no points)
       i. High pain threshold
       ii. Decreased vomiting
       iii. Temperature control problems
       iv. Scoliosis/kyphosis
       v. Early adrenarche
       vi. Osteoporosis
       vii. Unusual skill with jigsaw puzzles
       viii. Normal neuromuscular studies

Diagnostic Investigations

1. Cytogenetic studies
   a. Microscopic or submicroscopic del(15)(q11–q13) confirmed by fluorescence in situ hybridization (FISH probe for *SNRPN*) (60–80%)
   b. Paternally derived chromosome 15 that is deleted

c. De novo events in most cases with cytogenetically normal father's chromosomes
d. Balanced chromosomal rearrangement with break in 15q11–q13 (<1%)

2. Molecular analyses
   a. Uniparental disomy identified by using microsatellite repeat sequences of chromosome 15 in the patient and both parents
      i. Maternal uniparental disomy for chromosome 15 in most of nondeletion cases (20–40%)
      ii. Inheriting both copies of chromosome 15 from the mother
      iii. Absence of the paternally inherited copy of chromosome 15q11–q13
   b. Rare familial Prader–Willi syndrome: associated with very small mutations in 15q11–q13 region leading to the loss of expression of multiple genes from the paternal chromosome
   c. DNA methylation analyses (by Southern blotting and PCR) of the *SNRPN* or PW71 (D15S63) loci to detect absence of paternal methylation patterns on the basis of deletion, uniparental disomy, or defective methylation: detects over 99% of cases and is highly specific
   d. Imprinting defect (Cassidy and Schwartz 2009)
      i. Presumed to be present in individuals with an abnormality in the parent-specific methylation imprint without evidence of a deletion of UPD (Ohta et al. 1999)
      ii. Imprinting defects caused by microdeletions are detected using sequence analysis or MLPA of the PWS-SRO (smallest region of overlap)
      iii. Most imprinting defects are epimutations (i.e., alterations in the imprint, not the DNA) and cannot be detected by sequence analysis (Buiting et al. 1998; Buiting et al. 2003; Horsthemke and Buiting 2006)

Genetic Counseling

1. Recurrence risks (Cassidy and Schwartz 2009; Buiting 2010)
   a. Patient's sib
      i. De novo deletion or maternal uniparental disomy in an affected child: a low recurrence risk (≤1% due to possible paternal balanced insertion or gonadal mosaicism)
         a) Imprinting center mutation in an affected child
         b) No imprinting center deletion: <1%
      ii. With imprinting center deletion: up to 50% recurrence risk
      iii. Apparently de novo balanced chromosome translocation breaking within the PWS/AS critical region: <1%
      iv. Presence of a parental balanced chromosomal rearrangement: up to 25% recurrence risk
   b. Patient's offspring (Cassidy and Schwartz 2009)
      i. With rare exception, individuals with PWS do not reproduce.
      ii. The risk to the child of an affected individual depends on the etiology of the absence of the paternally derived PWS critical region and the sex of the affected individual.
      iii. If the proband has PWS as the result of a deletion, the offspring have a 50% risk of having Angelman syndrome (AS) if the proband is female (reported once) and PWS if the proband is male (never reported).
      iv. If the proband has UPD, there is a theoretical risk of the offspring inheriting two chromosomes 15 from the proband, which could lead to: (1) fetal demise if trisomy rescue does not occur, (2) PWS if the proband is female, and (3) AS if the proband is male. None of these possibilities have been reported. There is a single report of a female with PWS caused by UPD having a normal child (Schulze et al. 2001).
      v. If the proband has PWS as the result of an imprinting mutation, the offspring have a theoretical risk of ≤50% of having PWS (never reported).
      vi. If the proband has a chromosomal translocation, there is a theoretical increased risk to offspring of having PWS or AS, depending on the sex of the proband (never reported).
2. Prenatal diagnosis
   a. High-risk pregnancies
      i. Parents who have had a previous child with Prader–Willi syndrome, caused by deletion or uniparental disomy, are not routinely

offered prenatal testing in subsequent pregnancies but could be offered such testing for assurance.
   ii. Parents who have had a previous child with Prader–Willi syndrome, caused by a defect in the imprinting control center, should be offered prenatal testing because of the high recurrence risk; methylation analysis can also be used in these cases.
   iii. Prenatal testing for an inherited translocation involving chromosome 15 and resulting in a deletion is relevant because of the theoretical 25% risk of Prader–Willi syndrome in the offspring.
b. PWS may be a possibility for low-risk pregnancies in which no family history of Prader–Willi syndrome exists
   i. Cytogenetic study to detect del(15q11–q13) from amniocytes or CVS cells, complemented by FISH probe: Parent-of-origin studies should be performed after confirmation of a deletion to determine if the deletion is paternally derived (fetus has PWS). (If the deletion is maternally derived, the fetus has Angelman syndrome.)
   ii. If trisomy 15 or mosaic trisomy 15 is detected on CVS, and if subsequent amniocentesis reveals 46 chromosomes, the possibility of trisomy rescue leading to PWS (maternal UPD) through loss of a parental chromosome 15 [or leading to Angelman syndrome (maternal UPD) through loss of a maternal chromosome 15] can be considered. In this instance, parent-of-origin (UPD) studies or methylation analysis on amniocytes should be considered (European Collaborative Research on Mosaicism in CVS 1999; Shaffer et al. 2001).
   iii. If an inherited or de novo translocation involving chromosome 15 is present or if a supernumerary chromosome derived from chromosome 15 is detected, FISH (to rule out a deletion) and parent-of-origin studies (to rule out the possibility of UPD) are indicated.
c. Molecular studies of uniparental disomy 15 using microsatellite dinucleotide polymorphism analysis of amniocytes and parental DNA
d. DNA methylation analysis of amniocytes

3. Preimplantation genetic diagnosis (PGD)
   a. May be available for families in which a mutation in the imprinting control element has been identified
   b. Also can be used in cases of familial translocation to rule out UPD
4. Management
   a. Manage feeding problems with special nipples or gavage feeding if needed to assure adequate nutrition, to avoid failure to thrive, and to improve hypotonia
   b. Early intervention programs with speech, physical, and occupational therapies after careful educational, behavioral, and psychological assessments
   c. Dietary control
      i. Monitoring of weight and nutritional counseling
      ii. Low-calorie and well-balanced diet combined with a regular exercise program
      iii. Limit access to food
      iv. Close supervision to minimize food stealing
   d. Management of endocrine problems
      i. Growth hormone treatment improves growth, physical phenotype, and body composition (Cassidy and Driscoll 2009).
      ii. Testosterone treatment in males to improve changes in voice and body hair, beard growth, genital size, body mass and strength, and self-image
      iii. Treatment with estrogen, cycling hormones, or birth control pills in females has resulted in increasing breast size and menstrual periods.
   e. Management of scoliosis as in the general population
   f. Behavioral management
      i. Firm limit setting and enforcement
      ii. Consult with a behavioral psychologist or other behavior specialist for behavioral management programs
   g. Psychiatric management
      i. Psychosis
      ii. Manic-depressive illness
      iii. Obsessive-compulsive disorder
   h. Treatment of complications resulting from excessive obesity
      i. Cardiopulmonary compromise
      ii. Type II diabetes mellitus
      iii. Thrombophlebitis
      iv. Management of skin picking, chronic skin changes, and peripheral edema

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Fig. 1 A 10-month-old girl with Prader–Willi syndrome showing severe hypotonia, strabismus, and small hands and feet. Parent-of-origin specific DNA methylation studies at 15q11–q13 for Prader–Willi syndrome revealed the presence of maternal 4.2 kb hybridization band only but not paternal 0.9 kb band consistent with Prader–Willi syndrome. Uniparental disomy DNA analysis revealed that the patient has only maternal alleles based on the Mendelian inheritance of two informative markers (D15S205 and D15S1002) and two partial informative markers (D15S130 and D15S1007), indicative of uniparental disomy for chromosome 15

Fig. 2 A 17-month-old boy with Prader–Willi syndrome showing severe hypotonia. Methylation-specific PCR using SNRPN flanking primers revealed absence of paternal SNRPN and presence of maternal SNRPN, confirming the diagnosis of Prader–Willi syndrome

Fig. 3 An infant with Prader–Willi syndrome [del(15)(q11–q13)] showing hypotonia and failure to thrive

Fig. 4 (**a**, **b**) A girl with Prader–Willi syndrome [del(15)(q11–q13)] showing obesity, short stature, almond-shaped eyes, and small hands and feet

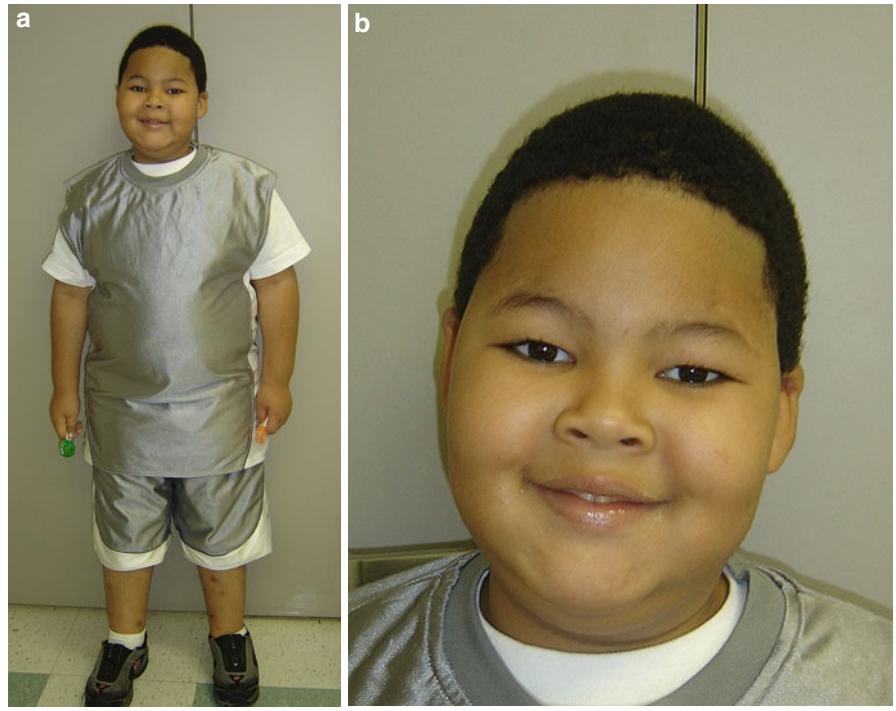

Fig. 5 (**a**, **b**) A boy with Prader–Willi syndrome [del (15)(q11–q13)] showing obesity, almond-shaped eyes, and bitemporal narrowing

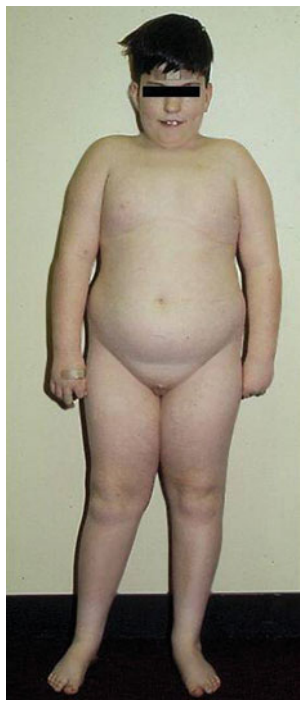

Fig. 6 A boy with Prader–Willi syndrome [del(15)(q11–q13)] showing almond-shaped eyes, bitemporal narrowing, obesity, hypogenitalism, and small hands and feet

Fig. 7 (**a**, **b**) A girl with Prader–Willi syndrome [del (15)(q11–q13)] showing extreme obesity, characteristic facial appearance, small hands and feet, and multiple skin sores from constant picking

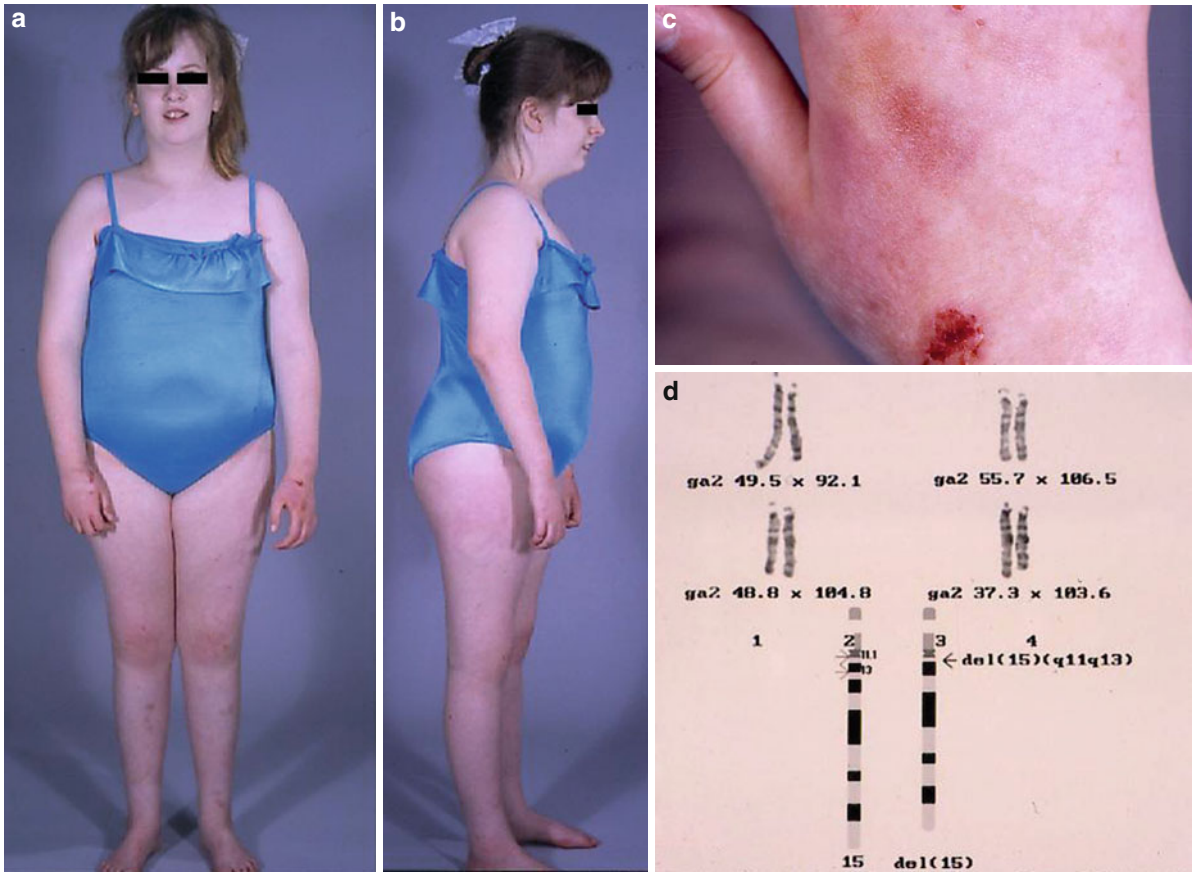

Fig. 8 (**a**–**d**) A patient with Prader–Willi syndrome [del(15)(q11–q13)] (shown by partial karyotypes and ideogram) and trimethylaminuria showing sores on the skin

Fig. 9 A woman with Prader–Willi syndrome [del(15)(q11–q13)] and neurofibromatosis 1 showing obesity and axillary freckles

Progeria

In 1886, Hutchinson described a boy with congenital alopecia, wrinkled atrophic skin, an odd facies, joint contractures, and normal intelligence. Subsequently in 1904, Gilford reported a second patient with similar features and suggested the term progeria, from the Greek word *geras* meaning old age, to describe the premature senile characteristics of the patients. Thus, the syndrome is also known as Hutchinson–Gilford progeria syndrome (HGPS).

Progeria is an extremely rare condition with characteristic clinical findings of premature and accelerated aging. Its incidence was estimated to be one per eight million live births in the United States. Male to female ratio is about 1.5–1. Most reported patients are Caucasians (Badame 1989).

Synonyms and Related Disorders

Hutchinson–Gilford progeria syndrome

Genetics/Basic Defects

1. Inheritance: autosomal dominant inheritance
   a. Advanced paternal age effect observed
   b. Germinal mosaicism responsible for rare instances of affected sibs
2. Basic defects
   a. Caused by mutations in lamin A (*LMNA*) gene
      i. *LMNA* gene encodes two protein products, lamin A/C (lamin A and lamin C), representing major constituent of the inner nuclear membrane lamina.
      ii. Mutations in *LMNA*.
         a) About 90% of patients have an identifiable mutation.
         b) Most common mutation: a de novo single-base substitution, G608G (GGC > GGT) in exon 11. G608G mutation responsible for the majority of progeria arises in the paternal germline (D'Apice et al. 2004)
         c) A second mutation in the same codon, G608S (GGC > AGC)
         d) E145K (exon 2) observed in a phenotypically unusual HGPS
      iii. Mutations in *LMNA* also cause the following different recessive and dominant disorders (Eriksson et al. 2003):
         a) Emery–Dreifuss muscular dystrophy type 1 (EMD1) (autosomal dominant)
         b) Emery–Dreifuss muscular dystrophy type 2 (EMD2) (autosomal recessive)
         c) A familial dilated cardiomyopathy and conduction system defects (CMD1A) (autosomal dominant)
         d) Dunnigan-type familial partial lipodystrophy (FPLD) (autosomal dominant)
         e) Limb-girdle muscular dystrophy type 1B (LGMD1B) (autosomal dominant)
         f) Charcot–Marie–Tooth disorder type 2B1 (CMT2B1) (autosomal recessive axonal neuropathy)
         g) Mandibuloacral dysplasia (MAD) (autosomal recessive)
   b. Hutchinson–Gilford progeria syndrome gene localized to chromosome 1q by observing two

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cases of uniparental isodisomy of 1q and one case with a 6-megabase paternal interstitial deletion (Eriksson et al. 2003)

c. Increased hyaluronic acid production by progeric fibroblasts postulated as the underlying metabolic abnormality in progeria
   i. Urinary excretion of hyaluronic acid found to be increased in some patients.
   ii. Elevated levels of hyaluronic acid may result in growth failure and accelerated senescence by inhibiting the growth of blood vessels.
d. Accumulation of type IV collagen due to an interaction between activated T lymphocytes and fibroblasts
e. Current results of microarray analysis: further support the notion that patients with progeria experience an accelerated form of aging
f. Reduced growth capacity in vitro in the skin fibroblasts from progeria patients with conflicting evidence on whether progeric cells can repair single-strand DNA breaks induced by X- or gamma-irradiation
g. Fibroblasts from progeric tissue (Ackerman and Gilbert-Barness 2002)
   i. Inability to subculture
   ii. Having short telomeres
   iii. Uncertain as to whether aging is the consequence of shortened telomeres with reduced cell replication, impaired telomerase activity, or the culmination of the effects of reactive oxygen species
h. Del(1)(q23) reported in a patient with Hutchinson–Gilford progeria
i. Inv ins(1;1)(q32;q44q23) reported in the postmortem skin biopsy specimens from identical twins raising the possibility that a gene for progeria may be located at the break point site of the inserted chromosome segment

Clinical Features

1. General features (Ackerman and Gilbert-Barness 2002)
   a. Normal appearance at birth
   b. Normal intelligence and personality
   c. High-pitched voice
2. Growth
   a. Profound growth failure/failure to thrive starting around 6 months to 1 year of age
   b. Extreme short stature
   c. No rapid growth during puberty
   d. Markedly diminished subcutaneous fat, especially on the face and limbs
   e. Absent sexual maturation
3. Skin
   a. Unremarkable at birth
   b. Generalized nonpitting edema suggestive of scleroderma shortly after birth
   c. "Sclerodermatous" skin over lower abdomen and proximal thighs, in which irregular bumps give appearance of lipodystrophy
   d. Becoming thin, dry, taut, and shiny in some areas, but lax and wrinkled in others, most commonly over the fingers and toes, by the second year
   e. Striking loss of subcutaneous tissue
   f. Prominent venous pattern
   g. Easy bruising
   h. Diminished eccrine sweating in some cases
   i. Progressive freckle-like hyperpigmentation (most evident in sun-exposed areas) and thickened sclerotic areas (usually on the lower parts of the trunk or thighs) after several years
4. Hair
   a. Partial alopecia progressing to generalized alopecia often beginning at birth or in the first year and becoming prominent by the end of the second year
   b. Few remaining hairs: white or blond, fine, and fuzzy
   c. Body hair as well as scalp and facial hair: equally affected
5. Nails
   a. Short, thin, and dystrophic fingernails and toenails
   b. Koilonychia (spoon nails)
   c. Onychogryposis (deformed overgrowth of the nails)
6. A striking facies after few months of life
   a. Typical "plucked bird" appearance related to disproportionate craniofacial growth
   b. Disproportionately large cranium
   c. Relatively small face
   d. Prominent eyes

e. Prominent scalp veins
f. Sparse to absent scalp hair (alopecia, balding, hypotrichosis)
g. Absent eyebrows and eyelashes
h. Thin lips
i. Circumoral cyanosis
j. Protruded ears with absent earlobes
k. "Beaked," pinched nose with sculptured tip
l. Micrognathia

7. Teeth (Yu and Zeng 1991)
   a. Anodontia/hypodontia, especially permanent teeth
   b. Delayed and incomplete dentition
   c. Discoloration (yellowish brownish)
   d. Crowded, rotated, displaced, overlapped, and maloccluded, especially the anterior teeth
   e. High incidence of caries
   f. Poor oral hygiene/gingivitis
   g. Irregularity in size and shape of the odontoblasts
   h. Delayed in ossification of the crown of the permanent teeth
   i. Narrow pulp chambers and root canals
   j. Reticular atrophy of pulp
   k. Calcification along the nerve fibers and the vascular walls
   l. Irregular width of predentin, secondary dentin and cementum
   m. Osteoclastic resorption at apical portion
   n. Incomplete formation of roots of deciduous molars
8. Endocrine manifestations
   a. Incomplete sexual maturation
   b. Occasional hypoplastic nipples
9. Cardiovascular disease
   a. Premature severe atherosclerosis
   b. Premature coronary artery disease
   c. Death from coronary artery disease frequent and may occur before 10 years of age.
   d. Angina pectoris
   e. Myocardial infarction
   f. Congestive heart failure
   g. Epidural hematoma formation after a mild head injury possibly due to progressive atherosclerosis of intracranial vessels
10. Musculoskeletal abnormalities
    a. Generalized osteoporosis with pathologic fractures
    b. Marked delay in bone healing after fractures
    c. Short/dystrophic clavicles
    d. Coxa valga
    e. Arthropathy
    f. Avascular necrosis of the femoral capital epiphysis
    g. Distal phalangeal osteolysis
    h. Delayed closure and persistently patent anterior fontanelle
    i. Joint contractures with contracted hands, elbows, and knees
    j. Dislocation of the hip
    k. Mild flexion of the knees resulting in a wide-gaited "horse-riding" stance and wide-based shuffling gait
    l. Short, tapered distal phalanges
    m. Thin limbs
    n. Muscle atrophy
11. Prognosis (Badame 1989)
    a. Absence of other factors associated with aging such as cancers, cataracts, and senility (not considered to be a phenocopy of normal aging)
    b. Death due to cardiovascular abnormalities in approximately 75% of patients
    c. Main cause of death due to cardiovascular complications
       i. Myocardial infarction
       ii. Congestive heart failure
    d. Other causes of death
       i. Marasmus
       ii. Inanition
       iii. Convulsions
       iv. Accidental head trauma due to thinned cortical bones
    e. Average life expectancy: 13 years (7–27 years)

Diagnostic Investigations

1. Histopathology (Badame 1989)
   a. Skin lesions indistinguishable from scleroderma
      i. Progressive hyalinization of dermal collagen (hyaline fibrosis)
      ii. Loss of subcutaneous tissue
      iii. Decreased sebaceous and sweat glands and hair follicles
   b. Bone lesions
      i. Osteoporosis
      ii. Osteolysis prominent in distal phalanges and clavicles

iii. Skeletal dysplasia manifesting as coxa plana, coxa valga, and attenuated diaphyses with dystrophic metaphyses
iv. Avascular hip necrosis
v. Nonunion of fractures
vi. Hip dislocations

c. Cardiovascular lesions
i. severe, progressive atherosclerosis with widely variable age of clinical manifestation
ii. Presence of atherosclerotic plaques in the large and small arteries
iii. Calcifications in the mitral and aortic valves as well as aorta, coronary, cerebral, subclavian, and axillary arteries
iv. Myocardial ischemia and infarction resulting from the coronary artery disease
v. Diffuse interstitial myocardial fibrosis
vi. Ventricular dilatation and hypertrophy

d. Increased lipofuscin in the brain, adrenal cortex, kidney, testis, liver, and heart

e. Gonads
i. Aspermatogenesis in males
ii. Presence of primordial follicles and corpora albicans in females with evidence of ovulation

f. Arterial biopsy
i. Premature atherosclerosis
ii. Subintimal fibrosis

2. Radiography (Badame 1989)
a. Widespread degenerative changes of bone in the first or second year of life
b. Skull and facial bones
i. Craniofacial disproportion
ii. Patent fontanelles
iii. Wormian bones with fractures
iv. Facial bone hypoplasia
v. Mandibular hypoplasia with dental crowding
vi. Delayed and abnormal dentition

c. Thorax
i. Clavicular resorption
ii. Rib tapering

d. Long bones
i. Indentations
ii. Attenuated cortices
iii. Widened metaphyses
iv. Coxa valga
v. Genu valgum

e. Phalanges
i. Distal resorption, one of the hallmarks of the disease
ii. Radiolucent terminal phalanges (acroosteolysis)

f. Other
i. Osteoporosis
ii. Fish-mouthed vertebral bodies
iii. Soft tissue loss

3. Blood chemistry for hyperlipidemia
a. Increased low-density lipoprotein levels
b. Increased β-lipoprotein and pre-β-lipoprotein levels of high-density lipoprotein
c. Increased serum cholesterol levels

4. Metabolic workup: inconsistent results
a. Insulin resistance
b. Abnormal collagen formation
c. Increased metabolic rate: could be the cause of the failure to thrive seen in progeria
d. Elevated growth hormone levels

5. Urine test
a. Excessive excretion of glycosaminoglycans
b. Excessive excretion of hyaluronic acid (unreliable)

6. Cultured skin fibroblasts
a. Exhibit 76.1% DNA repair capacity compared to normal (Sarkar and Shinton 2001)
b. Decreased cell growth in culture
c. Short telomeres
d. Whether aging is the consequence of shortened telomeres with reduced cell replication, impaired telomerase activity, or the culmination of the effects of reactive oxygen species is uncertain.

7. Immunofluorescence of cultured fibroblasts with antibodies directed against lamin A demonstrating visible abnormalities of the nuclear membrane in many cells

8. Molecular genetic analysis to detect *LMNA* p.gly608Gly point mutation: clinically available
a. Sequence analysis
b. Targeted mutation analysis

Genetic Counseling

1. Recurrence risk
a. Patient's sib
i. The lamin A gene mutations not found in patient's parents suggesting that it

occurs spontaneously in each patient and does not pass from parent to child
   ii. Recurrence risk very low, estimated at 1 in 500 with each subsequent pregnancy due to germline mutations (Wuyts et al. 2005)
   iii. Rare reports of siblings with progeria from consanguineous or nonconsanguineous marriages
   iv. Reported cases of monozygous twins with progeria
 b. Patient's offspring: inability of patients to reproduce
2. Prenatal diagnosis and preimplantation genetic diagnosis: possible in families in which the disease-causing mutation has been identified in a family member
3. Management (Gordon et al. 2011)
 a. Regular diet
 b. Combined nutritional treatment and growth hormone treatment
   i. Improve growth
   ii. Increase the levels of growth factors
   iii. Paradoxically result in a decreased BMR
   iv. Response decreases over time.
   v. Do not prevent the progression of atherosclerotic disease (Abdenur et al. 1997)
 c. Early and definitive surgical intervention for symptomatic oral pathosis
   i. Abnormal facial morphology
   ii. Dermal inelasticity
   iii. Potential anesthetic difficulties
   iv. Progressive ongoing deterioration in the medical condition
 d. Orthopedic cares for musculoskeletal abnormalities
   i. Routine treatment of fractures
   ii. Conservative treatment for hip dislocation. Avoid surgery if possible.
   iii. Routine physical therapy to maintain joint range of motion
 e. Management of cardiovascular complications
   i. Routine anticongestive therapy for congestive heart failure
   ii. Nitroglycerin for angina
   iii. Low doses of aspirin help delay heart attacks and strokes

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Fig. 1 (**a**–**h**) A boy with progeria showing short stature; senile appearance; small face in comparison with large cranial vault (craniofacial disproportion); alopecia with prominent scalp veins; absent eyelashes and eyebrows; prominent eyes; beak-like nose; mandibular hypoplasia; absent earlobes; contracted hands, elbows, and knees; short, tapered terminal phalanges; enlarged joints; and dry, brittle, hypoplastic nails

Prune Belly Syndrome

In 1895, Parker described the congenital triad of deficient abdominal musculature, cryptorchidism, and urinary tract abnormalities. Subsequently, the term "prune belly syndrome" was coined for this condition based on the characteristic wrinkled appearance of the abdomen. The incidence of the syndrome is estimated to be 1 in 35,000 to 1 in 50,000 live births.

Synonyms and Related Disorders

Absence of abdominal muscles with urinary tract abnormality and cryptorchidism; Eagle-Barrett syndrome; Potter sequence

Genetics/Basic Defects

1. Etiologies
   a. Questionable genetic inheritance
      i. Questionable autosomal dominant inheritance
      ii. Autosomal recessive inheritance suggested by some authors
   b. Fetal abdominal distension caused by urinary tract obstruction
      i. The most common cause of prune belly syndrome
      ii. Urethral obstruction causing dilatation of the fetal bladder and upper tracts thereby attenuating the abdominal musculature
      iii. Spontaneous relief of the urethral obstruction in some cases prenatally decompresses the abdomen, producing the shriveled, prune like appearance of the baby's abdomen.
      iv. Persistent urethral obstruction causing huge distention of the urinary bladder, bilateral hydronephrosis, and hydroureter complicated by oligohydramnios in more severe cases
   c. Fetal ascites from whatever cause: abdominal decompression during intrauterine life leading to prune belly appearance of the abdomen
   d. Prostatic hypoplasia resulting in a functional urethral obstruction leading to development of the prune belly syndrome (Hoagland 1988)
   e. Primary mesodermal defect simultaneously affecting the formation of abdominal musculature and abnormalities in the lower urinary tract (Mouriquand et al. 2001)
   f. Rare association of chromosome abnormalities
      i. Trisomy 13
      ii. Trisomy 18
      iii. Turner syndrome with fetal ascites (pathogenetic mechanism thought to involve abdominal distention by ascites rather than by urinary obstruction)
      iv. Ring X chromosome lacking *XIST* (Guillen 1997)
      v. Cat-eye syndrome
      vi. Rarely with trisomy 21
      vii. Mosaic unbalanced chromosome constitution of chromosome 16
      viii. Presence of a small additional chromosome fragment
      ix. Interstitial deletion of chromosome 1 [del (1)(q25q32)] (Scarbrough et al. 1988)

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2. Pathogenesis: abdominal wall hypoplasia as a nonspecific lesion resulting from fetal abdominal distension of various causes
3. Terminologies
   a. Prune belly: a descriptive term for a wrinkled and flaccid abdominal wall secondary to stretched skin, soft tissues, and muscles of the abdomen
   b. Prune belly syndrome generally used to indicate the condition having prune belly, cryptorchidism, and abnormalities of the urinary tract
4. Causes of urine flow impairment/obstruction (Mouriquand et al. 2001)
   a. Renal causes
      i. Pelviureteric junction anomaly
      ii. Vesicoureteric junction anomaly
      iii. Posterior urethral valves
      iv. Duplex systems
      v. Ureterocele/ectopic ureter
      vi. Urethral atresia
      vii. Cloacal anomaly
      viii. Vesicoureteric reflux
      ix. Megaureter
      x. Megacystis microcolon
      xi. Hypoperistalsis syndrome
   b. Extrarenal causes
      i. Sacrococcygeal teratoma
      ii. Hydrometacolpos
      iii. Other pelvic masses

Clinical Features

1. Broad spectrum in severity
2. Nearly 95% of cases occurring in males
3. Potter face
   a. Mandibular micrognathia
   b. Wide-set eyes
   c. Flattened palpebral fissures
   d. Prominent epicanthus
   e. Flattened nasal bridge
   f. Large, low-set ears with lacking cartilage
4. Abdomen
   a. Partial or complete absence of the abdominal musculature
   b. Thin/lax protruding abdominal wall
   c. Wrinkled abdominal skin
   d. Visible intra-abdominal intestinal patterns through thin abdominal wall
5. Other associated gastrointestinal abnormalities (Woods and Brandon 2007)
   a. Malrotation: midgut anomaly, intestines abnormally rotated or become twisted during embryologic development
   b. Atresia: failure of the intestinal tract to completely form, causing absence of a normal opening
   c. Stenosis: narrowing of the center passage within the intestines
   d. Volvulus: intestines or stomach lack normal attachments of the body, causing the intestines to become twisted, resulting in a lack of blood supply
   e. Clinical symptoms
      i. Bilious vomiting
      ii. Abdominal distention
      iii. Abdominal tenderness
      iv. Failure to pass meconium
      v. Rectal bleeding
      vi. Signs of shock and sepsis
6. Genitourinary anomalies
   a. Urethral obstruction
   b. Dilated/hypertrophic bladder
   c. Dilated urethra, particularly the prostatic urethra
   d. Dilated/tortuous ureters
   e. Renal dysplasia/hypoplasia with cystic changes
   f. Hydronephrosis
   g. Absence or hypoplasia of the prostate
   h. Ventral body wall defects
      i. Cloacal exstrophy
      ii. Bladder exstrophy
      iii. Hypo-/epispadias
   i. Genitalia
      i. Bilateral cryptorchidism in males
      ii. Pseudohermaphroditism in females
   j. Potter sequence
      i. Oligohydramnios
      ii. Potter face
      iii. Pulmonary hypoplasia
      iv. Other deformations
7. Secondary malformations
   a. Gastrointestinal obstruction
      i. Malrotation
      ii. Atresia
      iii. Stenosis
      iv. Volvulus
      v. Splenic torsion

vi. Imperforate anus
vii. Anorectal agenesis

b. Limb and other skeletal abnormalities believed to be the direct result of oligohydramnios with resultant fetal crowding (Green et al. 1993)
i. Talipes equinovarus
ii. Metatarsus adductus
iii. Vertical talus
iv. Hip dislocation
v. Arthrogryposis
vi. Pectus excavatum/carinatum
vii. Congenital muscular torticollis
viii. Bell shape chest
ix. Infantile scoliosis
x. Severe leg maldevelopment
a) Generalized hypoplasia
b) Complete absence
c) Terminal defects

c. Cardiac malformations
i. Tetralogy of Fallot
ii. Ventriculoseptal defect

d. Cleft lip
e. Spina bifida
f. Association with diverse chromosome syndromes
i. Trisomy 13
ii. Trisomy 18
iii. Turner syndrome
iv. Cat-eye syndrome
v. Trisomy 21
vi. Others

8. Grading of patients according to severity of renal and pulmonary malformations (Herman and Siegel 2009)
a. Grade 1: those with oligohydramnios-induced pulmonary hypoplasia and Potter facies
b. Grade 2: moderate-to-marked neonatal and infantile urinary tract involvement without pulmonary hypoplasia or Potter facies
c. Grade 3: mild renal involvement

9. Prognosis
a. High mortality although compatible with long-term survival
i. Stillbirth or death by 1 month of age in 20% of cases
ii. Death by the second year for additional 30% of cases
b. Causes of death (Christopher et al. 1982)
i. Renal failure secondary to renal dysplasia present at birth
ii. Pulmonary complications including lung hypoplasia
iii. Infection associated with urinary stasis or operative interventions

Diagnostic Investigations

1. Renal and bladder ultrasound
2. Contrast voiding cystourethrogram
3. Radiography
a. Hypoplastic lungs with flared lower ribs secondary to the distended abdomen
b. Diffusely distended flanks
c. Dilated/dysplastic calyces of the kidneys
d. Markedly dilated/tortuous ureters
e. Vertical and trabeculated bladder
f. A wide and long posterior urethra
g. Cryptorchidism
4. Histology of the abdominal wall (Moerman et al. 1984a, b)
a. Muscle atrophy (degeneration of already formed muscle), not of primitive muscle
b. The finding supports the theory that the abdominal muscle hypoplasia is a nonspecific lesion, resulting from fetal abdominal distension of various causes.
5. Chromosome analysis for multiple congenital anomalies

Genetic Counseling

1. Recurrence risk
a. Patient's sib: not increased unless in autosomal recessive inheritance (which is still unclear)
b. Patient's offspring: not increased
2. Prenatal diagnosis by 2D and 3D ultrasonography (Leeners et al. 2000; Chen et al. 2010)
a. Signs of fetal abdominal laxity (characteristic abdominal appearance) associated with fetal urinary tract abnormalities
i. Amniotic fluid wave produced by fetal movement

ii. Sinusoidal undulation of the fetal anterior abdominal wall produced by tapping the maternal abdomen
   b. A distended bladder (megacystis) and ureters
   c. Cryptorchidism
   d. Oligohydramnios
   e. Fetal ascites
   f. Lung hypoplasia
   g. Associated anomalies
      i. Other renal anomalies (25%)
      ii. Extrarenal abnormalities (12%)
         a) Anorectal anomalies
         b) VATER syndrome
         c) Esophageal atresia
         d) Pattern compatible to specific chromosomal abnormality
3. Management
   a. Orchidopexy for cryptorchidism
   b. Treatment of vesicoureteral dysfunction
      i. Temporary diversion
      ii. Ureteral reconstruction
   c. Treatment of vesicourethral dysfunction
      i. Reduction cystoplasty
      ii. Internal urethrotomy
      iii. Megalourethra repair
   d. Abdominal wall reconstruction
   e. Vesicoamniotic shunting with percutaneous placed catheters: useful in some lower urinary tract obstructions such as those that occur with prune belly syndrome (Woods and Brandon 2007). However, vesicoamniotic shunt placement for suspected prenatal obstructive uropathy remains controversial (Freedman et al. 1996).

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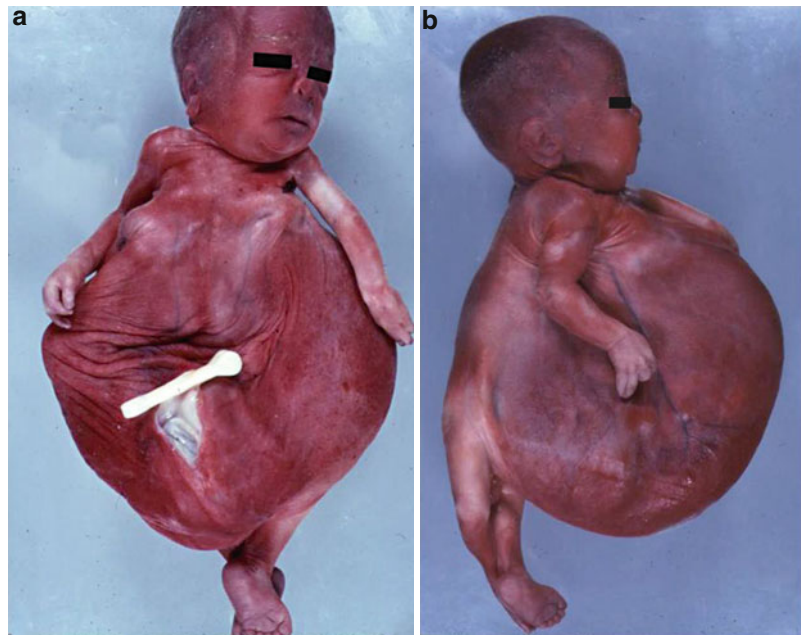


Fig. 1 (**a**, **b**) A premature male neonate with prune belly syndrome due to urethral atresia. He lived for 2 h. There was a massive dilation and hypertrophy of the urinary bladder. Mild hydronephrosis was seen in one kidney but the second kidney was hypoplastic. The anterior abdominal wall showed muscle deficiency. Additional anomalies included imperforate anus with vesicorectal fistula, secundum-type atrial septal defect of the heart, mild coarctation of the aorta, and bilateral talipes equinovarus

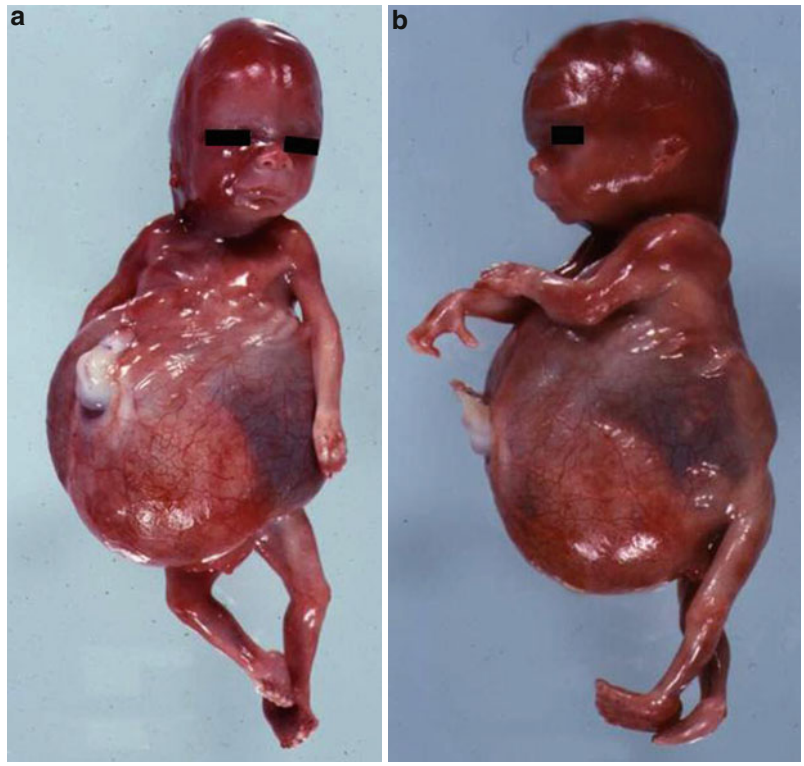
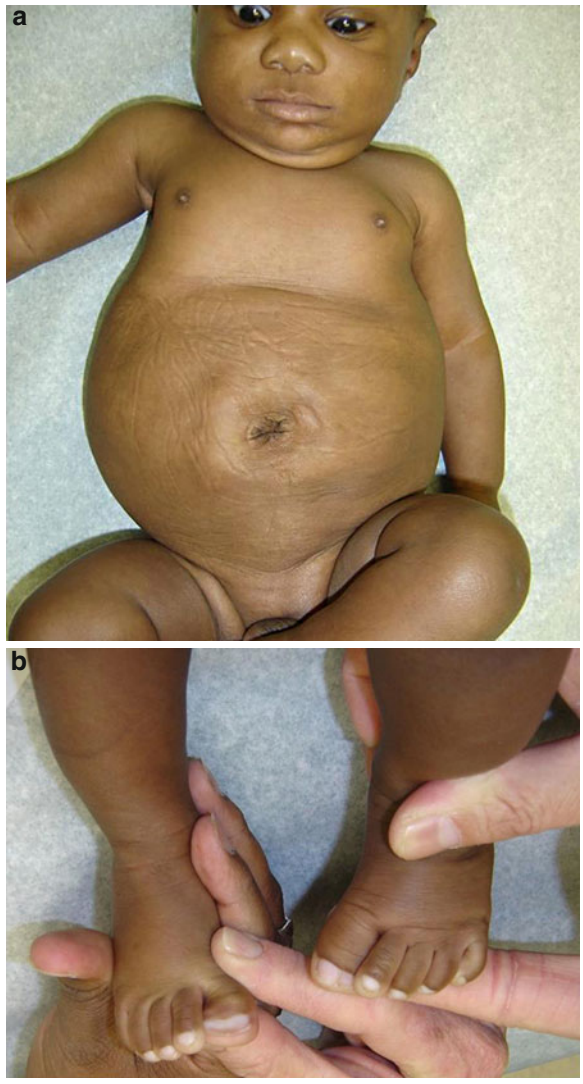


Fig. 2 (**a**, **b**) A male fetus with prune belly syndrome due to severe urethral stenosis. There were marked dilatation of the proximal urethra, bladder, and bilateral ureters. Mild hydronephrosis and cystic renal dysplasia were seen in both kidneys. There were no other anomalies

Fig. 3 An infant with prune belly syndrome showing thin, flaccid abdominal wall through which intra-abdominal intestinal patterns are visible

Fig. 4 A postmortem infant with prune belly syndrome showing flaccid and wrinkling abdominal wall with visible intestinal patterns



Figs. 5 (**a**, **b**) A neonate with prune belly syndrome showing wrinkling abdominal wall due to multicystic kidneys. The infant also has duplicated great toes

Pseudoachondroplasia

Pseudoachondroplasia is a type of short-limbed dwarfism, deriving its name from phenotypic similarity to achondroplasia. It is characterized by normal facies, short-limbed dwarfism, joint laxity, and epiphyseal and metaphyseal abnormalities in the growing child.

Synonyms and Related Disorders

Pseudoachondroplastic dysplasia; Peudoachondroplastic spondyloepiphyseal dysplasia

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant with complete penetrance
   b. Autosomal recessive unlikely (Ferguson et al. 1997)
      i. Somatic mosaicism was demonstrated in two pseudoachondroplasia families that were originally considered to represent autosomal recessive inheritance.
      ii. The results suggest that autosomal recessive inheritance is unlikely, and all cases of pseudoachondroplasia should be studied for mutations in *COMP*.
2. Cause
   a. Mutations in the gene encoding cartilage oligomeric matrix protein (*COMP*) on the centromeric region of 19p (19p13.1-p12)
      i. Deletions: Approximately 40–50% of cases of pseudoachondroplasia have deletion mutations in exon 13 of the *COMP* gene.
      ii. Specific base substitutions
      iii. Duplications
   b. Allelic to multiple epiphyseal dysplasia, which is also caused by *COMP* mutations
   c. All mutations associated with pseudoachondroplasia and multiple epiphyseal dysplasia: found in exons encoding the type III repeat region or C-terminal domain of *COMP*
   d. Mutations in extracellular matrix proteins, *COMP*, types II and IX collagens, and matrilin-3
      i. Producing a spectrum of mild to severe chondrodysplasias characterized by epiphyseal and vertebral abnormalities
      ii. Disruption of protein processing and excessive accumulation of some of these proteins in the rough endoplasmic reticulum that appears to compromise cellular function

Clinical Features

1. Normal at birth
2. Normal intelligence
3. Normal craniofacial appearance
4. Waddling gait and diminished linear growth at about 2 years of age
5. Rhizomelic short-limbed dwarfism
   a. Body proportion resembling achondroplasia
   b. Usually detectable at age 2–4 years
6. Spine
   a. Accentuated lumbar lordosis
   b. Scoliosis
   c. Kyphosis

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   d. Chronic compression myelopathy secondary to habitual atlantoaxial dislocation
7. Extremities
   a. Bowing of the long bones
   b. Deformities of the lower limbs
      i. Secondary to ligamentous laxity
      ii. Ranging from genu varum (bowed legs), genu valgum (knock-knees), and genu recurvatum
      iii. A "wind-swept deformity" (bowleg on one side and knock-knee on the other side)
   c. Markedly shortened hands (without trident configuration) and feet
   d. Ulnar deviation of the wrist
   e. Flexion contractures of the elbow and knees
   f. Brachydactyly
   g. "Telescoping" fingers
8. Joint
   a. Lax ligament
   b. Premature osteoarthritis
   c. Contractures of the hips
9. Prognosis
   a. Good survival
   b. Early arthrosis, notably in the hip and knee joints
   c. Possible myelopathy secondary to atlantoaxial dislocations
10. Differential diagnosis (Cohn 2010)
   a. Dominant multiple epiphyseal dysplasia (see the chapter): Mutations in *COMP*, *COL9A1*, *COL9A2*, *COL9A3*, or *MATN3* genes can be demonstrated in about 50% of cases.
   b. Recessive multiple epiphyseal dysplasia (see the chapter)
      i. *SLC26A2* (*DTDST*) is the only gene known to be associated with recessive multiple epiphyseal dysplasia.
      ii. Diagnosis can be confirmed by molecular genetic testing of the *SLC26A2* gene.
   c. Other forms of spondyloepimetaphyseal dysplasia: need complete skeletal survey for diagnosis

Diagnostic Investigations

1. Radiography
   a. Tubular bones
      i. Irregularities and fragmentations of the developing epiphyses
      ii. Shortened tubular bones
      iii. Brachydactyly
      iv. Delayed epiphyseal ossification (delayed bone age)
      v. Small phalangeal epiphyses (miniepiphyses)
      vi. Small, irregular carpal bones
      vii. Irregular, widened (frayed), mushroomed metaphyses
      viii. Coxa vara
   b. Pelvis
      i. Delayed ossification of the capital femoral epiphyses, which become flattened and small when ossified
      ii. Commonly observed sclerosis and irregularity of the acetabular roof
   c. Vertebrae
      i. Characteristic anterior beaking or tonguing (in lateral view of the lumbar spines)
         a) Due to delayed ossification of the annular epiphyses
         b) Vertebrae becoming more normal in appearance after puberty
      ii. Characteristic platyspondyly in childhood
      iii. Kyphoscoliosis
      iv. Lumbar lordosis
      v. Odontoid hypoplasia
      vi. Atlantoaxial dislocations
   d. Ribs: spatulate
2. Histology of growth plates
   a. Irregular arrangement of chondrocytes without column formation
   b. Irregular provisional calcification
   c. Intracytoplasmic inclusions in chondrocytes
3. EM of chondrocytes
   a. Showing distinctive giant rough endoplasmic reticulum cisternae filled with punctuate material
   b. The material composed of alternating electron-lucent and electron-dense layers in a unique lamellar appearance
4. Serum COMP concentration may be suggested as an additional diagnostic marker to aid clinical findings in suspected cases of Pseudoachondroplasia (Liu et al. 2010).
5. Molecular diagnosis
   a. Sequence analysis of selected exons or the entire coding region (Cohn 2010)
      i. Detect p.Asp473del (about 30%)
      ii. Detect missense and small in-frame deletions (about 70%)
   b. Particularly useful in adult patients where radiological diagnosis can be difficult

Genetic Counseling

1. Recurrence risk: according to autosomal dominant inheritance (Cohn 2010)
   a. Patient's sib
      i. Fifty percent if one of the parent is affected
      ii. Not increased if parents are normal
      iii. If the disease-causing mutation identified in the proband cannot be detected in the DNA of either parent, two possible explanations are germ line mosaicism in a parent or a *de novo* mutation in the proband.
         a) The risk to the sibs of the proband depends on the probability of germ line mosaicism in a parent of the proband and the spontaneous mutation rate of *COMP*.
         b) Germ line mosaicism for a *COMP* mutation has been reported (Hall et al. 1987, Ferguson et al. 1997), but the frequency is unknown and the empiric risk to sibs of a proband has not been determined.
   b. Patient's offspring: 50%
2. Prenatal diagnosis
   a. Prenatal ultrasonography unlikely to detect the skeletal changes which will not manifest until about 2 years of age
   b. Prenatal diagnosis and preimplantation genetic diagnosis: possible in the family at risk and the disease-causing *COMP* mutation has been characterized in an affected individual
3. Management
   a. Supportive
   b. Surgical correction of the leg deformities
   c. Hip replacement for severe hip contractures
   d. Cervical stabilization procedures for cervical cord compression with progressive neurologic symptoms and signs

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Fig. 1 (**a**–**d**) A girl with pseudoachondroplasia at 2 ½ years (*upper*) with normal craniofacial appearance, mild short stature, and waddling gate and at 6 years (*lowers*) with short limbs, accentuated lumbar lordosis, and short stature

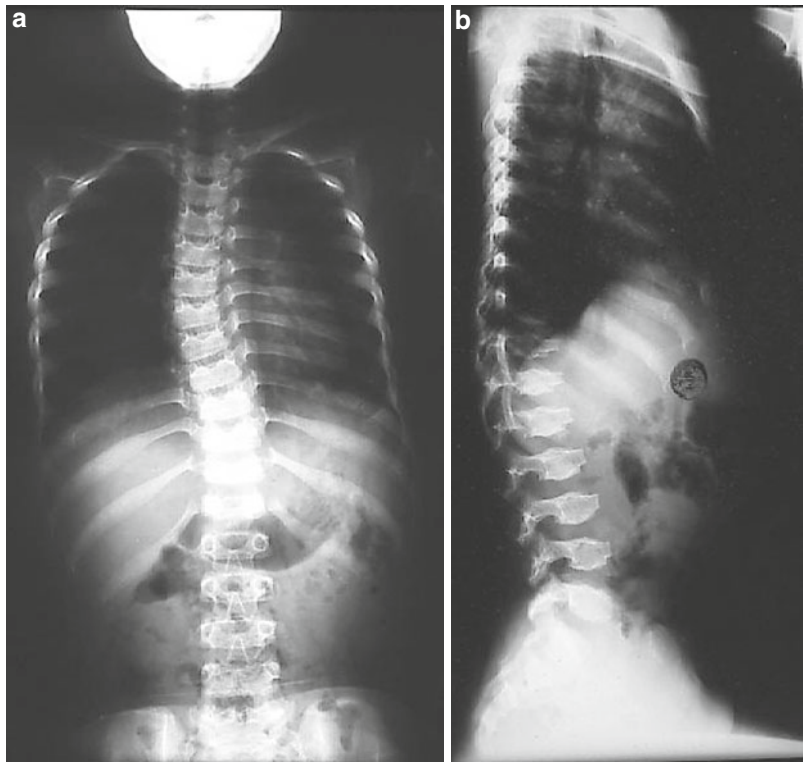

Fig. 2 (**a**, **b**) Radiographs of the spine show characteristic anterior beaking of the lumbar spine and mild scoliosis

Fig. 3 Radiographs of the pelvis and lower extremities showing irregular, horizontal acetabular roof, delayed epiphyseal ossification, and wide mushroom-shape metaphyses

Fig. 4 Radiograph of the upper extremities showing markedly widened and defective metaphyseal and epiphyseal ossifications in the proximal humerus, distal radius, and ulna

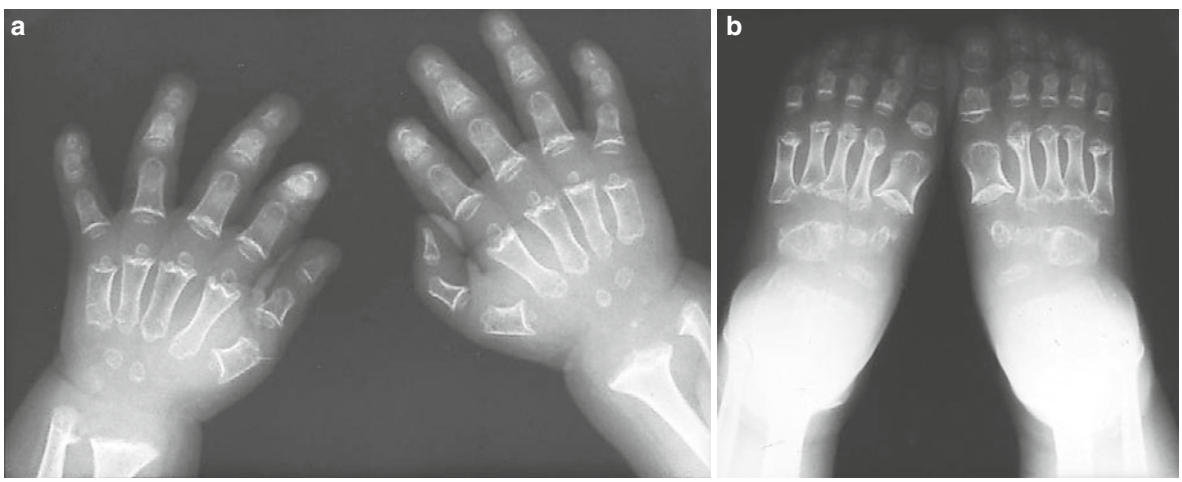

Fig. 5 (**a**, **b**) Radiographs of the hands and feet show grossly disturbed metaphyseal and epiphyseal ossification, short and stubby tubular bones, somewhat widened metacarpals and metatarsals, and small and markedly irregular carpal and tarsal bones

R(18) Syndrome

In 1962, Wang et al. reported the first observation of the ring chromosome 18. Ring chromosome 18 syndrome is a rare chromosome disorder resulting from loss (deletion) of genetic material from one or both ends of a chromosome 18 and joining of the chromosomal ends to form a ring.

Ring chromosome 18 has been reported in many cases of liveborns. The phenotype may vary greatly in range and severity from normal fertile persons in a majority of cases to those with severe malformations, depending upon the amount and location of lost genetic material. Ring chromosome 18 is usually caused by spontaneous (de novo) errors very early in the development of the embryo.

Synonyms and Related Disorders

Mosaic ring chromosome 18 syndrome; Ring chromosome 18 syndrome

Genetics/Basic Defects

1. Formation of a ring chromosome 18.
   a. Ring chromosomes arise from chromosomal breakages occurring on either side of the centromere and subsequent rejoining of the segment containing the centromere.
   b. One of the breakpoints is generally at or adjacent to the centromere. Thus, two types of ring chromosomes may arise:
      i. One derived from the short arm
      ii. One derived from the long arm
2. Supernumerary ring chromosome 18.
   a. The r(18) was additional to the two existing chromosome 18 copies, leading to trisomy for the chromosome 18 segment carried on r(18).
   b. May show the characteristics of trisomy 18 or duplications of 18p or 18q.
3. Mosaic ring chromosome 18.
   a. Ring chromosomes are known to be unstable and are often found in a mosaic state.
   b. Instability of a ring may lead to a monosomic cell line.
4. Haploinsuficiency of several genes have been postulated to play a role in the 18q- and 18p- syndrome phenotypes:
   a. HPE4 (18p11.3): holoprosencephaly
   b. GALNR1 (18q23)
   c. Growth hormone deficiency
   d. MBP (18q23): hypomyelination
5. Phenotypic variability depends on the extent of the deleted chromosome 8 segments: Most patients show the symptoms of 18q- syndrome, 10p- syndrome, or combination of these two.
6. Rare occurrence of a ring chromosome 18 together with a duplication of a segment of chromosome 18 or with a marker chromosome.

Clinical Features

1. Clinical features of r(18) syndrome.
   a. Growth and development
      i. Mental retardation
      ii. Hypotonia
      iii. Short stature

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b. Head/brain
   i. Microcephaly
   ii. Dolichocephaly
   iii. Holoprosencephaly
   iv. Cebocephaly
   v. Arhinencephaly
c. Midface: flat
d. Ears
   i. Asymmetric
   ii. Low-set
   iii. Atretic external ear canals
   iv. Prominent antihelix
e. Eyes
   i. Deep-set
   ii. Hypertelorism
   iii. Down slanting palpebral fissures
   iv. Epicanthal folds
   v. Nystagmus
   vi. Strabismus
   vii. Ptosis
   viii. Coloboma
f. Nose
   i. Broad base
   ii. Depressed nasal bridge
   iii. Broad tip
g. Mouth
   i. Micrognathia
   ii. Carp-like down-turned corners
   iii. Thin upper and lower lips
   iv. High/narrow palate
   v. Dental caries
h. Neck: short
i. Chest
   i. Pectus excavatum
   ii. Wide-spaced nipples
j. Congenital heart defect
   i. PDA
   ii. PS
   iii. VSD
   iv. AS
k. Abdomen
   i. Umbilical hernia
   ii. Inguinal hernia
l. Genitourinary
   i. Male genitalia
      a) Cryptorchidism
      b) Hypoplastic scrotum
      c) Micropenis
   ii. Female genitalia: hypoplastic labia minora
m. Musculoskeletal
   i. Spine: scoliosis
   ii. Hands
      a) Clinodactyly
      b) Camptodactyly
      c) Short fingers
      d) Long tapering fingers
      e) Proximally placed thumbs
      f) Single transverse palmar crease
   iii. Legs/feet
      a) Club feet (varus)
      b) Overriding toes
      c) Long/broad toes
      d) Genu valgum
n. Other features
   i. Hypothyroidism
   ii. Hypoparathyroidism
   iii. Growth hormone deficiency
o. Atypical features
   i. Van der Woude syndrome
   ii. Insulin-dependent diabetes mellitus
   iii. Agammaglobulinemia

2. Most patients share the features of del(18q) syndrome which are highly variable depending on the extent of the terminal or interstitial 18q deletion:
   a. Mental retardation
   b. Hypotonia
   c. Microcephaly
   d. Short stature
   e. Flat midface
   f. Carp-shaped mouth
   g. Prominent antihelix and antitragus
   h. Atretic/stenotic ear canals
   i. Proximally placed thumbs
   j. Long tapering digits
   k. Foot deformity
   l. Abnormal male genitalia
3. Some patients share the features of del(18p) syndrome which are highly variable depending on the extent of the terminal or interstitial 18p deletion:
   a. Mental retardation
   b. Speech delay
   c. Hypotonia
   d. Short stature
   e. Midface defects including holoprosencephaly
   f. Ptosis of eyelids
   g. Small mandible
   h. Dental caries

i. Short neck
j. IgA deficiency
4. Some patients share the combined features of del (18p) syndrome and del(18q) syndrome.

Diagnostic Investigations

1. Conventional cytogenetic studies
   a. Nonmosaic r(18)
   b. Mosaic r(18)
2. Molecular cytogenetic studies using fluorescence in situ hybridization (FISH) technique
   a. Ring chromosome positive for chromosome 18 centromeric probe
   b. Absence of 18q subtelomeric probe
3. Microdissection followed by FISH to determine the origin of the marker chromosome
4. Using a number of microsatellite markers to determine the parental origin and possible mode of formation of the r(18)
5. Low IgA

Genetic Counseling

1. Recurrence risk
   a. Patient sibling
      i. A low recurrence risk if both parents are normal phenotypically and karyotypically (in cases of de novo instances in majority of cases).
      ii. Careful chromosome analysis to rule out parental mosaicism which may contribute to a recurrent risk of giving birth to a child with either partial trisomy or monosomy of different regions of chromosome 18.
      iii. A ring chromosome 18 can be transmitted from a phenotypically normal parent with 46, XX or XY/47,XX or XY,+r(18) karyotype to offspring with a 46,XX or XY,r(18) karyotype.
   b. Patient's offspring
      i. Patients with an r(18): 50%
      ii. Patients with mosaic form of an r(18): lower than 50% depends on the percentage of the marker chromosomes
2. Prenatal diagnosis
   a. Prenatal ultrasonography for congenital anomalies
   b. Chromosome analysis by amniocentesis or CVS
      i. Presence of an r(18) chromosome
      ii. FISH with a chromosome 18 probe to identify chromosome 18
3. Management
   a. Mainly supportive
   b. Multidisciplinary team approach with physical, occupational, and speech therapies
   c. Supportive treatment for chronic sinopulmonary infections associated with IgA deficiency
   d. Treat endocrine dysfunction if present
   e. Surgery for congenital anomalies

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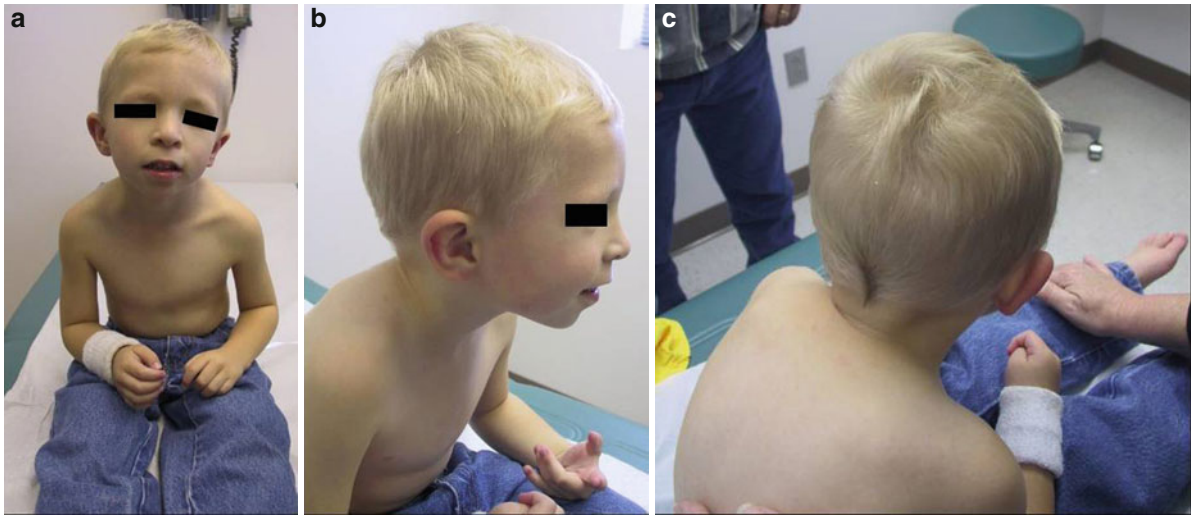

Fig. 1 (**a**–**c**) A 4-year-old boy with de novo r(18) syndrome showing growth deficiency (prenatal and postnatal), speech delay, hypertelorism, downward slanting of the palpebral fissures, strabismus, slightly low-set ears, mild pectus carinatum, clinodactyly of the 5th fingers, and syndactyly of toes. He also has IgA deficiency

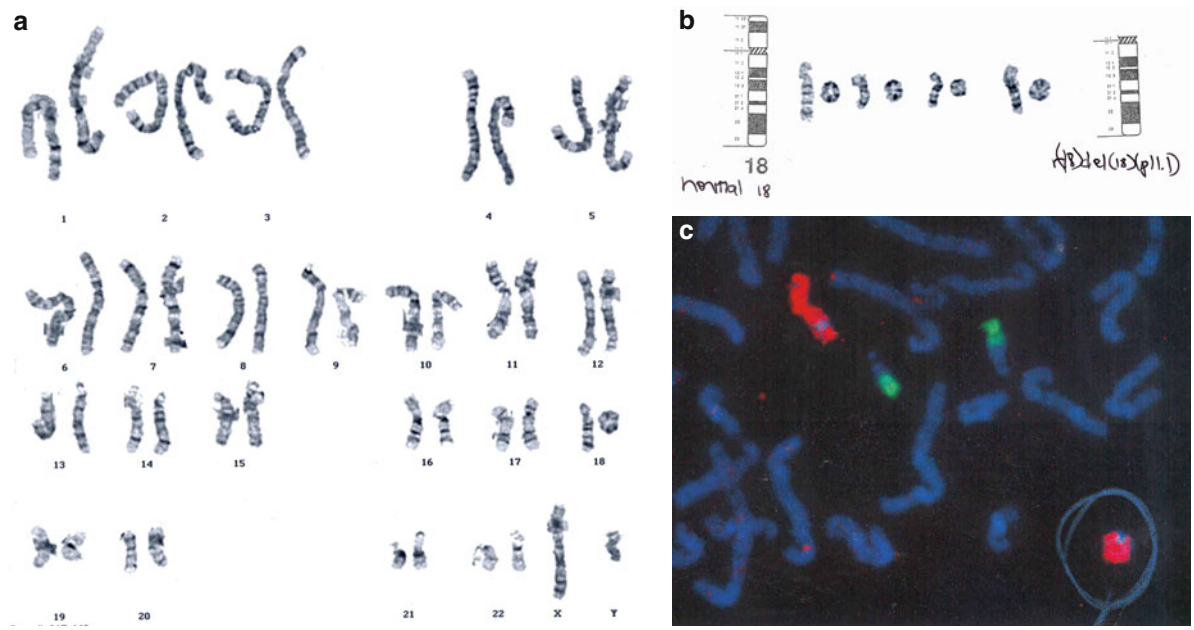

Fig. 2 (**a**–**c**) Chromosome analysis of the patient showed 46,XY,r(18), illustrated by a G-banded karyotype, a partial karyotype with idiograms, and FISH with whole chromosome 18 painting probe

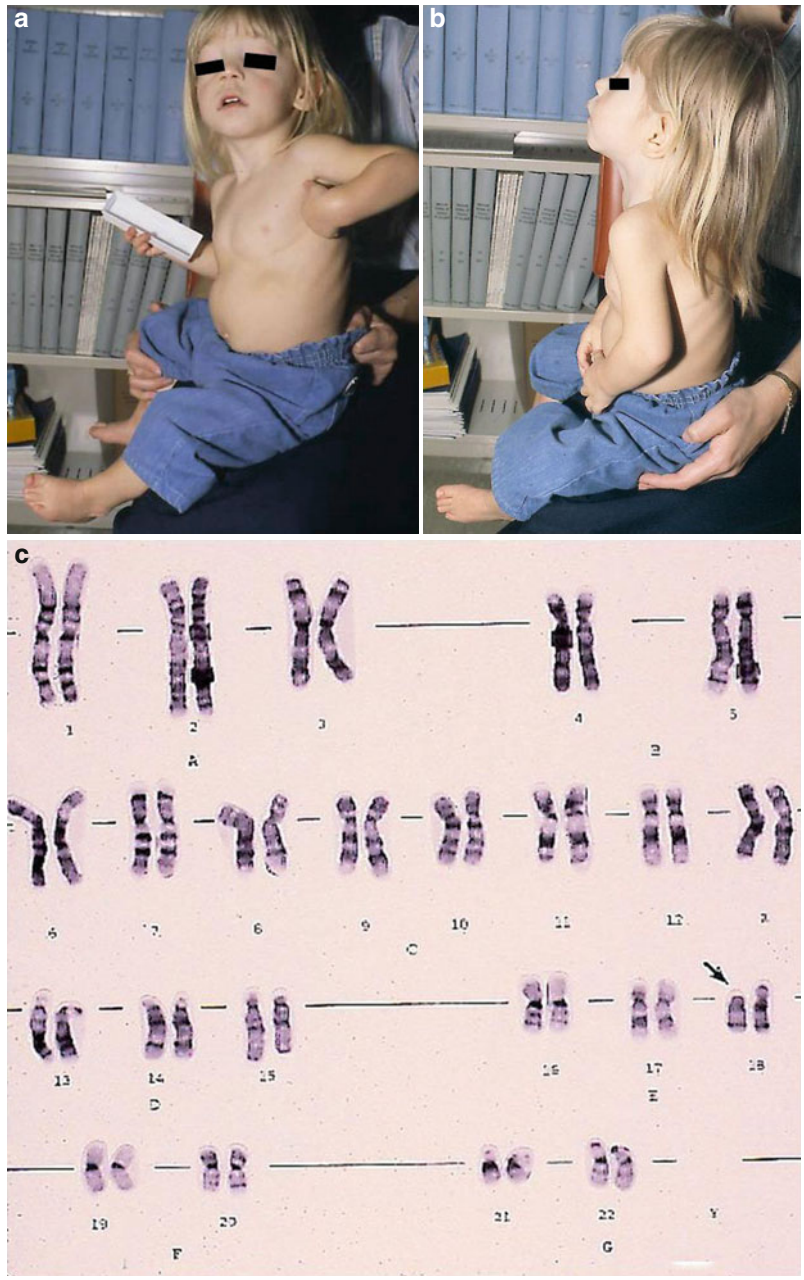

Fig. 3 (**a**–**c**) A girl with del (18p) showing hypotonia, ptosis of the eyelids, and small mandible. The G-banded karyotype shows deletion of the short arm of a chromosome 18

Fig. 4 (**a**, **b**) A boy with del(18q) showing hypotonia, ptosis of the eyelids, and carp-like mouth

Retinoid Embryopathy

Oral retinoids, isotretinoin (Accutane) and etretinate, uniquely effective in the treatment for severe cystic and keratinization disorders, are potent human teratogens.

Synonyms and Related Disorders

Isotretinoin embryopathy

Genetics/Basic Defects

1. Synthetic retinoids (isotretinoin, etretinate, acitretin)
   a. Closely resemble naturally occurring vitamin A, which is essential for the maintenance of visual and reproductive function and for proliferation and differentiation of epithelial tissues
   b. Isotretinoin and etretinate
      i. Released in the United States and Europe in 1982
      ii. Isotretinoin: uniquely effective in severe cystic acne
      iii. Etretinate (and acitretin): uniquely effective in severe psoriasis and other keratinization disorders which proved recalcitrant to all other therapies, account for their availability on prescription despite their teratogenicity
   c. Acitretin released later to replace etretinate as it is more rapidly eliminated from the body
   d. Adverse reactions
      i. Commonly reported adverse reactions: largely dose-related, of early onset, and reversible on discontinuation
         a) Dryness of the lips, mouth, and eyes
         b) Hair loss
         c) Pruitis
      ii. Less common and more severe idiosyncratic reactions
         a) Altered vision
         b) Headache
         c) Joint and muscle pain
         d) Abnormally raised serum transaminases levels
         e) Serum lipid changes
         f) Increased serum triglyceriode and cholesterol levels
         g) An increase in low-density/high-density lipoprotein ratio
      iii. Rare reactions
         a) Mental depression
         b) Severe hepatitis
         c) Diffuse hyperostosis of the spine
         d) Benign intracranial hypertension
   e. Teratogenicity of retinoids
      i. Foreshadowed by animal studies with strong warnings against exposure during pregnancy
      ii. Believed to interfere with the activity and migration of cranial neural crest cells during development and thus cause craniofacial, thymic conotruncal heart, and CNS malformations
      iii. Intellectual deficits

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2. Teratogenicity (Chan et al. 1996)
   a. Isotretinoin
      i. Teratogenic during the first trimester fetal exposure within the therapeutic dose range
      ii. Has a short elimination half-life of about 20 h
      iii. Recommended contraception period after cessation of therapy: 1 month
      iv. Risk of teratogenicity for isotretinoin
         a) Exposure within first trimester: about 28%.
         b) Pregnancy occurring within 1 month after cessation of treatment: about 4%.
         c) Pregnancy occurring after 1 month: The risk of fetal malformations returns to baseline (isotretinoin is no longer detectable in the maternal circulation) (Ellis and Krach 2001).
   b. Etretinate
      i. Readily absorbed into adipose tissue and slowly released from it
      ii. Has a long elimination half-life ($\geq$120 days)
      iii. Recommended contraception period after therapy: 2 years
      iv. Risk for teratogenicity for exposure to etretinate
         a) During pregnancy: about 26%
         b) Within 2 years of treatment cessation: about 2%
   c. Acitretin
      i. A shorter elimination half-life of 50 h
      ii. Recommendation of a 2-year contraception period after therapy for acitretin, as in some women, there is conversion of acitretin to etretinate during therapy

Clinical Features

1. Isotretinoin embryopathy (Chan et al. 1996)
   a. Craniofacial abnormalities
      i. Microtia/anotia
      ii. Agenesis or marked stenosis of external ear canals
      iii. Hypertelorism
      iv. Depressed nasal bridge
      v. Micrognathia
      vi. Cleft palate
      vii. Low-set ears
   b. Central nervous system abnormalities
      i. Hydrocephalus
      ii. Dandy–Walker malformation
      iii. Microcephaly
      iv. Microophthalmia
      v. Cerebellar defects
         a) Hypoplasia
         b) Microdysgenesis
      vi. Cortical defects
      vii. Cortical blindness
      viii. Facial nerve palsy
      ix. Optic nerve hypoplasia
      x. Retinal defects
      xi. Spina bifida
      xii. Mental retardation
   c. Cardiovascular abnormalities
      i. Conotruncal malformations
         a) Transposition of the great vessels
         b) Tetralogy of Fallot
         c) Truncus arteriosus
         d) Double-outlet right ventricle
         e) Ventricular septal defect
         f) Atrial septal defect
      ii. Coarctation of the aorta
      iii. Interrupted aortic arch
      iv. Hypoplastic left ventricle
      v. Retroesophageal right subclavian artery
   d. Other abnormalities
      i. Thymic abnormalities
         a) Ectopia
         b) Hypoplasia
         c) Aplasia
      ii. Nystagmus
      iii. Decreased muscle tone
      iv. Hepatic abnormality
      v. Hydroureter
      vi. Simian crease
      vii. Limb reduction
      viii. An increased risk of spontaneous abortions (about 15%) but no long-term effects on fertility
2. Retinate embryopathy
   a. Craniofacial abnormalities
      i. Microtia
      ii. Micrognathia
      iii. Low-set ears
   b. Central nervous system abnormalities
      i. Menigomyelocele
      ii. Anophthalmia
      iii. Brain defect
   c. Skeletal abnormalities
      i. Syndactyly

ii. Shortened or absent digits
iii. Club foot
iv. Multiple synostosis

Diagnostic Investigations

1. Sonogram/CT/MRI of the brain for CNS anomalies
2. Radiography/CT for auditory canal malformations
3. Echocardiography for congenital heart defects
4. Audiological assessment by brainstem auditory evoked response
5. Visual and somatosensory evoked potential to detect cortical response
6. Electroencephalography

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased unless the mother exposes to retinoid again during the pregnancy
   b. Patient's offspring: not increased unless exposure to retinoid during pregnancy
2. Prenatal diagnosis
   a. History of maternal exposure to retinoid
   b. Prenatal ultrasonography
      i. Craniofacial anomalies
         a) Microtia/anotia
         b) Anophthalmia/microphthalmia
         c) Other facial abnormalities
      ii. CNS anomalies
         a) Microcephaly
         b) Dandy–Walker malformation
         c) Hydrocephalus
      iii. Cardiac defects by fetal echocardiography
      iv. Skeletal abnormalities
3. Management (Atanackovic and Koren 1999b; Abroms et al. 2006)
   a. Pregnancy Prevention Program, developed by the manufacturer and the US Food and Drug Administration since 1988, to prevent fetal exposure to the drug Accutane
      i. Distribute printed material to prescribing physicians to be used in educating their female patients about the serious teratogenic effects
      ii. Instruct physicians to delay therapy until the second or third day of the patient's next normal menstrual period
      iii. Stress to patients, the importance of using two forms of contraception concurrently
      iv. A consent form to be signed by female patients
         a) Acknowledging that they have been instructed through the program
         b) Aware of the need to use two forms of contraception during isotretinoin therapy
         c) Agree to undergo pregnancy testing before, during, and after the therapy
      v. Internet-based, performance-linked system called iPLEDGE (Abroms et al. 2006)
         a) The most recent and most stringent system
         b) To ensure that the drug is dispensed only when there is documentary proof that the patient is not pregnant and is using two forms of birth control
   b. Adhere to strict prescription guidelines, but exposure during pregnancy still occurs. The most common reasons for unwanted or mistimed pregnancies with isotretinoin therapy are (Perlman et al. 2001) as follows:
      i. Unsuccessful attempts at abstinence
      ii. Use of ineffective contraception
      iii. Inconsistent use of contraception
      iv. Unexpected sexual activity
      v. Contraceptive failure
   c. The need to improve pregnancy prevention programs (Crijns et al. 2011)
      i. Taking responsibility and enhancing the performance by health care professionals
      ii. Give explicit instructions
      iii. Monitor the performance and adjusting, if necessary
   d. Surgical shunting for hydrocephalus
   e. Surgical repair of congenital heart defects
   f. Surgical reconstruction of the external ear canal and middle ear
   g. Orthopedic management of limb reduction
   h. Multidisciplinary approach to multiple handicapped conditions

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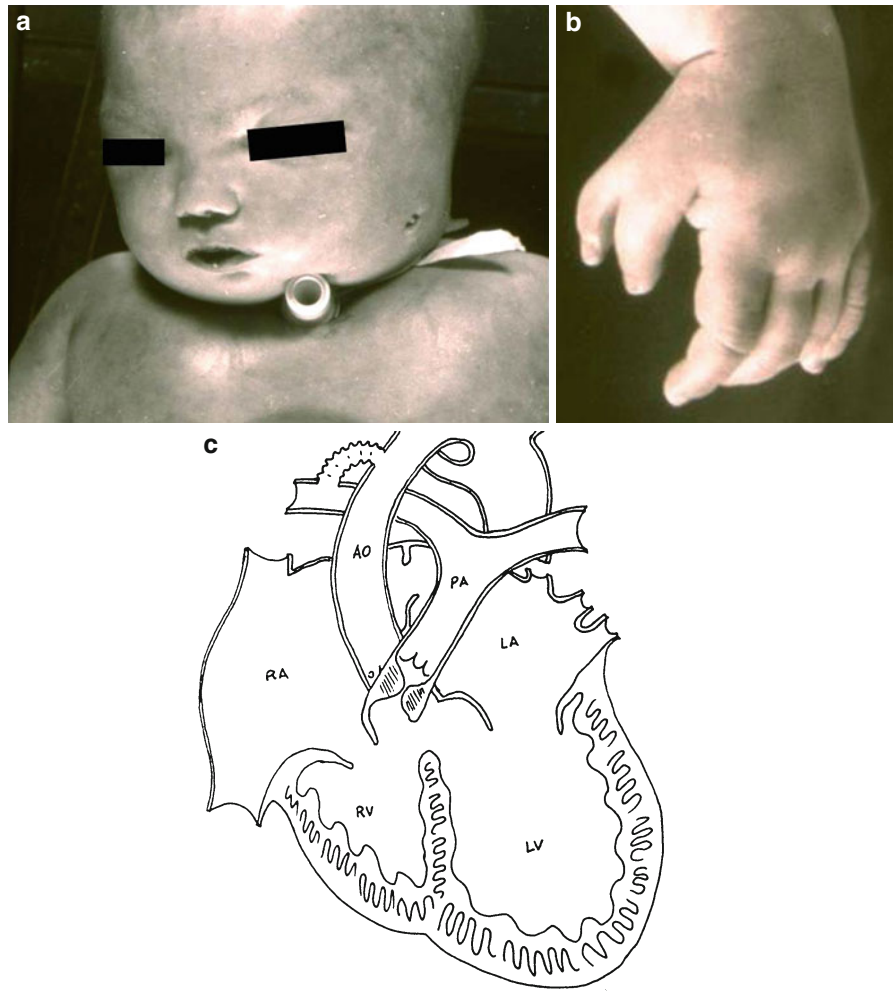

Fig. 1 (**a**–**c**) An infant with isotretinoin embryopathy. The mother took Accutane in the first trimester. Prenatal ultrasound examinations revealed intrauterine growth retardation, apparent ocular hypertelorism, flat nasal bridge, and tetralogy of Fallot. Parents elected to continue the pregnancy. The infant was born with dysmorphic craniofacial features (microcephaly, hypertelorism, flat nasal bridge, microretrognathia, cleft palate, absent ear canals and anotia, duplicated thumb on the left hand, anteriorly placed anus, and tetralogy of Fallot (illustrated in a drawing))

Rett Syndrome

Rett syndrome, a neurodevelopmental disorder affecting girls almost exclusively, was first described by Rett in 1966. The disorder now bears his name and became widely known after a report of 35 cases by Hagberg et al. in 1983. The prevalence is estimated to be 1/10,000–1/15,000 female births; over 95% of cases arise de novo due to the fact that most females with Rett syndrome do not reproduce. Rett syndrome is considered to be one of the most common genetic causes of mental retardation in girls, second only to Down syndrome.

Synonyms and Related Disorders

Autism, dementia, ataxia, and loss of purposeful hand use

Genetics/Basic Defects

1. Inheritance
   a. Sporadic cases (99.5%), occurring almost exclusively in females
      i. A de novo mutation in the child with Rett syndrome
      ii. Disease-causing mutation inherited from one parent who has somatic or germ line mosaicism
   b. Several reports of familial recurrence support X-linked dominant inheritance with lethality in hemizygous males.
2. The region of interest has been localized to Xq28 by linkage analysis from available familial cases.
3. Caused by mutations in the *MECP2* (methyl-CpG-binding protein 2) gene in Xq28
   a. Result in a loss of function by either disrupting the methylated DNA-binding properties of the protein or interfering with its association with transcriptional corepressors
   b. *MECP2* mutations in sporadic or atypical cases
      i. Up to 80% of sporadic affected females
      ii. One third of the clinically atypical cases
   c. *MECP2* mutations in familial cases (lower incidence)
      i. Germ line mosaic mothers
      ii. Asymptomatic carrier mothers due to nonrandom patterns of X-inactivation. The pattern of X-inactivation most likely protects the mutation carriers from expression of the disease by preferential inactivation of the mutant *MECP2* allele.
4. Females with the *MECP2* mutations (Takahashi et al. 2008)
   a. Exhibit a broad spectrum of clinical presentations ranging from classical Rett syndrome to asymptomatic carriers due to differences in X chromosome inactivation (XCI), and mechanisms other than XCI may contribute to the phenotypic heterogeneity associated with *MECP2* mutations
5. Males with the *MECP2* mutations
   a. May suffer from severe neonatal encephalopathy and die from breathing difficulties before their second year
   b. The almost absence of men with classic Rett syndrome suggests a lethal effect of the *MECP2* mutation in hemizygous affected men.

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c. However, males with Rett syndrome are not always lethal although neurologic impairment is slowly progressive and much more severe in men than in women.
d. Affected men have been reported in association with Klinefelter syndrome and somatic mosaicism.
e. Most *MECP2* mutations have originated in the paternal germ line. The paternal X *MECP2* never passed on from father to their sons.
f. Only way for a male to have Rett syndrome is a de novo mutation of a maternal X or inheritance of a *MECP2* gene mutation from his mother.
g. Some reported *MECP2* mutations may actually represent genetic variant rather than true pathogenetic novel mutations in the *MECP2* gene in males.
h. Genotype-phenotype correlations in males with MECP2 mutations (Moretti and Zoghbi 2006; Villard 2007)
    i. The first group
        a) Boys with Rett syndrome: have XXY karyotype or somatic mosaic and carry the same *MECP2* mutations that cause classic Rett syndrome in girls
        b) The affected boys have severe neonatal encephalopathy and usually die in their first year of life.
        c) These mutations can also lead to a milder phenotype when they are diluted among normally expressing cells.
    ii. The second group
        a) Has mutations that are not found in females with Rett syndrome
        b) These mutations are usually compatible with life into adulthood.
        c) The neurological presentation ranges from severe to mild nonspecific mental retardation.
    iii. The third group
        a) Composed of males having a duplication of the whole *MECP2* gene (and sometimes genes in its vicinity)
        b) The primary clinical features associated with this microduplication are nonspecific, but they comprise a severe phenotype.
        c) Affected individuals experience infantile hypotonia, recurrent respiratory infection, severe mental retardation, absence of speech development, seizures, and spasticity.
6. Clinical phenotypes of MeCP2 dysfunction in Rett syndrome and related disorders (Moretti and Zoghbi 2006; Chahrour and Zoghbi 2007)
    a. Females (loss-of-function of MeCP2)
        i. Classic Rett syndrome
        ii. Atypical Rett (preserved speech or normal hand use)
        iii. Infantile encephalopathy
        iv. Angelman syndrome phenotype
        v. Mental retardation with seizures
        vi. Mild mental retardation
        vii. Learning disability
        viii. Autism
        ix. Normal
    b. Males (loss-of-function of MeCP2)
        i. Infantile encephalopathy
        ii. Classic Rett syndrome (47,XXY or somatic mosaics)
        iii. Mental retardation with motor deficits
        iv. Bipolar disorder, mental retardation, and tremors
        v. Juvenile-onset schizophrenia, mental retardation, and tremors
        vi. Mental retardation, psychosis, pyramidal signs, and macroorchidism
    c. MECP2 gene duplications (overexpression of MeCP2)
        i. Preserved speech variant of Rett syndrome
        ii. Severe mental retardation and clinical features of Rett syndrome
        iii. Nonspecific X-linked mental retardation

Clinical Features

1. Normal prenatal and perinatal history
2. Appropriate head circumference
3. Apparently normal psychomotor development until about 6–18 months of life in affected girls
4. Developmental milestones afterward beginning to slow down and regress with loss of skills already achieved
    a. Deterioration of communicative skills
    b. Social withdrawal
    c. Loss of purposeful hand movement

5. Continued deterioration over the next few years
   a. Loss of language
   b. Poor motor function (truncal and gait apraxia/ataxia)
   c. Stereotypic hand movements (hand wringing and flapping)
   d. Deceleration of head growth (acquired microcephaly)
   e. Autistic behavior
6. Period of stabilization
   a. Severe psychomotor dysfunction
   b. Some patients may make small recoveries in contact and communication skills.
7. Breathing difficulties
   a. Periodic apnea
   b. Hyperventilation
   c. Breath holding
   d. Forced explosion of air/saliva
   e. Bruxism
8. Swallowing difficulties
9. Dystonia and hand and foot deformities as affected girls grow older
10. Later development of scoliosis
11. Osteoporosis at risk for fractures
12. Seizures (epilepsy) in 50% affected females
13. Possible survival into adulthood without further deterioration
14. An increased risk for sudden, unexplained death
    a. Longer corrected QT intervals
    b. T-wave abnormalities
    c. Reduced heart rate
15. Rett syndrome variants (<10% of cases)
    a. Patients with a milder clinical course ("forme fruste" phenotype): considered to be the most common variant of nonclassical Rett syndrome
       i. Less dramatic regression
       ii. Mild learning disability
       iii. Milder mental retardation
       iv. Preserved speech
       v. Ability to walk
       vi. Some hand use
       vii. Usually without seizures
       viii. No apparent symptoms observed in a few women who demonstrate skewed X chromosome inactivation
    b. Patients with a severe phenotype
       i. Lack of normal postnatal developmental period
       ii. Congenital hypotonia
       iii. Infantile spasms
    c. Patients with late regression
    d. Male patients with Rett syndrome
       i. Males with XXY (Klinefelter syndrome)
       ii. Males with somatic mosaicism
       iii. Males with XY (normal karyotype)
16. Clinical stages in classic Rett syndrome (Jedele 2007)
    a. Stagnation stage (6–18 months)
       i. Developmental arrest
       ii. Deterioration of eye contact and possible loss of communication
    b. Rapid destructive stage (1–4 years): developmental regression
       i. Developmental deterioration
       ii. Loss of acquired skills, including fine motor, babbling of words, and active playing
       iii. Loss of purposeful hand use
       iv. Stereotyped hand movements
       v. Apparent cognitive impairment
       vi. Intermittently "in another world"
       vii. Autistic features
       viii. Gait ataxia and apraxia
       ix. Irregular breathing (hyperventilation)
       x. Seizures in only 15%
    c. Pseudostationary stage (preschool–early school years)
       i. Some communication improvements
       ii. "Wake-up" period
       iii. Decreased autistic features
       iv. Preserved ambulation (A few are never ambulant.)
       v. Prominent gait ataxia and hand apraxia
       vi. Slow neuromotor regression
       vii. Seizures most frequent and severe
    d. Late motor deterioration stage (5–25 years)
       i. Decreased mobility (loss of ambulation)
       ii. Severe debilitation in patients who never walked
       iii. Spasticity
       iv. Improved emotional contact
       v. Scoliosis
       vi. Severe wasting and debilitation leading to "frozen stiffness"
       vii. Cachexia and growth retardation
       viii. Staring, unfathomable gaze
       ix. Complete wheelchair dependency
       x. Seizures may lessen or disappear

17. Wide spectrum of clinical features associated with an *MECP2* mutation
    a. Male patients with early-onset lethal encephalopathy
    b. Adult cases with severe mental retardation
    c. Female cases
        i. Asymptomatic
        ii. Mildly mentally retarded
        iii. Severe variant of Rett syndrome with congenital onset
18. Relatively restrictive international diagnostic criteria (Rett syndrome Diagnostic Criteria Work Group 1988)
    a. Apparently normal prenatal and perinatal period*
    b. Normal head circumference at birth
    c. Apparently normal development through age 6 months*
    d. Deceleration of head growth occurring anytime between ages 3 months and 48 months
    e. Loss of acquired hand skills and purposeful hand use between ages 5 months and 30 months, with subsequent development of stereotyped hand movements
    f. Severe impairment of expressive and receptive language together with severe psychomotor retardation
    g. Development of gait apraxia and truncal ataxia between ages 12 months and 48 months

* Clinical criteria "a" and "c" may not be applicable to severely affected females; other criteria will not apply to those who are mildly affected and are identified as having mutations in *MECP2*.

19. Modified diagnostic criteria (proposed by Clarke in 1996)
    a. Necessary criteria
        i. Normal prenatal and perinatal development
        ii. Loss of acquired skills such as communication and speech
        iii. Normal head circumference at birth with acquired microcephaly
        iv. Marked developmental delay
        v. Loss of hand skills
        vi. Autistic features
        vii. Gait apraxia
        viii. Stereotypic hand movements
    b. Supportive criteria
        i. Seizures
        ii. Abnormal EEG
        iii. Apnea
        iv. Hyperventilation
        v. Breathing dysfunction with breath holding
        vi. Scoliosis
        vii. Growth retardation
        viii. Cold feet
        ix. Spasticity with muscle wasting
20. Revised diagnostic criteria for classical and variant Rett syndrome (Hagberg et al. 2002; Williamson and Christodoulou 2006)
    a. Classical Rett syndrome
        i. Necessary criteria
            a) Normal prenatal and perinatal history
            b) Normal psychomotor development for the first 6 months
            c) Normal head circumference at birth
            d) Postnatal deceleration of head growth in most individuals
            e) Loss of purposeful hand skills between 6 months and 2.5 years
            f) Hand stereotypes
            g) Evolving social withdrawal, communication dysfunction, loss of acquired speech, and cognitive impairment
            h) Impairment or deterioration of locomotion
        ii. Supportive criteria
            a) Breathing disturbances during waking hours
            b) Bruxism
            c) Impairment of sleeping pattern from early infancy
            d) Abnormal muscle tone associated with muscle wasting and dystonia
            e) Peripheral vasomotor disturbances
            f) Progressive kyphosis or scoliosis
            g) Growth retardation
            h) Hypotrophic small and cold feet and/or hands
        iii. Exclusion criteria
            a) Evidence of a storage disorder including organomegaly
            b) Cataract, retinopathy, or optic atrophy
            c) History of perinatal or postnatal brain damage

d) Confirmed inborn error of metabolism or neurodegenerative disorder
e) Acquired neurological disorder due to severe head trauma or infection

b. Variant Rett syndrome
i. Inclusion criteria
a) At least three of the six main criteria
b) At least 5 of the 11 supportive criteria
ii. Main criteria
a) Reduction or absence of hand skills
b) Loss or reduction of speech (including babble)
c) Hand stereotypes
d) Loss or reduction of communication skills
e) Deceleration of head growth from early childhood
f) Regression followed by recovery of interaction
iii. Supportive criteria
a) Breathing irregularities
b) Abdominal bloating or air swallowing
c) Bruxism
d) Abnormal locomotion
e) Kyphosis or scoliosis
f) Lower limb amyotrophy
g) Cold, discolored and usually hypotrophic feet
h) Night time screaming and other sleep disturbances
i) Inexplicable episodes of screaming or laughing
j) Apparently diminished sensitivity to pain
k) Intense eye contact and/or eye pointing

Diagnostic Investigations

1. Mutational analyses of *MECP2* gene
   a. Sequence analysis and mutation scanning
   b. Mutations detected in 35–90% of patients (detected in almost every patient with classical Rett syndrome)
   c. Wide spectrum of mutations of the *MECP2* gene
   d. Mutations extending to phenotypes that are not easily recognized as Rett syndrome
   e. No significant correlation exists between the clinical course and mutation type.
   f. *MECP2* mutations have been identified in patients previously diagnosed with the following conditions:
      i. Autism
      ii. Mild learning disability
      iii. Clinically suspected but molecularly unconfirmed Angelman syndrome
      iv. Mental retardation with spasticity or tremor
2. X-chromosome inactivation pattern: not tested routinely
3. EEG: not specific
4. CT and MRI
   a. Cortical atrophy predominantly in the frontal area
   b. No abnormalities in the white matter, basal ganglia, thalamus, or hippocampus
   c. Narrowing of the brain stem in some patients
5. Photon emission CT
   a. Lower cerebral blood flow in the prefrontal and temporoparietal association regions with sparing of the sensorimotor regions
   b. The flow distribution in Rett patients
      i. Similar to that observed in infants of a few months of age
      ii. Suggesting a neurodevelopmental abnormality rather than a neurodegenerative process

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. 50% risk to sibs of inheriting *MECP2* allele from the carrier mother
      ii. Low risk to sibs (<1/300) (Killian 1986) when a mutation present in the proband is not identified in a parent, provided germ line mosaicism is not present in either parent (Amir et al. 1999; Mari et al. 2005)
   b. Patient's offspring
      i. Unlikely to have offspring due to mental retardation and other handicaps
      ii. Reproduction reported in mildly affected females
         a) Each offspring of a carrier female with 50% risk of inheriting the disease-causing mutation
         b) Daughters who inherit the mutation are at high risk of developing classic Rett

syndrome although skewed X chromosome inactivation may result in a milder phenotype.

c) Sons who inherit the mutation may suffer a severe neonatal encephalopathy or severe mental retardation in those who survive beyond the first year of age.

iii. Healthy sisters of a girl with Rett syndrome
   a) Possibility of being carriers of the *MECP2* mutation but with little or no symptoms because of favorable skewed X chromosome inactivation
   b) At risk of transmitting the disease-causing *MECP2* mutation to their own children

iv. No male with a *MECP2* mutation known to reproduce

2. Prenatal diagnosis
   a. Amniocentesis or chorionic villus sampling available to pregnancies at risk for women with a known *MECP2* mutation identified in a family member
   b. Appropriate to offer prenatal diagnosis to couples who have had a child with Rett syndrome or mental retardation due to a *MECP2* mutation, whether or not the disease-causing mutation has been identified in a parent since germ line mosaicism cannot be excluded in either parent
   c. A male fetus with the mutation
      i. May suffer from a severe neonatal encephalopathy
      ii. May survive with a severe mental retardation syndrome
   d. A female fetus with the mutation
      i. Difficult to predict the phenotype in a female fetus with a *MECP2* mutation which can range from apparently normal to severely affected
      ii. At high risk of developing classic Rett syndrome although skewed X chromosome inactivation may result in a milder phenotype
3. Management
   a. No treatment is known to improve the neurologic outcome of Rett patients.
   b. Supportive and symptomatic therapies
      i. Anticonvulsants for seizures
      ii. Chloral hydrate for agitation
      iii. Carbidopa and levodopa for rigidity
      iv. Melatonin for sleep disturbances
      v. Nutritional management to insure adequate caloric and fiber intake
      vi. Management of gastroesophageal reflux
         a) Antireflux agents
         b) Smaller and thickened feedings
         c) Positioning
   c. Occupational and physical therapies
      i. Maintain function
      ii. Prevent scoliosis and deformities
   d. Augmentative communication
   e. Therapeutic horseback riding, swimming, and music therapy

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Fig. 1 A girl with Rett syndrome

Fig. 2 A girl with Rett syndrome who has *MECP2* mutation (R106W)

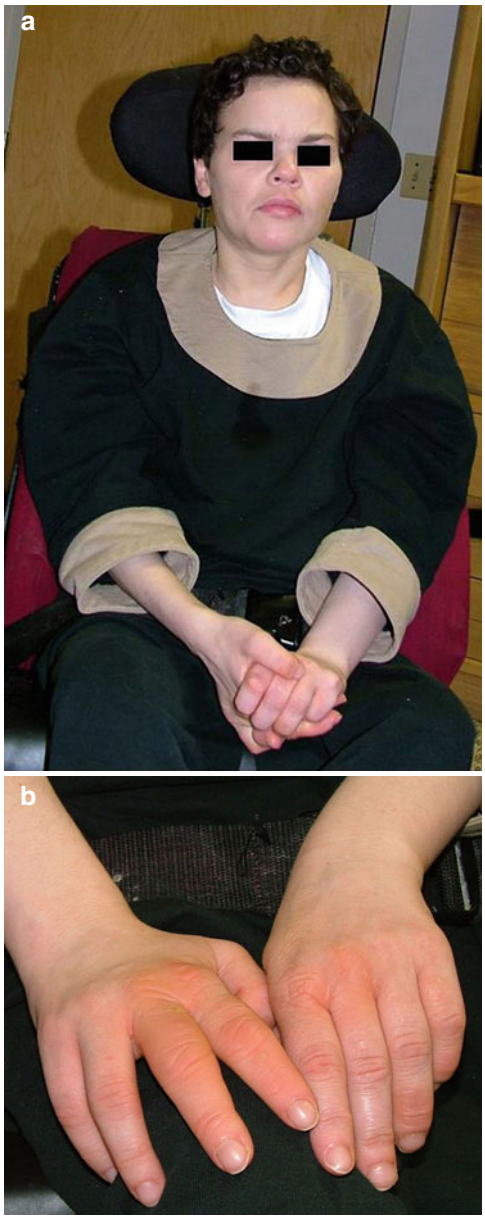

Fig. 3 (**a**, **b**) A 33-year-old female with Rett syndrome showing severe psychomotor retardation and hand wringing so severe that the part of the hand and fingers are red, rough, and swollen from constant irritation by stereotypic hand movement. She was normal developmentally until about 18 months of age when she started to have hand washing/wringing, tip toe walking, fell easily, and lost the skills she already attained. Shortly after, she started to lose eye contact with people and has seizures. DNA sequence analysis identify a nucleotide change of 763 C > T in one copy of the *MECP2* gene which predicts an amino acid change of arginine to a premature translation stop at codon 255 (R255X). This nonsense mutation was previously identified in multiple Rett syndrome patients as a disease-causing *MECP2* mutation

Rickets

Normal bone mineralization requires adequate supplies of calcium and phosphate and normal vitamin D metabolism. Defective supply or function of any of these factors can cause rickets and osteomalacia.

Synonyms and Related Disorders

Familial hypophosphatemic rickets; Nutritional rickets; Vitamin-deficiency rickets; Vitamin D-dependent rickets

Genetics/Basic Defects

1. Causes
   a. Younger than 6 months of age
      i. Hypophosphatasia
      ii. Prematurity
      iii. Primary hyperparathyroidism
      iv. Maternal factors
         a) Vitamin D deficiency
         b) Poorly controlled hyperparathyroidism
         c) Poorly controlled renal insufficiency
   b. Older than 6 months of age
      i. Nutritional rickets in children
         a) Inadequate levels (deficiency) of vitamin D due to either inadequate oral intake or insufficient exposure to sunlight
         b) With resultant decreased calcium absorption in the small intestine
         c) Thereby decreasing the available calcium for epiphyseal cartilage and skeletal mineralization
         d) Secondary hyperparathyroidism due to limited calcium availability and attendant renal phosphate losses contributes to the bone and growth plate pathophysiology that lead to the clinical manifestations of rickets.
      ii. Liver disease (impaired 25-vitamin D formation)
         a) Chronic liver diseases (extrahepatic biliary atresia, total parenteral nutrition, tyrosinemia)
         b) Anticonvulsant therapy
      iii. Malabsorption
         a) Celiac disease
         b) Inflammatory bowel disease
         c) Pancreatic insufficiency
      iv. Renal tubular insufficiency (hypophosphatemia)
         a) Vitamin D-resistant rickets
         b) Vitamin D-dependent rickets
         c) Fanconi syndrome
         d) Lowe syndrome
         e) Cystine storage disease
      v. Chronic renal disease (renal osteodystrophy)
         a) Pyelonephritis
         b) Polycystic kidney disease
         c) Chronic glomerulonephritis
         d) Renal tubular acidosis

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2. Vitamin D deficiency rickets: caused by low endogenous vitamin D
   a. Selected pediatric populations at high risk for vitamin D deficiency
      i. Dietary factors (breast-fed infants with marginal calcium stores due to low levels of vitamin D in breast milk)
      ii. Skin pigmentation (African American children due to dark skin absorbing ultraviolet radiation less available for vitamin D production)
      iii. Sun screen application
      iv. Insufficient sun exposure (far northern latitudes, during the winter months, cultural traditions)
   b. Other predisposing factors
      i. Severe liver failure
      ii. Nephrotic syndrome
      iii. Severe malnutrition
      iv. Gastrointestinal diseases leading to malabsorption, including impaired fat absorption or enterohepatic recirculation
3. Vitamin D-dependent rickets: caused by reduced activity of 25(OH)1-alphahydroxylase
   a. Vitamin D-dependent rickets type I (1-alpha-hydroxylase mutation): also known as hereditary pseudovitamin D deficiency rickets
      i. Autosomal recessivedisorder
      ii. Commonly found in the French Canadian population
      iii. The gene locus mapped to chromosome 12q14
      iv. Caused by mutation in the vitamin D 1-alpha-hydroxylase gene
      v. Impaired 1 alpha-hydroxylation in the renal proximal tubule that converts 25(OH)D to $1,25(OH)_2D$
   b. Vitamin D-dependent rickets type II (receptor mutation): also known as hereditary vitamin D-resistant rickets
      i. Autosomal recessive inheritance
      ii. Caused by mutations in the vitamin D receptor (VDR) that result in end-organ resistance to active vitamin D (1,25-dihydroxyvitamin D) [$1,25\text{-}(OH)_2D_3$]
      iii. Major defect caused by the mutant VDR: a decrease of intestinal calcium and phosphate absorption which leads to decreased bone mineralization and rickets
      iv. The major biochemical distinction between type I and type II
         a) Low circulating $1,25\text{-}(OH)_2D_3$ levels in patients with type I
         b) High circulating $1,25\text{-}(OH)_2D_3$ levels in patients with type II
4. Familial hypophosphatemic rickets
   a. A heterogeneous disease with an incidence of 1 in 20,000 newborns
   b. Caused by defect in reabsorption of phosphatein the proximal tubule, resulting in hypophos phatemia, defective bone mineralization, normoc alcemic rickets, and short stature
   c. Types of hypophosphatemia
      i. Dominant X-linked hypophosphatemic rickets (also called vitamin D-resistant rickets)
         a) The gene locus: mapped to Xp22.1
         b) The gene responsible: phosphate regulating (*PHEX*) gene with homologies to endopeptidases in the X chromosome (Chandran et al. 2010)
         c) Complete penetrance
         d) This is the most common form of metabolic rickets.
      ii. Autosomal dominant hypophosphatemic rickets
         a) The gene locus: mapped to 12p13
         b) Caused by mutations in *FGF23*
         c) Incomplete penetrance
      iii. Autosomal recessive hypophosphatemic rickets (Farrow et al. 2009; Levy-Litan et al. 2010; Lorenz-Depiereux et al. 2010)
         a) Caused by mutations in Dentin matrix protein-1 (*DMP1*) gene, which is associated with elevated fibroblast growth factor 23 (FGF23), or ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*) gene
         b) Surprisingly, *ENPP1* loss-of-function mutations have previously been described in generalized arterial calcification of infancy, suggesting an as yet elusive mechanism that balances arterial calcification with bone mineralization.

iv. Hereditary hypophosphatemic rickets with hypercalcinuria (Pettifor 2008)
a) Caused by *SLC34A3* mutations
b) Gene product: inactivating mutation in NaPi-IIc (renal Na-P_i cotransporter)
c) Elevated $1,25(OH)_2D$

Clinical Features

1. Rickets vs osteomalacia
   a. Rickets: occurs only before fusion of the epiphyses
   b. Osteomalacia: occurs in adults deficient in calcium, phosphate, or vitamin D
2. Signs of rickets in osseous tissues (Wharton and Bishop 2003)
   a. Craniotabes in newborn baby and young infant
      i. Softening of skull bones
      ii. May be present but not pathognomonic
   b. Frontal bossing in early infancy
      i. Expansion of cranial bones relative to facial bones
      ii. Also possibly due to hydrocephalus ("rickets hydrocephalus")
   c. Fontanelle
      i. Delayed closure
      ii. Occasional intracranial hypertension
   d. Wrists: an apparent bracelet of bone around the wrist (specificity 81%)
   e. Rickety rosary: swollen costochondral junctions of ribs (specificity 64%)
   f. Skeletal deformities
      i. Particularly "bow legs" once the child is walking
      ii. Genu valgum generally not due to rickets
      iii. Spinal curvature most likely due to nonrickets cause
      iv. Narrowed pelvic outlet used to cause obstructed labor
   g. Brown tumor: rare fibrous-cystic osteitis associated with the secondary hyperparathyroidism
   h. Limb pain
      i. Bone pain and pseudoparalysis uncommon
      ii. Osteomalacia and the subperiosteal hematoma of scurvy: more likely causes of pain
   i. Teeth
      i. Delayed eruption of teeth
      ii. Enamel hypoplasia: greater susceptibility to caries in the first dentition
3. Nonosseous effect of vitamin D deficiency (Wharton and Bishop 2003)
   a. Symptomatic hypocalcemia with convulsions: particularly in young infants less than 6 months of age born to mothers with untreated osteomalacia, many of whom are subclinical cases.
   b. Myopathy
      i. Proximal myopathy in infants and adolescents
      ii. Heart failure simulating cardiomyopathy with severe hypocalcemia
      iii. Responding to treatment for rickets and inotropes
   c. Myelofibrosis
      i. With pancytopenia or microcytic hypochromic anemia
      ii. Returning to normal when treated with vitamin D
   d. Possible link between early vitamin D deficiency and other disorders in later life
      i. Type I diabetes
      ii. Multiple sclerosis
      iii. Schizophrenia
      iv. Hear disease
   e. Intrauterine and infant growth: Vitamin D supplement in the last trimester of pregnancy improves growth in utero and during infancy in some studies.
4. Vitamin D deficiency rickets
   a. Not clinically apparent before 6 months of age because of prenatal stores of vitamin D imparted by the mother
   b. Decreased linear growth/short stature
   c. Poor weight gain/small for age
   d. Delayed development
   e. Incidental finding on radiograph or physical examinations
   f. Nonspecific musculoskeletal complaints
   g. Bowing of the legs
   h. Seizures
   i. Tetany
   j. Weakness
   k. Drowsiness

l. Development of secondary hyperparathyroidismdue to increasing severity of vitamin D deficiency, progressing to frank osteomalacia and fractures

5. Vitamin D-dependent rickets
   a. Vitamin D-dependent rickets type I (hereditary pseudovitamin D deficiency rickets)
      i. Clinical presentation within the first few months of life
      ii. First clinical sign: acute or chronic hypocalcemia because the major physiologic role of 1,25-dihydroxyvitamin D is to promote intestinal calcium absorption
      iii. Hypocalcemic seizures as early as 4 weeks of age or usually before 2 years of age
      iv. Growth retardation
      v. Bowing of the extremities
      vi. Bone pain secondary to rickets and osteomalacia
      vii. Enamel hypoplasia and oligodentia
      viii. Hypocalcemia accompanied by secondary hyperparathyroidism resulting in hypophosphatemia and occasional aminoaciduria
   b. Vitamin D-dependent rickets type II (hereditary vitamin D-resistant rickets)
      i. Onset of disease: infancy or childhood
      ii. Major clinical findings: hypocalcemia and rickets due to defective intestinal calcium absorption leading to impaired mineralization of newly forming bone and preosseous cartilage.
      iii. Rickets
         a) Often severe
         b) Usually exhibits within months of birth
      iv. Bone pain
      v. Muscle weakness
      vi. Hypotonia
      vii. Occasional convulsions from hypocalcemia
      viii. Often growth retarded
      ix. Enamel hypoplasia, oligodentia, and severe dental caries
      x. Hypocalcemia accompanied by secondary hyperparathyroidism results in hypophosphatemia and occasional aminoaciduria.
      xi. Pneumonia secondary to severe rickets of the chest wall and poor respiratory effort causes death in some infants.
      xii. Alopecia
         a) Sparse body hair in many patients
         b) Alopecia totalis observed in some kindreds, including eyebrows and in some cases eyelashes

6. Hereditary hypophosphatemic rickets
   a. X-linked dominant hypophosphatemic rickets
      i. Characterized by renal phosphate wasting with hypophosphatemia
      ii. Disease severity similar in males and females but differs among individuals (some patients with isolated hypophosphatemia; others with disabling severe bone disease)
      iii. The disease may persist into adulthood.
      iv. Short stature
      v. Rickets with resultant lower-extremity deformities
      vi. Bone pain.
      vii. Enthesopathy (calcification of tendons, ligaments, and joint capsules)
      viii. Dental abscesses
      ix. Cranial abnormalities (e.g., craniosynostosis) (Murthy 2009) and spinal stenosis in some severely affected individuals
   b. Autosomal dominant hypophosphatemic rickets
      i. Isolated renal phosphate wasting
      ii. Short stature
      iii. Impressive windswept deformity (valgus on one side and varus on the other side)
      iv. Marked tendency for fracture with or without trauma
      v. Delayed onset of disease in some patients
      vi. Patients who present as adults: osteomalacia with bone pain, weakness, and fractures
   c. Autosomal recessive hypophosphatemic rickets: severe disease course (Stamp and Baker 1976; Farrow et al. 2009)
      i. Marked hypophosphatemia
      ii. Persistent osteomalacia upon bone biopsy
      iii. Increased bone density by dual-energy X-ray absorptiometry
      iv. Stunted growth
      v. Nerve deafness
      vi. Facial and dental abnormalities
      vii. Learning disabilities

Diagnostic Investigations

1. Vitamin D deficiency rickets
   a. Decreased levels of 25-OH vitamin D (best screening test for vitamin D stores in otherwise healthy individuals)
   b. Normal or increased levels of 1,25 $(OH)_2$ vitamin D
   c. Increased levels of parathyroid hormone
   d. Decreased levels of calcium (hypocalcemia)
   e. Decreased levels of phosphate (hypophosphatemia)
2. Vitamin D-resistant rickets
   a. Renal tubular phosphate leakage and subsequent hypophosphatemia in all affected individuals
   b. Normal levels of 25-OH vitamin D
   c. Normal or decreased levels of 1,25 $(OH)_2$ vitamin D
   d. Normal or increased levels of parathyroid hormone
   e. Normal levels of calcium
   f. Decreased phosphate (hypophosphatemia)
3. Vitamin D-dependent rickets
   a. Elevated or normal levels of 25-OH vitamin D
   b. Low levels of 1,25 $(OH)_2$ vitamin D in type I and elevated levels in type II
   c. Normal or increased levels of parathyroid hormone
   d. Normal or decreased levels of calcium
   e. Decreased levels of phosphorous (hypophosphatemia)
   f. Elevated serum alkaline phosphatase activity
4. Radiographic findings
   a. Cupping, fraying, and widening of the metaphyses: a requirement for diagnosis of rickets
   b. Rachitic rosary (enlargement of the wrists, knees, and costochondral beadings)
   c. Flaring of ribs at diaphragm level (Harrison's groove)
   d. Bowing of the lower extremities in the newly ambulating child
   e. Widening and irregularity of all the physes
   f. Osteopenia (decreased mineralization of the bone matrix) with blurred or nonapparent cortical outlines of the epiphyseal ossification centers
   g. Multiple fractures in various stages of healing
   h. Deformities caused by softening of bone or poor muscle tone
      i. Femoral bowing
      ii. Tibial bowing
      iii. Genu valgum (knock knees)
   i. Genu valgum or varum
   j. Lordosis/kyphosis/scoliosis
   k. Pelvis
      i. Coxa valga
      ii. Protrusio acetabuli
   l. Thorax: hourglass shape
   m. Skull
      i. Postural molding
      ii. Frontal bossing
      iii. Craniotabes
      iv. Delayed closure of anterior fontanel
   n. Dental abnormalities
   o. The zone of provisional calcification appearing as a dense metaphyseal band due to calcium deposit in response to vitamin D therapy
      i. Seen as early as 2–3 weeks after initiation of therapy in children with nutritional rickets
      ii. Seen after 2–3 months in children with renal rickets
      iii. Persistence of deformities caused by bone softening despite successful treatment
5. Histological findings
   a. Primary metabolic abnormality at the zone of provisional calcification
   b. Diminished calcification of cartilage columns in the metaphysis
   c. Continued osteoid production by osteoblasts, but ossification of the osteoid tissue is impaired because of insufficient calcium deposition
   d. Widened, irregularly calcified physis resulting from resorption of osteoid and calcium because of impaired osteoclast function
   e. Metaphyseal broadening or "cupping" likely caused by stress at sites of ligament attachment
   f. Splaying of cartilage cells peripherally
   g. Microfractures of the primary spongiosa by herniation of cartilage into this area
6. Molecular genetic diagnosis
   a. X-linked dominant hypophosphatemic rickets (*PHEX* gene mutations)
      i. Sequencing of entire coding region
      ii. Deletion/duplication analysis

b. Autosomal dominant hypophosphatemic rickets (*FGF23* gene mutations)
   i. Sequencing of entire coding region
   ii. Mutation scanning
   iii. Targeted mutation analysis
   iv. Deletion/duplication analysis
c. Hypophosphatemic rickets, autosomal recessive 1 (*DMP1* gene mutations)
   i. Sequencing of entire coding region
   ii. Deletion/duplication analysis
d. Hypophosphatemic rickets, autosomal recessive 2 (*ENPP1* gene mutations): sequencing of the entire coding region
e. Vitamin D-dependent rickets, type I (*CYP27B1* gene mutations)
   i. Sequencing of entire coding region
   ii. Targeted mutation analysis
   iii. Deletion/duplication analysis
f. Vitamin D-dependent rickets, type II (VDR gene mutations): sequencing of the entire coding region
g. Hereditary hypophosphatemic rickets with hypercalcinuria (*SLC34A3* gene mutations): sequencing of the entire coding region

Genetic Counseling

1. Recurrence risk: depends on the etiology
   a. Vitamin D deficiency rickets: recurrence risk high if conditions leading to vitamin D deficiency exist
   b. Autosomal recessive inheritance
      i. Patient's sib: 25%
      ii. Patient's offspring: not increased unless the spouse is a carrier or affected
   c. Autosomal dominant inheritance
      i. Patient's sib: not increased unless a parent is affected
      ii. Patient's offspring: 50%
   d. X-linked dominant inheritance
      i. Patient's sib: not increased unless a parent is affected
      ii. Patient's offspring
         a) Affected female: 50% of daughters and 50% of sons will be affected.
         b) Affected male: All daughters will be affected and all sons normal.
2. Prenatal diagnosis
   a. Fetal radiography, particularly in mothers with osteomalacia
      i. Poorly mineralized fetal bones
      ii. Thin cortices of the limb bones and penciled outlines of the vertebral bodies
      iii. Cupped tibial/radial metaphysis with indistinct border to the epiphyseal aspect
   b. Fetal echocardiography
      i. Atrial flutter with heart failure reported in a fetus affected with X-linked dominant hypophosphatemic rickets.
      ii. Causal relationship in this case remained unknown.
   c. Prenatal diagnosis by molecular analysis of cultured fetal cells obtained from CVS and amniocentesis in pregnant women from high-risk families to look for disease-causing mutation, previously identified in an affected individual
      i. X-linked dominant hypophosphatemic rickets
      ii. Autosomal dominant hypophosphatemic rickets
      iii. Autosomal recessive hypophosphatemic rickets, I
      iv. Vitamin D-dependent rickets type I and type II
      v. Hereditary hypophosphatemic rickets with hypercalciuria
3. Management
   a. Hypocalcemia and "simple rickets" (Wharton and Bishop 2003)
      i. Hypocalcemia (early infancy)
         a) IV calcium gluconate to control continuing seizures
         b) Oral calcium daily
         c) Oral calciferol daily
         d) Look for evidence of rickets in the baby (radiographs of the knees and wrists).
         e) Look for maternal osteomalacia (elevated maternal alkaline phosphatase).
         f) Slowly withdraw treatment when the plasma calcium is normal.
         g) Continue prophylactic vitamin D thereafter.
      ii. Rickets without hypocalcemia (early infancy): oral calciferol daily for 2–4 months
      iii. Older infants, toddlers, and adolescents
         a) Oral calciferol
         b) Add oral calcium if dietary deficiency may be a factor.

c) Phosphorus not needed in simple rickets since phosphorus is abundant in the diet
d) Necessary to supplement phosphorus for very preterm babies and in the phosphate-wasting causes of rickets

b. Vitamin D deficiency rickets
   i. Increase dietary intake of vitamin D
      a) The new recommended adequate intake of vitamin D by the National Academy of Sciences to prevent vitamin D deficiency in normal infants, children, and adolescents is 200 IU per day.
      b) An intake of at least 200 IU per day of vitamin D will prevent physical signs of vitamin D deficiency and maintain serum 25-hydroxy-vitamin D at or above 27.5 nmol/L.
   ii. Increased sun exposure
   iii. Prevent other predisposing factors
c. Vitamin D-resistant rickets
   i. Increase dietary intake of vitamin D.
   ii. Increased sun exposure
   iii. Prevent other predisposing factors.
d. Vitamin D-dependent rickets: lifelong treatment with 1-alpha-hydroxyvitamin D or 1,25-dihydroxyvitamin D
e. Dominant X-linked hypophosphatemic rickets: treat bone lesions and impaired longitudinal growth
   i. Medical treatment remains the main pillar of therapy in affected children.
      a) Vitamin D supplement
      b) Oral phosphate supplement: risks of stimulating secondary hyperparathyroidism
   ii. Surgery can be safely performed in XL vitamin D-resistant hypophosphatemic rickets, independent of age or bone maturation (Fucentese et al. 2008).

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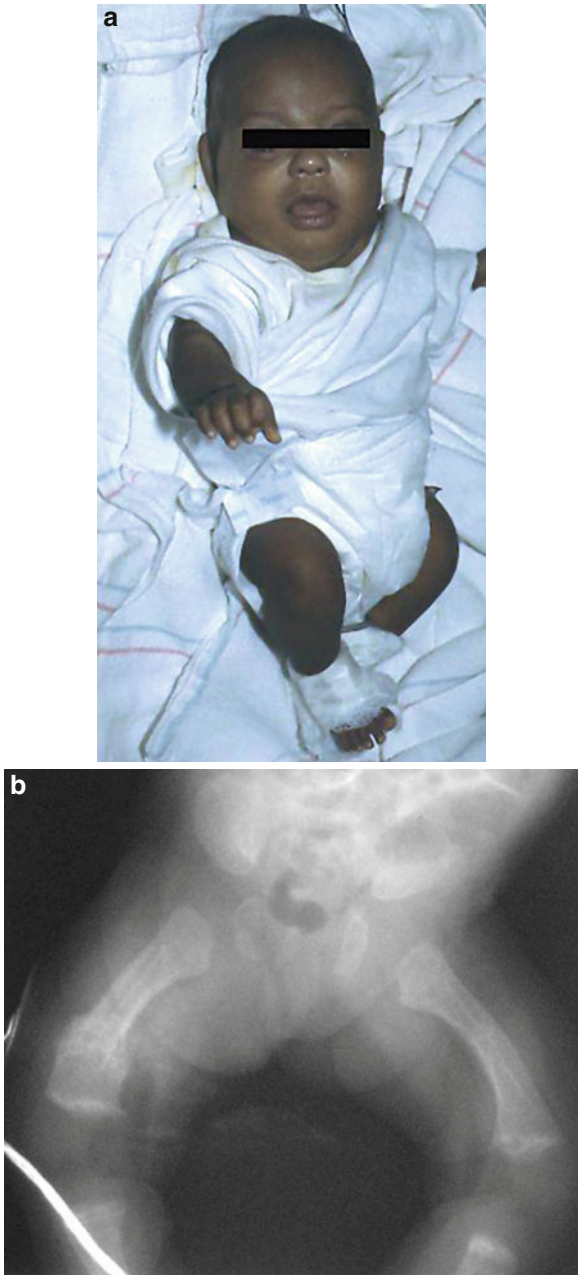

Fig. 1 (**a**, **b**) An infant with healing nutritional rickets. The radiograph shows femoral bowing and a healing fracture with callus formation in the right femur

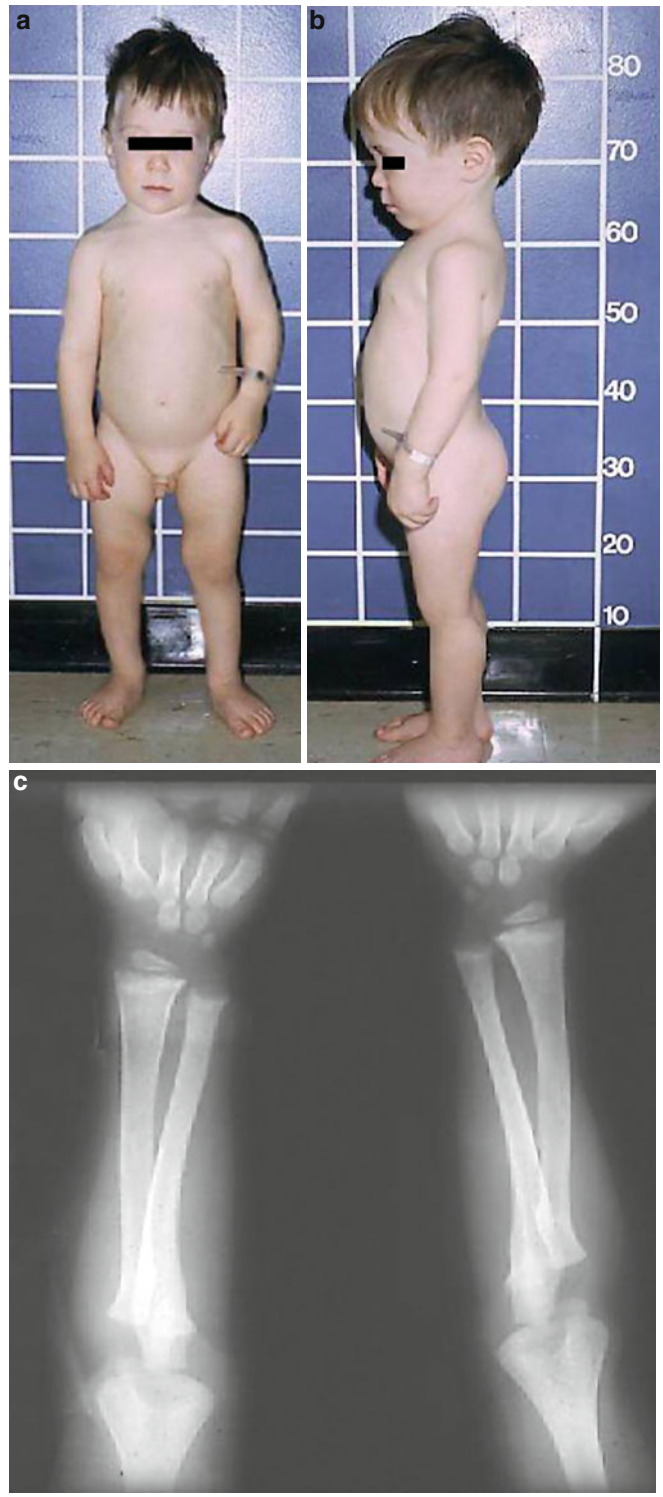

Fig. 2 (**a**–**c**) A boy with vitamin D-resistant rickets showing short stature. The radiograph shows widening, cupping, and fraying of the distal radius and ulna

Fig. 3 (**a**, **b**) Another boy with vitamin D-resistant rickets

Fig. 4 (**a**, **b**) Radiograph from a patient with renal rickets shows widening, cupping, and fraying of the distal radius and ulna

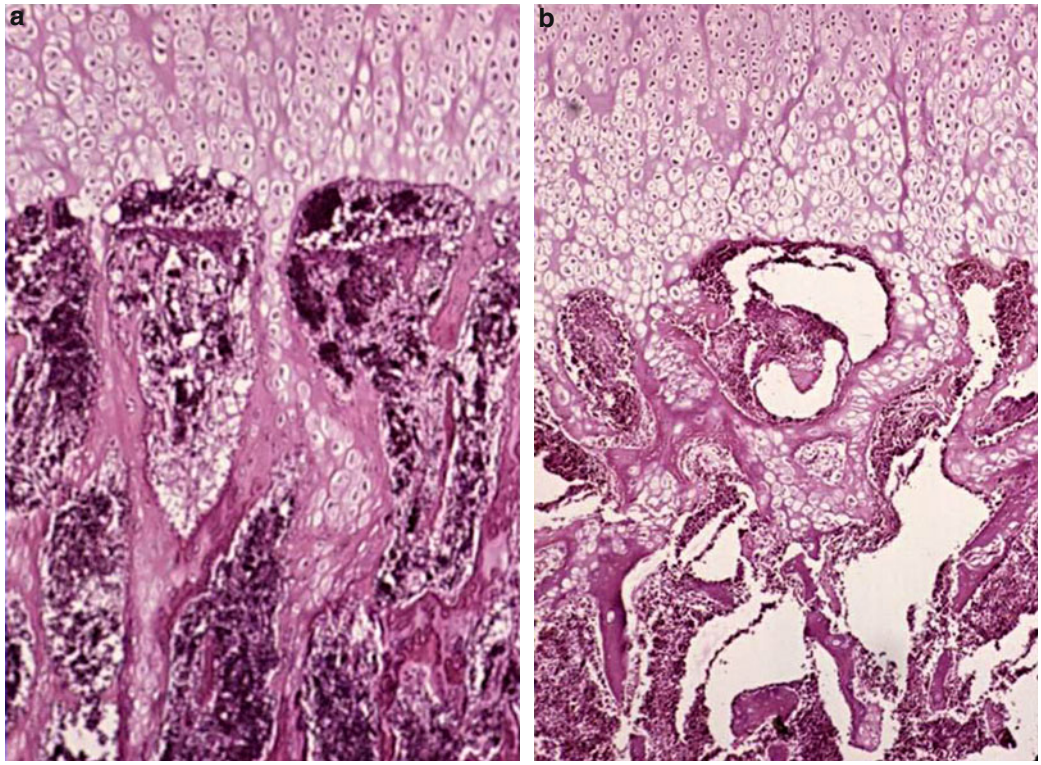

Fig. 5 (**a**, **b**) Photomicrograph of the humerus (*left*) and the rib (*right*) of a female neonate who lived 43 min. Broad cartilage columns with many large chondrocytes are present in the metaphysis. They have broad osteoid seams and are poorly ossified. The abnormal area corresponds to the radiographic metaphyseal irregular lucency. The findings are similar to those of hypophosphatasia, though the changes are milder. The cause of congenital rickets in this case is unknown. The mother did not have history of malabsorption, vitamin D intake deficiency, renal failure, or preeclampsia

Fig. 6 Three sisters with hypophosphatemic rickets showing short stature and bowed legs. They have an affected father

Fig. 7 Two sisters and a brother with hypophosphatemic rickets showing short stature. The brother had severe short stature and bowed legs. The oldest sister had surgeries on her legs to correct the lower leg deformities. The middle sister was mildly affected. Their mother was affected

Rigid Spine Syndrome

The peculiar phenotype caused by the combination of muscle wasting and prominent spinal rigidity was first proposed by (Dubowitz 1965, 1973) and termed "rigid spine syndrome."

Synonyms and Related Disorders

Congenital muscular dystrophy with spinal rigidity

Genetics/Basic Defects

1. *SEPN1* gene mutations resulting in rigid spine congenital muscular dystrophy were first identified by Moghadaszadeh et al. in (Moghadaszadeh et al. 2001).
2. Several different forms of autosomal recessive muscle disorders caused by mutations in the *SEPN1* gene (Rederstorff et al. 2007)
   a. Different forms
      i. Congenital muscular dystrophy with spinal rigidity (RSMD1) (Moghadaszadeh et al. 2001)
      ii. Multiminicore myopathy (MmD) (Ferreiro et al. 2002)
      iii. Desmin-related myopathy with Mallory body-like inclusions (MB-DRM) (Ferreiro et al. 2004)
      iv. Congenital fiber-type disproportion myopathy (CFTD) (Clarke et al. 2006)
   b. Share identical clinical features, despite distinctly different histopathological descriptions of these different disorders
      i. Early weakness of axial muscles
      ii. Development of spinal rigidity and scoliosis
      iii. Severe respiratory insufficiency
   c. These phenotypes are now grouped under the generic term of *SEPN1*-related myopathy (Ferreiro et al. 2002).
3. *SEPN1* gene mutations
   a. *SEPN1* gene, mapped on chromosome 1p35–36 (Moghadaszadeh et al. 1998), codes for selenoprotein N, an endoplasmic reticulum glycoprotein.
   b. Numerous mutations scattered all over the *SEPN1* gene (Deniziak et al. 2007)
   c. Most mutations are nonsense mutations and deletions, likely to induce a loss of function.

Clinical Features

1. Early spine rigidity: a predominant feature (limitation in flexion of dorsolumbar and cervical spine due to contracture of spinal extensors)
2. Diffuse, mild to severe muscle wasting with failure to thrive
3. Muscle weakness/axial hypotonia
   a. Diffuse, more prominent in the neck and trunk
   b. Facial weakness
   c. Finger extensors and trunk flexors weakness
4. Contractures
   a. Limitation in mouth opening
   b. Joint contractures (knees, ankles, elbows, and/or hips)
5. Lumbar scoliosis

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6. Delay of gross motor milestones evident, though ambulation is eventually achieved and preserved in most patients
7. Nasal speech common due to palatal weakness
8. Impaired respiratory function
   a. Respiratory failure due to skeletal abnormalities and diaphragmatic weakness
   b. Nocturnal hypoventilation may be an early feature and a cause of mortality (Morita et al. 1990; Ras et al. 1994).
   c. May require mechanical ventilation by teens
9. Rare reports of various cardiac involvement (Stübgen et al. (Stübgen 2008a))
   a. Complete heart block
   b. Interventricular septum hypertrophy
   c. Left atrial and ventricular hypertrophy
   d. Cardiomyopathy may occur concomitantly.
10. Differential diagnosis of spine rigidity associated with various neuromuscular and movement disorders (Sponholz et al. 2006)
    a. Classic form of multiminicore disease
    b. Desmin-related myopathy with Mallory body-like inclusions
    c. Emery-Dreifuss muscular dystrophy
    d. Bethlem myopathy
    e. Ullrich congenital muscular dystrophy
    f. Dysferlinopathy
    g. Other congenital myopathies
    h. Mitochondrial myopathies
    i. Metabolic diseases (e.g., lysosomal storage disorders)
    j. Dystonias
    k. Ankylosing spondylitis

Diagnostic Investigations

1. CK serum levels: normal or only mildly elevated (Lisi and Cohn 2007)
2. Muscle biopsy: nonspecific myopathic changes
   a. Fiber diameter variability
   b. Prevalence of type I fibers
   c. Atrophy and internalization of nuclei
   d. Marked fibrosis
   e. Some specimen contain minicores typical of classical minicore myopathies (Ferreiro et al. 2002).
3. Electromyogram: myopathic pattern in spinal muscles
4. MRI imaging of muscles
5. MRI of the brain: normal
6. Antibodies directed against the 70-kDa SEPN1 show absence of the protein in fibroblasts of patients with nonsense mutations.
7. Screening for mutations in the *SEPN1* gene is required to establish the diagnosis of rigid spine muscular dystrophy.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25% affected, given the parents are carriers
   b. Patient's offspring
      i. When the spouse is not a carrier, all offspring obligate heterozygotes.
      ii. When the spouse is a carrier, 50% of offspring affected and 50% of offspring carriers
2. Prenatal diagnosis
   a. Not reported to date
   b. Possible for pregnancies at increased risk if the disease-causing gene mutation has been identified in the family
3. Management (Jungbluth 2007)
   a. No curative treatment currently available
   b. Regular physiotherapy
      i. Promote endurance
      ii. Preserve muscle function
      iii. Prevention of contractures, especially Achilles tendon
   c. Swimming and riding for promoting truncal stability
   d. Management of scoliosis
      i. Conservative approaches often unsuccessful due to the progressive nature of the deformity
      ii. Eventually need to be managed surgically
   e. Mobilization following surgery ought to be early in order to avoid the detrimental effects of prolonged immobilization on muscle strength
   f. Appropriate rehabilitative measures to promote independent ambulation
   g. Management of severe respiratory impairment; mechanical ventilation may eventually be needed.

h. Echocardiography for cardiomyopathy
i. Therapeutic perspectives (Reed 2009)
   i. Recently, (Rederstorff et al. 2007) reported a patient with a homozygous point mutation at the selenocysteine (Sec) codon (c.G1385A) that converted the normal codon UGA to UAA, therefore preventing synthesis of a full-length active SePN protein.
   ii. (Lescure et al. 2008) subsequently "engineered a mutant tRNASec gene carrying a point mutation in the anticodon, thereby restoring the base-complementarity with the SEPN1-mutated codon; in patient-derived primary fibroblasts, the corrector tRNASec gene allowed read-through of the UAA stop codon, thus enabling synthesis of the full-length SePN protein" (Rederstorff et al. 2007).
   iii. This is the first attempt of a therapeutic strategy for rigid spine CMD and other SEPN related disorders, using a mutation-specific approach.

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Fig. 1 This 8-year-and-6-month-old boy was evaluated for poor weight gain, hypotonia, and muscle weakness. On examination, he was noted to be very hypotonic with poor head control, inability to flex the spine or the neck and limited rotation of the neck, mild scoliosis, and chest wall asymmetry. Metabolic panel revealed a minimally elevated AST (40 μ/L), a minimally elevated CPK (362 μ/L), and a mildly elevated aldolase (7.8 μ/L). The radiographs of the spine showed straight lateral view of the spine without normal cervical and thoracic curvatures with minimal scoliosis. Because of the radiographs, rigid spine muscular dystrophy, a selenoprotein N1-related myopathy, was suspected. The SEPN1 mutation analysis revealed that the patient is heterozygous for a mutation in exon 1 of the SEPN1 (c.1A > G) and a mutation in exon 7 of the SEPN1 gene (c.943 G > A) which are both known to be pathogenic. The results are consistent with a diagnosis of SEPN1-related myopathy, an autosomal recessive myopathy. Note the myopathic face

Fig. 2 Note the stiff neck and spine with minimal scoliosis

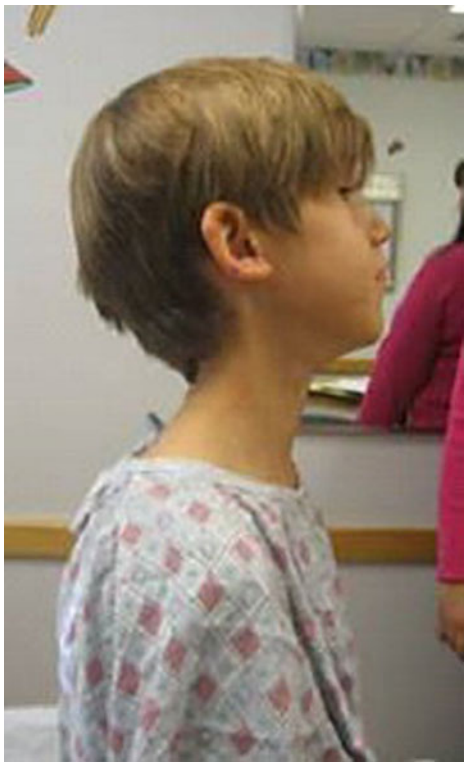

Fig. 3 Note his rigid neck that cannot bend

Fig. 4 Note difficulty in bending his neck and spine

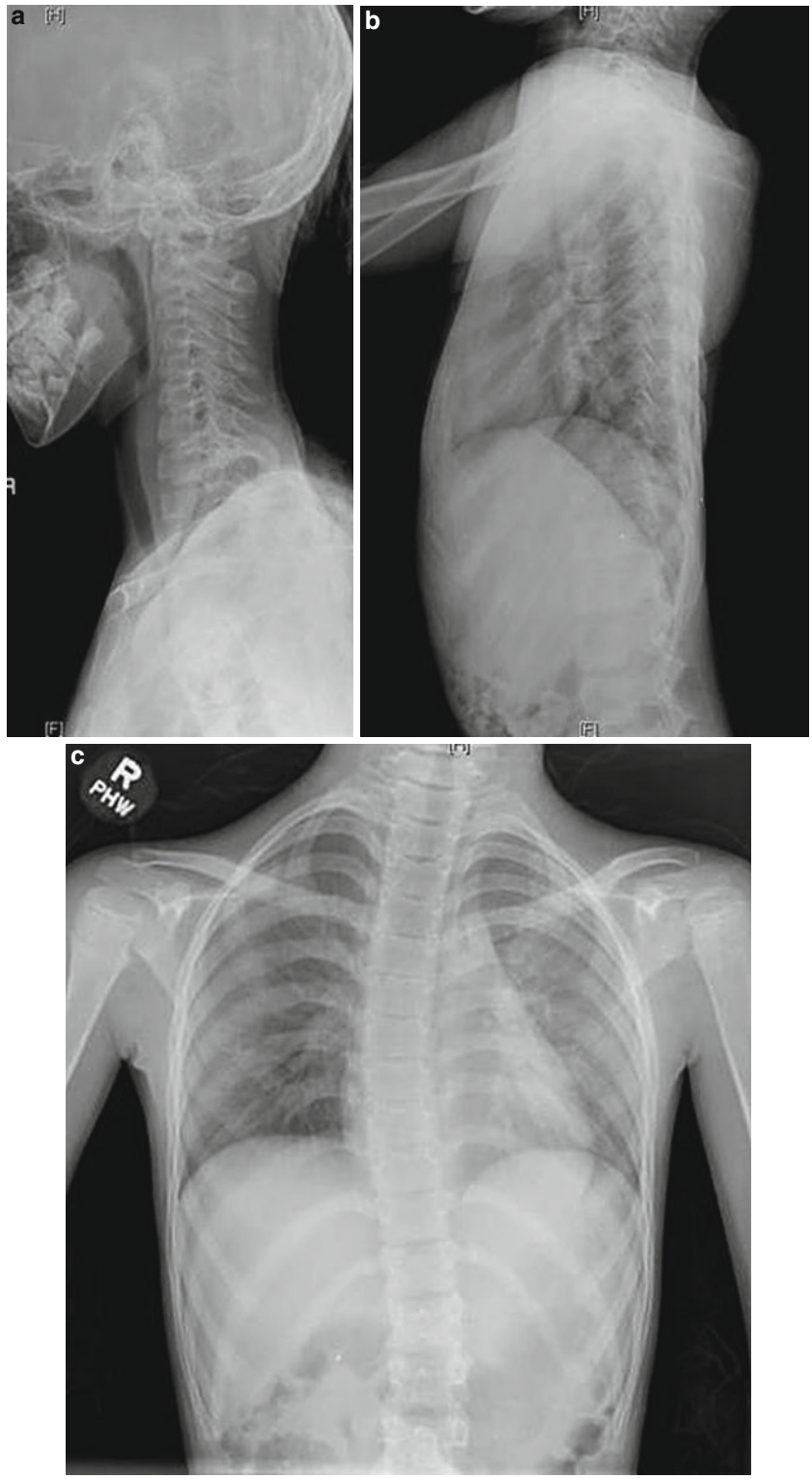

Fig. 5 (**a**–**c**) Radiographs of the spine showed stiff spinal column (lateral views) and mild scoliosis (AP view)

Roberts Syndrome

Roberts syndrome is a rare hereditary disorder characterized by symmetrical reduction of all limbs and a unique cytogenetic abnormality of premature centromere separation, which disrupts the process of chromatid pairing.

Synonyms and Related Disorders

Roberts-SC Phocomelia syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Associated with unique cytogenetic abnormality: premature centromere separation
   a. Disrupts the process of chromatid pairing
   b. Responsible for the development of multiple structural anomalies observed in Roberts syndrome
3. Caused by mutations in *establishment of cohesion 1 homologue 2* (*ESCO2*) on 8p21.1, a human homolog of yeast *ECO1* that is essential for the establishment of sister chromatid cohesion (Vega et al. 2005)
4. Loss of ESCO2 acetyltransferase activity was recently implicated in the molecular mechanism of Roberts syndrome (Gordillo et al. 2008).

Clinical Features

1. Craniofacial malformations: marked variability
   a. Bilateral cleft lip and cleft palate in severe cases
   b. No clefting of the lip or palate in some cases
   c. Hypertelorism secondary to widely spaced orbits
   d. Ophthalmic manifestations
      i. Exophthalmos due to shallow orbits
      ii. Microphthalmia
      iii. Peter anomaly
      iv. Cloudy cornea
      v. Cataracts
   e. Wide nasal bridge
   f. Hypoplastic nasal alae
   g. Hemangiomata of the lip, nose, face, or forehead
   h. Micrognathia
   i. Dark scalp hair becomes thin and silvery blond.
2. Limb defects
   a. Phenotype varies from a complete absence of arms and legs with rudimentary digits to mild growth reduction in the limbs.
   b. Limb reduction defects tend to be symmetric and more severely involved in the upper extremities than the lower extremities.
   c. Presence of phocomelia
      i. Tetraphocomelia: a prominent characteristic of the syndrome
      ii. Two deficient limbs in 11% of cases
      iii. No phocomelia in 2% of cases
   d. Often reduced number of fingers (oligodactyly)
   e. Radial aplasia or dysplasia common
   f. Lack of 1st metacarpal, thumb, or first phalanx
3. Other associated anomalies
   a. CNS anomalies
      i. Mental retardation
      ii. Microcephaly
      iii. Hydrocephalus
      iv. Absent olfactory lobes
      v. Calcification of the basal ganglia
      vi. Encephalocele

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vii. Cranial nerve paralysis
viii. Seizures
b. Congenital heart defects
i. Atrial septal defect
ii. Patent ductus arteriosus
iii. Pulmonic stenosis
iv. Aortic stenosis
v. AV canal defect
c. Renal anomalies
i. Polycystic kidneys
ii. Dysplastic kidneys
iii. Horseshoe kidney
iv. Hydronephrosis
v. Renal agenesis
d. Gastrointestinal obstruction
e. Splenogonadal fusion
f. Cryptorchidism
g. Enlarged phallus
h. Failure to thrive
i. Neoplasms
i. Sarcoma botryoides
ii. Malignant melanoma
4. Prognosis
a. Severe cases
i. Often resulting in spontaneous abortions or stillbirths
ii. Few cases survive past one month of life.
b. Phenotypically milder cases
i. Requiring minimal to full time care depending on the degree of mental retardation
ii. May require surgical interventions to correct craniofacial and limb anomalies
5. Differential diagnosis (Gordillo et al. 2009)
a. SC phocomelia (Herrmann et al. 1969)
i. Clinical characteristics
a) Tetraphocomelia
b) Scanty silvery blond hair
c) Microcephaly
d) Mild mental retardation
e) Facial hemangioma
f) Cloudy cornea
g) Hypoplastic nasal alae and ears
ii. Originally thought to differ from Roberts syndrome by
a) Usual absence of midfacial clefting
b) Prolonged survival
c) Lesser degree of mental and physical retardation
d) Relatively milder degree of phocomelia
iii. Now considered to be the same entity as Roberts syndrome (Roberts-SC phocomelia syndrome) based on the following observations (Schüle et al. 2005):
a) The presence of severely and mildly affected individuals in the same sibship raised the suspicion that the two disorders are allelic, representing spectrum of severity.
b) Furthermore, both are characterized by heterochromatin repulsion (HR) or premature centromere separation in mitotic cells (Judge 1973; Freeman et al. 1974a, 1974b; Tomkins et al. 1979).
c) Somatic-cell complementation studies revealed that cells positive for HR (HR+) from individuals with Roberts syndrome and from those with SC do not complement each other, further supporting the notion that the same gene is affected in the two disorders (McDaniel et al. 2000).
b. Thrombocytopenia-absent radius (TAR) syndrome (see the chapter on Thrombocytopenia-Absent Radius (TAR) Syndrome).
i. Absent radii with thumbs present
ii. Hypomegakaryocytic thrombocytopenia
iii. Absent cleft palate
c. Baller-Gerold syndrome
i. Autosomal recessive disorder
ii. Craniosynostosis (brachycephaly)
iii. Ocular proptosis
iv. Bulging forehead
v. Radial ray defect (oligodactyly)
vi. Aplasia or hypoplasia of the thumb and/or aplasia or hypoplasia of the radius
vii. Growth retardation
viii. Poikiloderma
ix. Caused by mutations in *RECQL4*
d. Fanconi anemia (see the chapter on Thrombocytopenia-Absent Radius (TAR) Syndrome).
e. Tetra-amelia, X-linked (Zimmer tetraphocomelia)
i. Tetra-amelia
ii. Facial clefts
iii. Absence of ears and nose
iv. Anal atresia
v. Absence of frontal bones
vi. Pulmonary hypoplasia with adenomatoid malformation
vii. Absence of thyroid

viii. Dysplastic kidneys, gallbladder, spleen, uterus, and ovaries
ix. Imperforate vagina

f. Tetra-amelia, autosomal recessive
i. Caused by mutations in the WNT3
ii. Amelia
iii. Severe lung hypoplasia and aplasia of the peripheral pulmonary vessels
iv. Cleft lip/palate
v. Hypoplasia of the pelvis
vi. Malformed uterus
vii. Atresia of the urethra, vagina, and anus
viii. Diaphragmatic defect
ix. Agenesis of the kidney, spleen, and adrenal glands

g. Splenogonadal fusion with limb defects and micrognathia
i. Autosomal recessive inheritance
ii. Abnormal fusion between the spleen and the gonad or the remnants of the mesonephros
iii. Tetramelia
iv. Mild mandibular and oral abnormalities (micrognathia, multiple unerupted teeth, crowding of the upper incisors, and deep, narrow, V-shaped palate without cleft)

h. DK phocomelia syndrome
i. Autosomal recessive inheritance
ii. Phocomelia
iii. Absence of radius and digits
iv. Thrombocytopenia
v. Encephalocele
vi. Cleft palate and absence of radius and digits
vii. Anal atresia
viii. Abnormal lobation of the lungs
ix. Diaphragmatic agenesis

i. Holt-Oram syndrome (see the chapter)

j. Thalidomide embryopathy (see the chapter on dysmelia)
i. Abnormalities of the long bones of the extremities
a) Upper limb bones are affected in an order of frequency starting with the thumb, followed by the radius, the humerus, the ulna, and finally the fingers on the ulnar side of the hand.
b) In extreme cases, the radius, ulna, and humerus are lacking; the hand bud arises from the shoulders.
c) Legs may be affected but less severely.
ii. The second major group of defects involves the ears (anotia, microtia, accessory auricles) and the eyes (coloboma of the iris, anophthalmia, microphthalmia).
iii. Internal defects commonly involve the heart, kidneys, and urinary, alimentary, and genital tracts.

k. Cornelia de Lange syndrome (see the chapter)

l. Mosaic variegated aneuploidy syndrome
i. Autosomal recessive inheritance
ii. Caused by mutations in *BUB1B* which encodes BUBR1, a key protein in the mitotic spindle checkpoint, which have been found in individuals with this disease
iii. Severe microcephaly
iv. Growth deficiency
v. Mental retardation
vi. Childhood cancer predisposition
vii. Associated with constitutional mosaicism for chromosomal gains and losses
viii. Cytogenetic findings include premature centromere division, in which mitotic cells show split centromeres and splayed chromatids in all or most chromosomes (Plaja et al. 2001).

Diagnostic Investigations

1. Cytogenetics
a. Distinctive abnormality of the constitutive heterochromatin (the RS effect): premature centromere separation (PCS)
i. Detected in
a) Fibroblasts and lymphocytes in neonates
b) Chorionic villi and amniocytes in the fetus
ii. Consists of "puffing" or "repulsion" of the constitutive heterochromatin
a) Chromosome puffing most obvious at the large heterochromatic regions of chromosomes 1, 9, and 16
b) Chromosome repulsion most evident at the short arms of the acrocentrics and the distal long arm of the Y chromosome
iii. A "railroad-track" or "tram-track" appearance of the sister chromatids due to the

absence of a constriction at the centromere in several other chromosomes
    a) This phenomenon, called heterochromatin repulsion, is observed in cells of different tissue origin with several chromosomes in each metaphase showing a visible abnormality.
    b) Most evident in chromosomes containing the largest amount of heterochromatin
  b. Sporadic aneuploidy was noted with the pattern of aneuploidy different in each patient. The possible relationship between centromere "splaying" and aneuploidy is yet to be determined.
  c. Normal karyotypes lacking any microdeletion or chromosomal rearrangement from either leukocytes or fibroblasts in about a fifth of all cases
2. Radiography for phocomelia evaluation
  a. Absence of the radius and fibula: the most common skeletal abnormalities in the upper and lower limbs
  b. Absent, short, deformed, and/or hypoplastic ulna and tibia: the second most common bone defects
  c. Absent, short, deformed, or hypoplastic humerus and femur: the third and least common abnormalities
3. Echocardiography for congenital heart defect
4. Renal ultrasound for renal anomalies
5. MRI of the brain for CNS anomalies
6. Molecular genetic testing: sequence analysis of the *ESCO2* gene available clinically

Genetic Counseling

1. Recurrence risk
  a. Patient's sib: 25%
  b. Patient's offspring: not increased (not surviving to reproduction in severe cases)
2. Prenatal diagnosis for pregnancies at risk (Schulz et al. 2008)
  a. Ultrasonography
    i. Intrauterine growth retardation
    ii. Bilateral phocomelia (tetraphocomelia in majority of cases) of varying degree
    iii. Cleft lip and palate
    iv. Associate anomalies
      a) Hydrocephalus
      b) Congenital heart defects
      c) Renal anomalies
  b. DNA from fetal cells obtained from amniocentesis or CVS
    i. Confirmed by characteristic disjunction of centromeres (premature centromere separation in metaphases)
    ii. Molecular diagnosis of *ESCO2* gene mutations
3. Management
  a. Special education
  b. Cornea grafting
  c. Corrective surgery
    i. Cleft lip/palate
    ii. Limb defects
  d. Prosthetic devices
    i. For underdeveloped or missing limbs
    ii. Used to increase independence

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Fig. 1 The G-banded metaphase spread from fibroblast culture of a male infant with Roberts syndrome showing characteristic heterochromatin separation: puffing of the centromeric heterochromatin of some chromosomes and splaying of the Yqh region (arrows). The patient had profound psychomotor retardation, corneal clouding, and tetraphocomelia

Fig. 2 A newborn with Roberts syndrome variant showing bilateral cleft lip and cleft palate, phocomelia, club hands with an appendage-like thumb on the right, and a missing thumb on the left. The infant also had intrauterine growth retardation, hydrocephalus, cloudy cornea, AV canal heart defect, and normal lower extremities. Cytogenetic studies revealed no premature centromere separation. The mother took Diflucan during pregnancy and the teratogenic etiology was a possibility

Robinow Syndrome

In 1969, Robinow et al. described a new dwarfing syndrome characterized by mesomelic shortening of extremities, hemivertebrae, genital hypoplasia, and "fetal facies." The incidence is estimated to be approximately 1 in 500,000.

Synonyms and Related Disorders

Acral dysostosis with facial and genital abnormalities; Costovertebral segmentation defect with mesomelia; Fetal face syndrome; Robinow dwarfism

Genetics/Basic Defects

1. Autosomal recessive form
   a. Phenotype tends to be more severe than the autosomal dominant form.
   b. Caused by different homozygous (and compound heterozygous) missense, nonsense, and frameshift mutations of the *ROR2* gene (Tufan et al. 2005)
   c. *ROR2* gene
      i. Mapped to chromosome 9q22
      ii. Encoding an orphan receptor tyrosine kinase 2 with orthologues in mouse and other species
      iii. Allelic to dominant brachydactyly type B (characterized by terminal deficiency of fingers and toes)
2. Autosomal dominant form (Person et al. 2010)
   a. Caused by missense mutations in *WNT5A*, which result in amino acid substitutions of highly conserved cysteines, are associated with autosomal dominant Robinow syndrome
   b. One mutation has been found in all living affected members of the original family described by Meinhard Robinow and another in a second unrelated patient.

Clinical Features

1. Characteristic craniofacial appearance
   a. Early childhood
      i. Midfacial hypoplasia
      ii. Occasional midline capillary hemangioma
      iii. Eyes
         a) Marked hypertelorism
         b) Prominent eyes giving the appearance of exophthalmos (pseudoexophthalmos)
      iv. A short upturned nose
      v. Mouth
         a) "Tented" upper lip having an inverted-V appearance with tethering in the center
         b) Midline clefting of the lower lip
         c) Gum hypertrophy at birth
         d) Dental crowding/irregular teeth
         e) "Tongue tie" (ankyloglossia) resembling a bifid tongue when the tongue tie is marked
      vi. Ears
         a) Low-set
         b) Simple
         c) Deformed pinna

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vii. Resemblance to a fetal face
a) Relatively small face
b) Laterally displaced eyes
c) Forward-pointing alae nasi
d) "Fetal facies" becomes less prominent over time

b. Adulthood
i. Loss of fetal facial proportions
ii. Absent midfacial hypoplasia
iii. Persistent hypertelorism with a broad nasal root and broad forehead

2. Short stature
a. Reduced birth length
b. Not a universal finding with some reports of normal growth

3. Limb abnormalities
a. Mesomelic or acromesomelic limb shortening
b. Shortening of the forearms more striking than the shortening of the legs
c. Occasional Madelung deformity
d. Hands/feet
i. Brachydactyly with shortening of the distal phalanx and nail hypoplasia or dystrophy
ii. Thumbs
a) Displaced
b) Occasionally bifid
c) Partial cutaneous syndactyly
d) Ectrodactyly (especially patients reported from Turkey)

4. Other skeletal abnormalities
a. Chest deformities
b. Kyphoscoliosis
c. Vertebral anomalies
d. Rib defects
e. Pectus excavatum
f. Acrodysostosis
g. Delayed bone age

5. Genital hypoplasia
a. Genital abnormalities: may be present at birth causing concern regarding gender assignment
i. Males
a) Micropenis
b) Normal scrotum and testes
ii. Females
a) Reduced clitoral size
b) Hypoplasia of the labia minor
c) Associated vaginal atresia and hematocolpos
iii. Onset of puberty normal in both sexes
iv. Several reports of both male and female patients having normal children

6. Congenital heart defects (15%)
a. Severe pulmonary stenosis or atresia (the most common cardiac abnormalities)
b. Atrial septal defect
c. Ventricular septal defect
d. Coarctation of the aorta
e. Bicuspid aortic valve
f. Tetralogy of Fallot
g. Tricuspid atresia
h. Double-outlet right ventricle
i. Patent ductus arteriosus

7. Renal abnormalities
a. Hydronephrosis (relatively common)
b. Cystic dysplasia of the kidney

8. Developmental delay but intelligence is usually normal

9. Dermatoglyphics
a. Absent interphalangeal creases
b. Bilateral transverse creases
c. Hypothenar whorl pattern

10. Clinical characteristics of recessive Robinow syndrome: more frequently manifests orthopedic involvement (vertebral/rib anomalies and more severe mesomelic brachymelia) than the dominant form
a. Short stature
b. Mesomelic and acromelic brachymelia
c. Thick abnormally modeled radius and ulna
d. Characteristic face
i. Hypertelorism
ii. Wide palpebral fissures
iii. Broad-based nose with everted nares
iv. Large mouth
v. Gum hypertrophy
vi. Irregular and crowded teeth
e. Costovertebral anomalies
f. Endocrine dysfunction
i. Empty sella
ii. Partial insensitivity of Leydig cells to HCG
iii. Low basal testosterone in prepubertal boys
iv. Defective sex-steroid feedback mechanism
g. Micropenis in males

11. Clinical characterization of autosomal dominant and recessive variants of Robinow syndrome,

based on inheritance pattern in familial cases and presence of rib fusions as diagnostic of the recessive variant (Mazzeu et al. 2007):
   a. Clinical signs present in more than 75% of patients with either form, and therefore the most important for the characterization of this syndrome
      i. Hypertelorism
      ii. Nasal features (large nasal bridge, short upturned nose, and anteverted nares)
      iii. Midfacial hypoplasia
      iv. Mesomelic limb shortening
      v. Brachydactyly
      vi. Clinodactyly
      vii. Micropenis
      viii. Short stature
   b. Hemivertebrae and scoliosis were present in more than 75% of patients with the recessive form but in less than 25% of patients with the dominant form
   c. Umbilical hernia (32.3%) and supernumerary teeth (10.3%) were found exclusively in patients with the dominant form
12. Differential diagnosis of mesomelic dwarfism (Giedion et al. 1975)
   a. With Madelung deformity: dyschondrosteosis
   b. With malformations of long bones depending on various distribution/severity patterns and types of transmission
      i. Ulnofibular
         a) With mild triangular deformity
         b) With extreme variety: boomerang bone disease
      ii. Radio-tibial with "normal" fibula
      iii. Ulno-fibular-mandibular (Langer type, homozygous dyschondrosteosis)
      iv. Ulno-radio-fibular-tarsal with square, triangular, or rhomboid tibia
      v. Ulno-radio-tibial with absent fibula
   c. With associated malformations of spine
      i. Robinow syndrome
      ii. Wegmann syndrome
      iii. Campallia and Martinelli syndrome
      iv. "Spondylo-epiphyso-metaphyseal" dysplasia
   d. With acrodysplasia
      i. Acromesomelic dwarfism
      ii. Ellis-van Creveld syndrome
      iii. Grebe achondrogenesis

Diagnostic Investigations

1. Radiography
   a. Skull
      i. Macrocephaly
      ii. Prominent forehead
      iii. Hypertelorism
      iv. Hypoplastic mandible
      v. Dental anomalies
   b. Spine/ribs: widespread fusion of thoracic vertebrae with frequent hemivertebrae and fusion of the ribs, resembling Jarcho-Levin syndrome (spondylocostal dysostosis) in severe cases (autosomal recessive form)
      i. Hemivertebrae and vertebral fusions
      ii. Fusion of ribs
      iii. Shortened interpeduncular distance
   c. Extremities (long bones): mesomelic shortening
      i. Upper extremities
      ii. Lower extremities
      iii. Ulna shorter than radius
      iv. Luxation of the radius
   d. Hands and feet
      i. Brachymesophalangism of fifth digits
      ii. Clinodactyly of the fifth digits
      iii. Shortening of other phalanges
      iv. Brachymetacarpism
      v. Fusion of carpal bones
      vi. Bifid terminal phalanges (splitting of one or more distal phalanges)
      vii. Fusion of phalanges
      viii. Retarded bone age
2. Renal ultrasound for renal anomalies
3. Echocardiography for congenital heart disease
4. Growth hormone assay for possible growth hormone deficiency
5. DNA mutation analysis: available on clinical basis (Afzal and Taylor 2005)
   a. *ROR2* gene is the gene responsible for autosomal recessive *ROR2*-related Robinow syndrome
   b. Sequence analysis of *ROR2* gene detects 65–100% of affected individuals

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal dominant inheritance: not increased unless a parent is affected
      ii. Autosomal recessive inheritance: 25%
   b. Patient's offspring
      i. Autosomal dominant inheritance: 50%
      ii. Autosomal recessive inheritance: not increased unless the spouse is a carrier
2. Prenatal diagnosis
   a. Ultrasonography: possible by measuring the length of the long bones and the ulna/humerus ratio for the fetus at risk
   b. Prenatal diagnosis: also possible for pregnancies at increased risk for ROR2-related Robinow syndrome by sequencing of entire coding region of *ROR2* gene on fetal DNA obtained by amniocentesis or CVS, provided the disease-causing alleles have been previously identified in the proband (Afzal and Taylor 2005)
3. Management
   a. Anticipate difficult intubation because of midfacial hypoplasia
   b. Orthopedic care for vertebral anomalies and hip dislocation
   c. Orthodontics for dental malalignment
   d. Surgery for cleft lip and palate, inguinal hernia, and undescended testes
   e. Growth hormone therapy if associated with growth hormone deficiency
   f. Testosterone therapy for micropenis not proven useful
   g. Psychologic support

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Fig. 1 (**a**–**e**) A child with Robinow syndrome showing prominent forehead, ocular hypertelorism, short upturned nose, pectus excavatum, penile hypoplasia, and acromesomelic shortening of the limbs

Rubinstein-Taybi Syndrome

In 1963, Rubinstein and Taybi described a new syndrome characterized by broad thumbs and toes, facial abnormalities, and mental retardation. The prevalence of Rubinstein-Taybi syndrome (RTS) is estimated to be 1 in 100,000–1 in 125,000 live births in the Netherlands.

Synonyms and Related Disorders

Broad thumb-hallux syndrome; Broad thumbs and great toes, characteristic facies, and mental retardation; Rubinstein syndrome

Genetics/Basic Defects

1. Inheritance: autosomal dominant
2. Most cases are sporadic (~99%); familial cases are extremely rare (Bartsch et al. 2010).
3. Caused by deletions or heteroallelic mutations of *CREBBP*, the gene for cAMP-responsive element-binding (CREB) protein, which resides on chromosome 16p13.3. CREBBP is a large nuclear protein involved in transcription regulation, chromatin remodeling, and the integration of several different signal transduction pathways. The following mutations of *CREBBP* were reported in patients with Rubinstein-Taybi syndrome:
   a. Chromosomal translocations/inversions
   b. Deletions at the microscopic and submicroscopic levels
   c. Molecular mutations
4. Mutations in the *CREBBP* gene are responsible for:
   a. Rubinstein-Taybi syndrome
   b. t(8;16)-associated acute myeloid leukemia
5. Also rarely caused by mutations in *EP300* gene (located on 22q13.2): individuals reported with mutations in *EP300* have a milder skeletal phenotype, lacking typical broadening and angulation of the thumb and hallux (Bartholdi et al. 2007).
6. No clear phenotypic differences are observed between patients in whom microdeletions or truncating mutations were found.
7. Variable expression and somatic mosaicism contribute to the phenotypic variability of RTS. Somatic mosaicism may be more frequent in RTS than previously assumed (Bartsch et al. 2010).

Clinical Features

1. Characteristic craniofacial features
   a. Microcephaly (35–94%)
   b. Prominent forehead
   c. Down-slanting palpebral fissures
   d. Apparent ocular hypertelorism
   e. High-arched or heavy eyebrows
   f. Long eyelashes
   g. Epicanthal folds
   h. Prominent nose with columella (lower margin of the nasal septum) below the alae nasi
   i. Malpositioned ears with dysplastic helices
   j. Grimacing smile
   k. Hypoplastic maxilla
   l. Mild retrognathia
   m. High-arched palate
2. Skeletal abnormalities
   a. Thumbs
      i. Broad terminal phalanges

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   ii. Severe radial angulation deformity ("hitchhiker thumbs") with abnormal shape of proximal phalanx, which prevents opposition and functional gripping strength
  b. Great toes
   i. Broad terminal phalanges
   ii. Angulation deformity with abnormal shape of proximal phalanx or first metatarsal
   iii. Duplicated proximal phalanx
   iv. Duplicated distal phalanx
  c. Short stature (78%)
  d. Fifth finger clinodactyly
  e. Overlapping toes
  f. Broad terminal phalanges of other fingers
  g. Pelvic anomalies
   i. Flat acetabular angles
   ii. Flaring of the ilia
   iii. Notch in the ischia
  h. Stiff gait
  i. Lax ligaments
  j. Hyperextensible joints
  k. Vertebral anomalies
   i. Spina bifida
   ii. Kyphosis
   iii. Lordosis
   iv. Scoliosis
  l. Sternal or rib anomalies
   i. Premature fusion
   ii. Simian sternum
   iii. Pectus excavatum or carinatum
   iv. Forked ribs
   v. Cervical ribs
   vi. Fusion of the first and second ribs
3. History of maternal polyhydramnios (39%)
4. Hypotonia
5. Developmental delay
6. Variable mental retardation
  a. Severe in some patients
  b. Moderate degree in many patients
  c. Mild in some patients
7. Behavioral/psychiatric disorders
  a. Childhood
   i. Short attention span
   ii. Impulsiveness
   iii. Clinically nonsignificant stereotype
   iv. Withdrawal
   v. Nonspecific "maladaptive behavior"
   vi. Repetitive motions
   vii. Resistance to change
   viii. Distractibility
   ix. Aggressive outbursts
   x. Difficulty in sleeping
  b. Adulthood
   i. Mood disorders
   ii. Chronic motor tic disorder
   iii. Obsessive compulsive disorder
   iv. Depressive disorder
   v. Bipolar disorder
   vi. Tourette disorder
   vii. Trichotillomania
   viii. Pervasive developmental disorder
   ix. Self-injurious behaviors
   x. Autistic features
8. Seizures (27–28%)
9. Ophthalmologic problems
  a. Strabismus (60–71%) with subsequent risk of amblyopia
  b. Refractive errors (41–56%)
  c. Lacrimal duct obstructions (38–47%)
  d. Ptosis (29–32%)
  e. Coloboma (9–11%)
  f. Duane retraction syndrome (8%)
  g. Ghost vessels
  h. Peters anomaly
  i. Optic nerve hypoplasia
  j. Cataracts
  k. Corneal opacities
  l. Congenital glaucoma
  m. Retinal abnormalities
10. Dental manifestations (67%)
  a. Talon cusps of secondary dentition
  b. Crowding and malpositioned teeth
  c. Anterior and posterior crossbites secondary to a narrow palate or jaw size discrepancy
  d. Natal teeth
  e. Gingivitis
  f. Hypodontia/hyperdontia
  g. Increased rate of carries
11. Upper airway obstruction during sleep due to:
  a. Hypotonia
  b. Anatomy of the oropharynx and airway
   i. Small nasal passages
   ii. Retrognathia
   iii. Micrognathia
   iv. Hypertrophy of the tonsils and adenoids
   v. Obesity

12. Gastrointestinal problems
    a. Significant gastroesophageal reflux
    b. Feeding difficulties
    c. Constipation
13. Congenital heart disease (24–38%)
    a. ASD
    b. VSD
    c. PDA
    d. Coarctation of the aorta
    e. Pulmonary stenosis
    f. Bicuspid aortic valve
    g. Pseudotruncus
    h. Aortic stenosis
    i. Hypoplastic left heart syndrome
    j. Complex congenital heart defects
    k. Dextrocardia
    l. Vascular rings
    m. Conduction problems
14. Renal anomalies (52%)
    a. Hydronephrosis
    b. Duplications
    c. Vesicoureteral reflux
    d. Urinary tract infections
    e. Renal stones
    f. Nephrotic syndrome
    g. Neurogenic bladder
15. Cutaneous manifestations
    a. Tendency of keloid and hypertrophic scar formation
    b. Ingrown toenails
    c. Toenail paronychia (44%)
    d. Fingernail paronychia (9%)
    e. Pilomatrixomas
    f. Capillary hemangioma
        i. Forehead
        ii. Nape of the neck
        iii. Back
    g. Supernumerary nipples
    h. Hirsutism
    i. Transverse palmar creases
    j. Deep plantar crease between the first and second toes
16. Orthopedic problems
    a. Hypotonia
    b. Lax ligaments
    c. Tight heel cords
    d. Elbow abnormalities
    e. Legg-Perthes disease (3%)
    f. Dislocated patella (2.5%)
    g. Congenital hip dislocation (1.4%)
    h. Slipped capital femoral epiphysis (0.6%)
    i. Congenital or acquired scoliosis, kyphosis, and lordosis
    j. An increased risk of associated thickened filum terminale, tethering of the cord, and lipoma
    k. An increased risk of fractures
17. An increased risk of having benign and malignant tumors as well as leukemia and lymphoma
    a. Oligodendroglioma
    b. Medulloblastoma
    c. Neuroblastoma
    d. Meningioma
    e. Pheochromocytoma
    f. Nasopharyngeal rhabdomyosarcoma
    g. Leiomyosarcoma
    h. Seminoma
    i. Embryonal carcinoma
    j. Odontoma
    k. Choristoma
    l. Dermoid cyst
    m. Pilomatrixomas

Diagnostic Investigations

1. Developmental evaluation
2. Echocardiography for cardiac defects
3. Ophthalmologic examination
4. Renal ultrasound
5. Voiding cystourethrogram
6. Hearing evaluation
7. EEG abnormalities
8. Radiography
    a. Hands
        i. Broad first distal phalanx
        ii. Broad first ray
        iii. Duplicated first distal phalanx
        iv. Delta-shaped proximal phalanges of the thumbs
        v. Mushroom-shaped distal phalanges
        vi. Angulation of the distal phalanges
        vii. Thin tubular bones
        viii. Delayed bone age (74%)
    b. Feet
        i. Broad first distal phalanx
        ii. Broad first ray

iii. Duplicated first distal phalanx
iv. Duplicated first proximal and distal phalanges
v. Delta-shaped first proximal phalanx. A duplicated longitudinal bracketed epiphysis ("kissing delta" phalanx) always involves the proximal phalanx of the great toe.
vi. Angulation deformity of the hallux
vii. Mushroom-shaped distal phalanges
viii. Very small distal phalanges
ix. Thin tubular bones
x. Protruding calcaneus
xi. Synostosis of cuneiform ossicles
xii. Proximally split fifth metatarsal bone

c. Limbs
i. Thin tubular bones
ii. Fractures
iii. Patella luxations

d. Spine
i. Cervical hyperkyphosis
ii. Lumbar hyperlordosis
iii. Scoliosis
iv. Spina bifida occulta: cervical or lumbosacral
v. Spondylolisthesis
vi. Irregular thoracic endplates

e. Skull
i. Microcephaly
ii. Absent sinus frontalis
iii. Deviated nasal septum
iv. Steep skull base
v. Abnormally shaped sella turcica
vi. Foramina parietal permagna
vii. Prominent digital marking

f. Thorax
i. Narrow thoracic aperture
ii. 11 ribs
iii. Fusion of ribs
iv. High diaphragm

g. Pelvis
i. Small iliac wings
ii. Flaring iliac wings
iii. Irregularly formed acetabulum
iv. Symphysiolysis

9. Diagnosis of Rubinstein-Taybi syndrome
a. Made primarily by clinical examination
b. Confirmed by the presence of microdeletion

10. Cytogenetic analysis: chromosome abnormalities observed in about 10% of patients (Breuning et al. 1993; Blough et al. 2000; Petrij et al. 2000b)
a. FISH analysis with cosmids from the *CBP* region to detect chromosome 16p13.3
b. Chromosome abnormalities
i. t(2;16)(p13.3;p13.3)
ii. t(7;16)(q34;p13.3)
iii. Inv(16)(p13.3q13)

11. Clinical testing of *CREBBP* gene: available clinically
a. Fluorescent in situ hybridization (FISH) probes
i. Specific for chromosome region 16p13.3
ii. Containing regions of the cyclic AMP-responsive element-binding protein gene (*CBP* gene)
iii. Microdeletions identified in approximately 10% of patients by five cosmid probes containing almost the entire gene
b. Sequence analysis/mutation scanning available clinically: detects *CREBBP* mutation in another 30–50% of affected individuals
c. Deletion/duplication analysis using array CGH or quantitative multiplex fluorescent-PVR

12. Clinical testing of *EP300* gene: available clinically
a. *EP300* mutations available clinically can identify approximately 3% of affected individuals.
b. Deletion/duplication analysis.

Genetic Counseling

1. Recurrence risk
a. Patient's sib: Accumulating data suggest a recurrence risk of approximately 0.5–1.0% for parents of a child with RTS due to gonadal mosaicism, exceeding the so far empiric estimated risk of 0.1% for siblings (Chiang et al. 2009; Bartsch et al. 2010)
b. Patient's offspring: as high as 50%, particularly in individuals with deletions

2. Prenatal diagnosis: possible for fetuses at risk on fetal cells obtained by amniocentesis or chorionic villus sampling, provided the disease-causing *CREBBP* or *EP300* mutation or deletion in an affected family member is known (Stevens 2009)

3. Preimplantation genetic diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family (Stevens 2009)

4. Management
   a. Early intervention programs
      i. Physical therapy
      ii. Occupational therapy
      iii. Speech therapy
   b. Management of gastroesophageal reflux
   c. Prophylaxis for subacute bacterial endocarditis for patients at risk
   d. Requires assistance and training in self-help skills but can become self-sufficient in most self-help areas such as feeding, dressing, and toileting
   e. Special education
   f. Behavioral modification
   g. Surgery to correct a delta phalanx deformity
   h. Caution with general anesthesia in children
      i. Challenging to intubate due to airway anomalies
         a) Relatively anterior position of the larynx
         b) Easily collapsible laryngeal wall
      ii. Important to intubate due to the high risk of aspiration during induction and emergence
      iii. Presence of skeletal anomalies
      iv. Cardiac arrhythmia may result from use of cardioactive drugs.
         a) Atropine
         b) Neostigmine
         c) Succinylcholine
         d) Suxamethonium

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Fig. 1 (**a**–**l**) A patient with Rubinstein-Taybi syndrome at different ages (childhood and adulthood) showing typical facial appearance (prominent beaked nose with the columella below the alae nasi), broad thumbs, and broad/bifid great toes, which are illustrated by radiographs

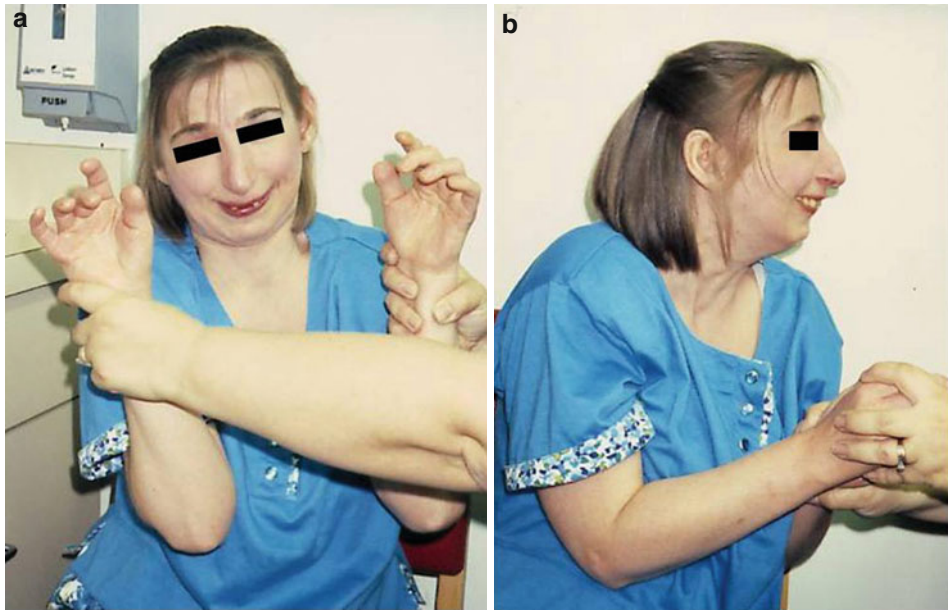

Fig. 2 (**a**, **b**) An adult with Rubinstein-Taybi syndrome showing the characteristic facies and broad thumbs

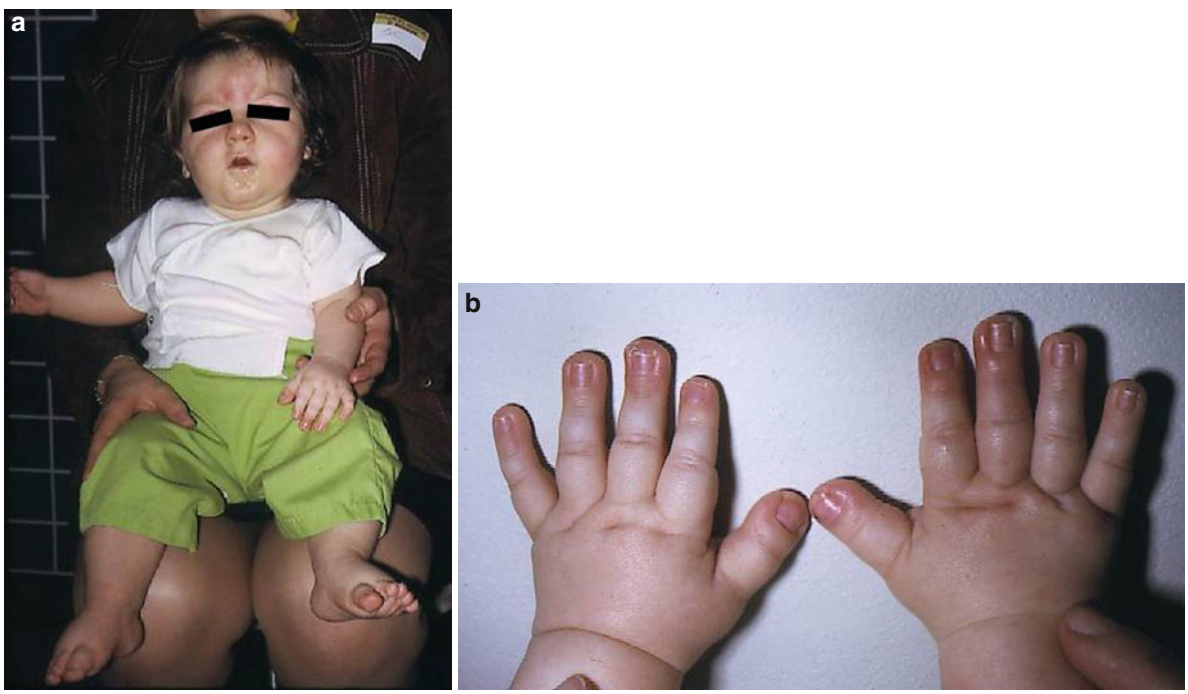

Fig. 3 (**a**, **b**) A young patient with Rubinstein-Taybi syndrome showing characteristic facies, broad thumbs, and great toes

Saethre-Chotzen Syndrome

Saethre in 1931 and Chotzen in 1932 separately described a group of patients with cranial vault dysmorphology ("acrocephaly"), skull asymmetry, and incomplete simple syndactyly of the index and middle fingers and the third and fourth toes.

Saethre-Chotzen syndrome (SCS) is one of the more common forms of syndromic craniosynostosis. Its prevalence was estimated to range from 1:25,000 to 1:50,000, approximately the same prevalence as Crouzon syndrome.

Synonyms and Related Disorders

Acrocephalosyndactyly, Type III; Acrocephaly, skull asymmetry, and mild syndactyly; Chotzen syndrome

Genetics/Basic Defects

1. An autosomal dominant disorder with high penetrance and wide variable expressivity
2. A variety of mutations, including missense and nonsense mutations, small insertions, duplications, and deletions (Gripp et al. 2000; Chun et al. 2002) on the *TWIST* gene, which was mapped at 7p21, lead to heterogeneous symptoms of the syndrome.
3. Also, patients with characteristics of Saethre-Chotzen syndrome but without *TWIST* mutations have been described (de Heer et al. 2005).
   a. Some of these patients harbored the *FGFR3* P250R mutation, nowadays considered to cause a distinct and unique craniosynostosis syndrome, Muenke syndrome (Muenke et al. 1997; Graham et al. 1998).
   b. Strikingly, it was found that all Saethre-Chotzen syndrome patients with large genetic deletions, encompassing the *TWIST* gene and extending onto chromosome 7p, had mental retardation, a rare feature in the syndrome (Johnson et al. 1998; Zackai and Stolle 1998; Chun et al. 2002).

Clinical Features

1. Widely variable phenotype
2. Craniosynostosis (premature fusion of one or more sutures of calvarium) (Paznekas et al. 1998)
   a. Coronal suture (unilateral or bilateral): most commonly affected
      i. Bilateral (59% of cases)
      ii. Unilateral (23% of cases)
   b. Other cranial sutures (21% of cases), such as sagittal, lambdoid, and metopic, and even pansynostosis, may be involved.
      i. Can undergo premature fusion
      ii. Reports of affected individuals with no evidence of pathologic suture
   c. Often presents with an abnormal skull shape
      i. Brachycephaly (short, broad skull)
      ii. Acrocephaly (tall skull)
3. Other craniofacial features
   a. Facial asymmetry (the most conspicuous facial feature), particularly in individuals with unicoronal synostosis
   b. Low frontal hairline
   c. Ptosis of the eyelids: often results from a defective functioning or agenesis of the levator palpebrae muscle
   d. Downslanting of the palpebral fissures

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e. Epicanthal folds
f. Strabismus
g. Amblyopia
h. Midface hypoplasia
i. A broad nose with depressed nasal bridge
j. Characteristic appearance of the ears: low-set and rotated ears with small pinna with a prominent superior and/or inferior crus

4. Limb anomalies
   a. Brachydactyly: most frequent finding
   b. Cutaneous syndactyly of the second and third digits of the hands and feet: highly variable degree but nearly diagnostic in the presence of limb anomalies
   c. Clinodactyly of the fifth fingers
   d. Transverse palmar creases often present
   e. Broad digit I of the feet
   f. Hallux valgus
   g. Duplicated distal phalanx of the hallux
   h. Triangular epiphyses of the hallux
5. Other variable clinical features
   a. Short stature
   b. Presence of foramina parietalia permagna (bony defects on both sides of the parietal suture exceeding 1 cm in diameter)
   c. Impressiones digitatae, considered to be an indicator of raised intracranial pressure, often recorded without the presence of increased intracranial pressure
   d. Conductive, mixed, and profound sensorineural hearing loss
   e. Ocular hypertelorism
   f. Occasional blepharophimosis
   g. Lacrimal duct stenosis
   h. Maxillary hypoplasia
   i. High-arched and/or cleft palate
   j. Congenital heart defects
   k. Vertebral fusion
   l. Radioulnar synostosis
   m. Increased risk of cancers (breast, kidney)
6. Intelligence
   a. More commonly normal intelligence
   b. Significant learning disability usually noted in affected individuals with microdeletion in 7p21 but severe delay or mental retardation is not typical
7. Family history of abnormal skull shape and/or a combination of other physical findings: usually present in SCS, however, craniosynostosis is not an obligatory finding (some affected relatives may not have been diagnosed with a craniosynostosis syndrome)
8. Differential diagnosis
   a. Muenke syndrome
      i. Characterized by "nonsyndromic" coronal craniosynostosis caused by the specific point mutation p.Pro250Arg in *FGFR3* (encoding fibroblast growth factor receptor-3)
      ii. Shares features with Saethre-Chotzen syndrome (SCS)
      iii. Individuals with *TWIST1* mutations distinguished from those with the *FGFR3* p.Pro250Arg mutations from a recent study of 39 pedigrees (71 affected individuals) ascertained on the basis of coronal synostosis with the following clinical features:
         a) A low frontal hairline
         b) Ptosis
         c) Small ears
         d) Parietal foramina
         e) Interdigital webbing
         f) Hallux valgus or broad great toe with bifid distal phalanx
   b. Isolated unilateral coronal synostosis
      i. Represents coronal suture fusion with no evidence of other malformations
      ii. Approximately ten times more common than SCS. Coronal synostosis is the second most common form of single-suture fusion after sagittal synostosis.
      iii. Facial asymmetry resembling SCS can result from untreated or incompletely treated isolated unilateral coronal synostosis.
   c. Baller-Gerold syndrome (BGS)
      i. Characteristic clinical features
         a) Coronal craniosynostosis manifesting as abnormal shape of the skull (brachycephaly) with ocular proptosis and bulging forehead
         b) Radial ray defect manifesting as oligodactyly (reduction in number of digits), aplasia or hypoplasia of the thumb, and/or aplasia or hypoplasia of the radius

c) Growth retardation
d) Poikiloderma

ii. *RECQL4*: the only gene currently known to be associated with BGS

iii. Clinical findings overlap with those of Rothmund-Thomson syndrome and Rapadilino syndrome, also caused by mutations in *RECQL4*.

Diagnostic Investigations

1. Diagnosis primarily based on clinical findings
2. Molecular genetic testing
   a. *TWIST1* mutations: identified in 46–80% of affected individuals using a combination of deletion/duplication analysis and sequence analysis (positive in 46–80% of cases)
   b. Consider testing for *FGFR3* (p.Pro250Arg) mutation if no *TWIST1* mutation is identified in an individual with a presumed diagnosis of Saethre-Chotzen syndrome since clinical findings of Muenke syndrome overlap with Saethre-Chotzen syndrome.
3. Cytogenetic analysis: a chromosome translocation or inversion involving 7p21 or ring chromosome 7 reported in occasional patients with atypical findings, including developmental delay

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. A 50% risk if a parent is also affected
      ii. An apparently low risk if the parents are clinically unaffected and do not have a *TWIST1* mutation
         a) Spontaneous mutation rate if the proband represents de novo mutation
         b) Possible parental germ line mosaicism exists although no instances of germ line mosaicism have been reported.
   b. Patient's offspring: a 50% recurrence risk for an affected individual to have an affected offspring
2. Prenatal diagnosis: possible for pregnancies at increased risk if the disease-causing mutation has been identified in the family

3. Management
   a. Cranioplasty in the first year of life
      i. To prevent progressive facial asymmetry in those with asymmetric coronal fusion
      ii. To prevent increased intracranial pressure (ICP) in those with multiple sutural synostosis
      iii. To prevent developmental delay and impaired vision secondary to increased intracranial pressure
   b. Midfacial surgery needed for dental malocclusion, swallowing difficulties, and respiratory problems
   c. Cleft palate surgery usually follows cranioplasty.
   d. Orthodontic treatment and/or orthognathic surgery as needed near the completion of facial growth; developmental intervention
   e. Routine treatment of hearing loss
   f. Prevention of secondary complications
      i. Attention to possible cervical vertebral instability secondary to vertebral anomalies
      ii. Periodic ophthalmologic evaluation for chronic papilledema
      iii. Brain imaging in later life for evidence of increased intracranial pressure
      iv. Routine evaluation for facial asymmetry, psychomotor development, and hearing loss

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Fig. 1 (**a**, **b**) A 2-month-old boy was evaluated for trigonocephaly (metopic suture premature synostosis)

Fig. 2 His mother was diagnosed to have Saethre-Chotzen syndrome clinically. Preoperatively, she was noted to have marked forehead asymmetry, retrusion of the right side of the supraorbital region, disproportion of the orbits with the right orbit higher, and temporal fossa hollowness. The diagnosis was confirmed molecularly by detection of a *TWIST* gene mutation (c.396–416 dup mutation, i.e., c.417ins21) which has been previously detected in other Saethre-Chotzen syndrome patients

Fig. 3 (**a**–**c**) Follow-up visit of the child and the mother

Fig. 4 (**a**–**f**) A 42-year-old man was diagnosed to have Saethre-Chotzen since childhood. He was noted to have a brachycephalic skull with midfacial hypoplasia, a high forehead with a low hairline, a small cranial vault, asymmetric face with a curved nose, marked ptosis, down turned upper lip, underbite, repaired cleft palate, an underbite, low-set ears with prominent crus, cutaneous syndactyly and contractures at the proximal interphalangeal joints in the second and fifth digits bilaterally, a single flexion crease in the fifth digit of both hands with unusual palmar creases, short toes with broad great toes bilaterally, minimal cutaneous syndactyly of toes 2–3 bilaterally, and bilateral hearing aids in place. In addition, he had developmental delay, seizures, heart murmur, and toeing-in requiring braces in childhood, keratoconus requiring corneal transplants, hypertension, and colon polyps and spastic colon. Southern blot analysis of genomic DNA showed complete deletion of one allele of the *TWIST* gene. Such mutations are diagnostic for Saethre-Chotzen syndrome

Sagittal Craniosynostosis Associated with Chromosome Abnormalities with a Brief Review on Craniosynostosis

Craniosynostosis, defined as the premature closure of >1 cranial suture with an estimated prevalence of 1 in 2,000–3,000 births (Cohen 2000), comprises a heterogeneous group of birth defects, including isolated forms and syndromic cases.

Sagittal craniosynostosis (or synostosis), usually an isolated congenital abnormality in otherwise normal infants, is characterized by scaphocephaly. It is the most common form of craniosynostosis with prevalence of 1 in 5,000 children, comprising approximately 50% of all craniosynostosis cases (Lajeunie et al. 1996, 2005). Rarely, when sagittal synostosis is a part of a syndrome, it can be due to a chromosome abnormality associated with multiple congenital abnormalities or due to a single gene abnormality such as Crouzon or Carpenter syndrome, invariably associated with obvious facial or digital anomalies, with clinically evident closure of multiple sutures.

Genetics/Basic Defects

1. Classification of craniosynostosis based on suture involvement (Kimonis et al. 2007)
   a. Simple (involving one suture) or complex (involving two or more sutures)
   b. Primary (caused by an intrinsic defect in the suture) or secondary (premature closure of normal sutures because of another medical condition such as deficient brain growth)
   c. Isolated (occurring without other anomalies) or syndromic (accompanied by other dysmorphic features or developmental defects)
   d. Frequencies of the various sutures involved
      i. Sagittal: 40–58%, etiology unknown
      ii. Coronal: 20–29%, estimated one-third caused by single-gene mutations
      iii. Metopic: 4–10%, etiology unknown
      iv. Lambdoidal: 2–4%, etiology unknown
2. Etiologies of nonsyndromic craniosynostosis (Passos-Bueno et al. 2008)
   a. Familial recurrence (Hennekam and Van den Boogaard 1990; Lajeunie et al. 1996, 1998, 2005; Cohen and McLean 2000)
      i. Nonsyndromic coronal synostosis (14%)
      ii. Nonsyndromic sagittal synostosis (6%)
      iii. Nonsyndromic metopic synostosis (3–9%) versus 22% in syndromic metopic synostosis
      iv. Pedigrees from familial recurrence: compatible with:
         a) Autosomal dominant inheritance
         b) Autosomal recessive inheritance
         c) X-linked inheritance
   b. Genetic etiology
      i. Poorly understood
      ii. *EFNA4*: The only gene that when mutated causes only nonsyndromic craniosynostosis (Merrill et al. 2006).
3. Etiologies of isolated (nonsyndromic) sagittal synostosis
   a. Suggestions of possible genetic and environmental factors (Johnson et al. 2000; Zeiger et al. 2002; Lajeunie et al. 2005)
   b. Possible intrauterine pressure on the neurocranium on the etiology of craniosynostosis (Johnson et al. 2000; Kirschner et al. 2002)

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c. Preference for (Butzelaar et al. 2009)
   i. Male sex
   ii. Twinning
   iii. Prematurity

4. Etiologies of syndromic craniosynostosis (Passos-Bueno et al. 2008; Jehee et al. 2008)
   a. To date, well over 180 syndromes are associated with craniosynostosis as a major clinical feature. Mendelian and chromosomal alterations are important causative mechanisms.
   b. Mutations associated with syndromic craniosynostosis
      i. Mutations in seven genes (*FGFR1*, *FGFR2*, *FGFR3*, *TWIST1*, *EFNB1*, *MSX2*, and *RAB23*): unequivocally associated with mendelian forms of syndromic craniosynostosis and explain the etiology of about 30% of syndromic cases (Wilkie et al. 2007)
      ii. Mutations in four other genes, *FBN1*, *POR*, *TGFBR1*, and *TGFBR2*: also associated with craniosynostosis, but not causing the major clinical feature of the phenotype and/or with an apparently low penetrance (Sood et al. 1996; Flück et al. 2004; Loeys et al. 2005)
5. Chromosome alterations in the etiology of craniosynostosis (Passos-Bueno et al. 2008)
   a. All types of chromosomal abnormalities have already been described in patients with craniosynostosis, including deletions and duplications in almost all human chromosomes.
   b. Approximately 16% of syndromic cases have been associated with chromosomal abnormalities in conventional cytogenetics studies (Cohen 2000).
      i. A high association of craniosynostosis with duplication 13q21–q34
      ii. A high association of craniosynostosis with deletion 7p15–p21, 9p21–p24, and 11q23–q25 (Brewer et al. 1998, 1999)
      iii. Deletion and/or duplication 1p36 (Gajecka et al. 2005; McDonald-McGinn et al. 2005)
   c. Jehee et al. (2008) screened 45 patients with craniosynostotic disorders with a variety of methods including conventional karyotype, microsatellite segregation analysis, subtelomeric multiplex ligation-dependent probe amplification, and array-based comparative genome hybridization with the following results:
      i. Causative abnormalities were present in 42.2% (19/45) of the samples.
      ii. 27.8% (10/36) of the patients with normal conventional karyotype carried submicroscopic imbalances.
      iii. Sagittal synostosis
         a) Del(1p)
         b) Dup(5)(p15.1–p14.1)
         c) Dup17q
         d) Dup(X)(p11.23)
      iv. Metopic synostosis
         a) Del(1q)
         b) Del(1q)/dup(15q)
         c) Del(9)(p22.3p24.2)
         d) Del(9q)/dup(17q)
         e) Del(11)(q23.3)
         f) Del(X)(p11.3)
         g) Del(Y)(q11)
         h) Der(9)t(9;4)(p22.3;q34)
         i) Der(9)t(9;?)(p21.3;?)
         j) Dup(3)(p25.2)
         k) Dup(6)(q27)
         l) Dup(15)(q13.2)
         m) Dup(22)(q11.23)
         n) Dup(X)(p22.3)
      v. Bilateral coronal synostosis: Dup(3)(q26.33)
      vi. Bilateral coronal and metopic synostosis: Dup(X)(q22.2)
6. Sagittal synostosis associated with chromosome abnormalities
   a. Our patient 1: del(4)(q26 → q28.3ter) and del(13)(q21.2 → q21.31)
   b. Our patient 2: del(13)(q33.1 → qter) and dup(17)(q25.3 → qter) [der(13)(13)(t13;17)(q33.1;q25.3)]
   c. Our patient 3: t(4;18)(p12p11.2)
7. Multiple craniosynostosis involving sagittal and other sutures associated with chromosome abnormalities
   a. Sagittal and metopic synostosis (Hiraki et al. 2006): 46,X,der(Y)(t(Y;1)(q12;p36.3) inherited from father [46,X,t(Y;1)(q12;p36.3)]
   b. Sagittal and bilateral lambdoid synostosis (called craniofacial dyssynostosis, "Mercedes Benz" syndrome, or nonsyndromic multisutural synostosis) (Hing et al. 2009)
      i. Case reported by Shiihara et al. (2004): sagittal and metopic suture synostosis
         a) An unbalanced translocation, 46,XX,der(13)t(5;13)(q33.3;q34)mat resulting in monosomy 13 q34–qter and trisomy 5q33.3–qter

b) FISH analysis showed three MSX2 signals indicating the presence of three copies of the MSX2 gene.

ii. Case reported by Cohen (2000): complex rearrangement of chromosome 5, resulting in three paracentric inversions/two insertions and a duplication of 5q35 inclusive of the MSX2 gene region

iii. Case reported by Tagariello et al. (2006)

a) A de novo–balanced translocation, t(9;11)(q33;p15)

b) Both breakpoint regions were cloned, and the chromosome 11p15 breakpoint was noted to disrupt the *SOX6* gene between exons 6 and 7. However, the potential role of the *SOX6* gene disruption in BLSS remains undetermined.

iv. Case reported by Hing et al. (2009): an Xp11.2 deletion

c. Sagittal, metopic, and coronary synostosis (Hiraki et al. 2008): 46,XX,der(15)(q15.2q22.1)

d. Sagittal, metopic, lambdoid, temporal, and squamosal synostosis (Jehee et al. 2007): De novo interstitial 11q duplication [46,XY,dup(11)(q11–q13.3)(/46,XY] included the duplication of genes FGF3 and FGF4.

Clinical Features

1. Natural history of sagittal synostosis (Chatterjee et al. 2007)
   a. As the condition occurs in utero, diagnosis should be possible at birth with careful attention to the sagittal suture and the deformity that is created.
   b. If uncorrected, sagittal synostosis leads to progression of the scaphocephalic deformity which can be an esthetic problem as well as raised intracranial pressure and speech and language impairment in almost 40% of patients.
2. Clinical features of sagittal synostosis
   a. Scaphocephaly or dolichocephaly due to growth restriction transverse to the sagittal suture resulting in a biparietally narrowed skull and continuing growth of the calvaria in the ventral-dorsal direction resulting in the elongation of the skull
   b. Variable appearance of the elongation of the skull depending on which portion of the sagittal suture is fused
   c. Ridging of the sagittal suture
   d. Frontal bossing: resulting from premature closure of the anterior portion of the sagittal suture (Jane et al. 2000)
   e. Variants of posterior sagittal synostosis (Jane et al. 2000): Closure of the posterior portion of the sagittal sutures occurs less commonly than anterior closure.
      i. Occipital knob: The occipital bone becomes the site of compensatory overgrowth because it is located distal and perpendicular to the fused suture.
      ii. "Golf tee" deformity
         a) An exaggerated form of the occipital knob, simulating a golf tee
         b) The skull is narrower posteriorly and protrudes more prominently. In addition, the unfused anterior portion of the sagittal suture may widen the parietal bone anteriorly, accentuating the occipital narrowing.
      iii. Bathrocephalic deformities: an extreme consequence of premature posterior closure of the sagittal suture
         a) Characterized by the appearance of a podium in the occipital region
         b) The posterior portion of the parietal bone slants inferiorly while the occipital bone juts superiorly.
   f. Complete sagittal synostosis: the most extreme form of the sagittal synostosis, resulting in both anterior and posterior deformity
3. Sagittal synostosis associated with chromosome abnormalities (our cases)
   a. Patient 1 (monosomies 4q and 13q)
      i. Sagittal suture synostosis (palpable bonny ridge along the sagittal suture)
      ii. Ocular hypertelorism
      iii. Proptotic eyes
      iv. Micrognathia
   b. Patient 2 (translocation 4p and 18p)
      i. Sagittal synostosis (scaphocephaly)
      ii. Tetralogy of Fallot
4. Multiple suture synostoses (including sagittal synostosis) associated with chromosome abnormalities: wide variation of clinical features depending on the gain or loss of the chromosome(s) and

chromosome segments involved. Following are some of the examples:

a. Multiple craniosynostoses involving the sagittal and metopic sutures with 1p36.3–pter trisomy (Hiraki et al. 2006)
   i. Borderline mental retardation
   ii. Bitemporal narrowing
   iii. Sloping forehead
   iv. Blepharophimosis
   v. Blepharoptosis
b. Multiple craniosynostoses involving sagittal and bilateral lambdoid sutures: Premature fusion of the sagittal and both lambdoid sutures results in a characteristic head shape with frontal bossing, turribrachycephaly, biparietal narrowing, occipital concavity, inferior displacement of the ears, and ridging of the sagittal and lambdoid sutures (Hing et al. 2009).
   i. Case reported by Shiihara et al. (2004)
      a) Sagittal and bilateral lambdoid sutures
      b) Developmental delay
      c) Atrial septal defect
      d) Patent ductus arteriosus
      e) Unbalanced translocation, 46,XX,der (13)t(5;13)(q33.3;q34)mat resulting in monosomy 13 q34–qter and trisomy 5q33.3–qter
      f) FISH analysis demonstrated three copies of the *MSX2* gene.
   ii. Case reported by Cohen (2000)
      a) Sagittal and bilateral lambdoid sutures
      b) Hypotonia
      c) Ventricular septal defect
      d) Coarctation of the aorta
      e) A complex rearrangement of chromosome 5 resulting in three paracentric inversions/two insertions and a duplication of 5q35 inclusive of the *MSX2* gene region
      f) MSX2 is known to play an important role in cranial bone formation as haploinsufficiency of MSX2 results in parietal skull defects and overexpression causes craniosynostosis.
   iii. Case reported by Tagariello et al. (2006)
      a) Sagittal and bilateral lambdoid sutures
      b) Mild speech delay
      c) A de novo balanced translocation, t(9;11)(q33;p15)
      d) Both breakpoint regions were cloned, and the chromosome 11p15 breakpoint was noted to disrupt the *SOX6* gene between exons 6 and 7.
   iv. Case reported by Hing et al. (2009)
      a) Sagittal and bilateral lambdoid sutures: frontal bossing, brachycephaly, narrow occiput
      b) Hypotonia at birth
      c) Progressive apnea
      d) Seizures
      e) Expired at 4 months of age
      f) Xp11.22 deletion: clinical significance unknown
c. Multiple craniosynostoses involving the sagittal, metopic, and coronary sutures
   i. Cases reported by Hiraki et al. (2008) with a de novo 15q15q22 deletion
      a) Hypotonia
      b) Profound growth and psychomotor retardation
      c) Craniofacial dysmorphic features (bow-shaped eyebrows, downslanting palpebral fissures, mild blepharophimosis, strabismus, nystagmus, optic nerve atrophy, low-set ears with stenotic bilateral ear canals, bulbous nasal tip, hypoplastic alae nasi, upturned nostrils, high-arched palate, bifid uvula, epiglottic hypoplasia, a thin upper lip, and tucked-in lower lip)
      d) Other anomalies (pectus excavatum, accessory nipples, small hands and feet, long fingers, abducted and proximally placed thumbs, clinodactyly of the fifth fingers, four finger creases, overlapping third and fifth over fourth toes, metatarsus adductus)
d. Sagittal, metopic, lambdoid, temporal, and squamosal synostosis (Jehee et al. 2007): de novo interstitial 11q duplication
   i. Developmental delay
   ii. Marked trigonocephalic, turricephalic, and scaphocephalic-shaped skull
   iii. Blue sclerae
   iv. Nystagmus
   v. Strabismus
   vi. Short neck
   vii. Short philtrum
   viii. Supernumerary maxillary lateral incisor
   ix. PDA

x. Patent foramen ovale
xi. Seizures
xii. Recurrent infections
xiii. Mild brachydactyly of the finger
xiv. Clinodactyly of the fifth fingers
xv. Slightly broad thumbs
xvi. Shortened distal phalanges
xvii. Hypoplastic nails

Diagnostic Investigations

1. Radiographic study to demonstrate sagittal synostosis
2. Three-dimensional computed tomographies to discern the characteristics of sagittal synostosis (David et al. 2009)
   a. Anterior type: characterized by a transverse retrocoronal band
   b. Central type: Prematurely fused sagittal suture is marked by a prominent heaped-up appearance.
   c. Posterior type: a significantly elongated occiput as the most striking radiographic feature
   d. Complex type: combined characteristics of anterior, central, and posterior types
3. Conventional karyotype
4. Microsatellite segregation analysis
5. Subtelomeric multiplex ligation-dependent probe amplification
6. Array-based comparative genome hybridization

Genetic Counseling

1. Recurrence risk (Kimonis et al. 2007; Wilkie et al. 2007)
   a. Patient's sib
      i. "Truly nonsyndromic craniosynostosis": thought to be a multifactorial trait with recurrent risk around 5% for coronal and around 1% for sagittal suture fusion
      ii. Autosomal dominant craniosynostosis
         a) Common in craniosynostosis syndromes with a relatively high proportion of new mutations
         b) Genetic counseling for the parents of a child with an apparently new mutation: difficult by uncertainties over the recurrence risk attributable to occult germ line mosaicism in a parent
         c) Negative parental mutation testing: still leaves a small (<1%) risk of recurrence because of potential gonadal mosaicism
      iii. Craniosynostosis associated with chromosome abnormality: recurrent risk depends on whether a de novo event or a parent is a carrier of the abnormality
   b. Patient's offspring
      i. "Truly nonsyndromic craniosynostosis": thought to be a multifactorial trait with recurrent risk around 5% for coronal and around 1% for sagittal suture fusion
      ii. Autosomal dominant craniosynostosis: Mutation carriers have a 50% risk of passing the affected gene to their offspring.
      iii. Chromosome aneuploidy: depends on the type and complexity of the chromosome rearrangement
2. Prenatal diagnosis: Craniosynostoses are rarely detected in utero (Fjortoft et al. 2007).
   a. Prenatal ultrasonography of the cranial suture
      i. Most craniosynostoses are missed during routine US screening examination.
      ii. Most of the prenatal diagnoses made have been severe syndromic synostosis elide mainly on cranial deformity and associated abnormalities, in particular limb malformations. Examples including:
         a) Pfeiffer syndrome
         b) Apert syndrome
         c) Saethre-Chotzen syndrome
   b. Prenatal MRI imaging of the cranial suture
      i. MRI cannot directly visualize calvarial sutures.
      ii. Diagnostic when craniosynostosis is suspected by prenatal ultrasound examination
      iii. Advantage of MRI: allows detection and provides better assessment of brain abnormalities which may be associated with craniosynostosis
   c. Prenatal 3-dimensional CT: useful as it allows direct visualization of the cranial vault sutures, which is not possible with MRI
   d. Prenatal testing strategies
      i. Chorionic villus sampling (typically at 10–14 weeks gestation)

ii. Amniocentesis (typically at 16–18 weeks gestation)
iii. Prenatal chromosome testing for syndromic craniosynostosis due to chromosome abnormality
iv. Molecular genetic testing of syndromic craniosynostosis due to single gene mutation

e. Preimplantation genetic diagnosis
i. A valuable option available for those who have been identified as carriers of the mutation but are interested in ensuring that their children are unaffected without making the decision to terminate a pregnancy in the event of a positive prenatal diagnosis
ii. Molecular testing enables the selection of only genetically normal embryos for use in in vitro fertilization.

3. Management (Adamo and Pollack 2009; Jimenez et al. 2008)
a. Goals of surgery in sagittal synostosis
i. Eliminate the biparietal constriction caused by the fused sagittal suture
ii. Increase the width of the skull
iii. Decrease the anterior-posterior (AP) length of the skull

b. In cases of mild scaphocephaly
i. Perform strip or extended craniectomies to remove the sagittal suture using either open or endoscopic techniques
ii. Then rely on future cranial vault remodeling with brain growth

c. In cases of more marked scaphocephaly
i. Extend the craniectomy to follow along the lambdoid sutures
ii. Add bilateral parietal bone wedge osteotomies

d. The pi technique (Jane et al. 1978): also widely used
i. Bilateral parasagittal strip craniectomies with outfracturing of the temporal bones
ii. Removal of the vertex bone
iii. AP shortening of the calvarial vault, in some instances with bifrontal osteotomies

e. In older children: The bone is more difficult to reshape.
i. A more extensive calvarial reconstructive procedure is performed with bifrontal, biparietal, and occipital bone removal and reconstruction.
ii. The bones are then angulated to reduce frontal bossing, and the grafts are shortened to reduce the AP dimension of the skull.

f. Surgical procedures used for the treatment of sagittal synostosis
i. Strip craniectomy procedure
ii. Total vertex craniectomy
iii. Peninsula craniectomy
iv. Pi procedure
v. Modified Pi procedure
vi. Clamshell procedure
vii. Distraction-contraction procedure
viii. Foreshortening and lateral expansion
ix. Spiral osteotomy technique
x. Parietal bone fixation technique
xi. Reversal exchange technique
xii. Sprint-assisted cranioplasty
xiii. Marchac transposition
xiv. Modified Marchac transposition
xv. Endoscopic craniectomy
xvi. Microscopic craniectomies

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Fig. 1 (**a**, **b**) An 8-month-old infant was evaluated for sagittal suture synostosis. Her craniofacial features were characterized by palpable bonny ridge along the sagittal suture, ocular hypertelorism with proptotic eyes, and mild retrognathia. Conventional cytogenetics showed a complex chromosomal rearrangement involving chromosomes 2, 4, and 13, and deletions in chromosomes 4 and 13 [46,XX,ins(2;4)(p21;q31.2q33),del(4)(q26q28.3),t(4;13)(q31.3;q21.32),del(13)(q21.2q21.31)]. Oligonucleotide array CGH analysis showed a 22-Mb deletion in bands 4q26 to 4q28.3 and a 3.5-Mb deletion in 13q21.2 to13q21.31. The karyotype is therefore monosomic for genes in these regions

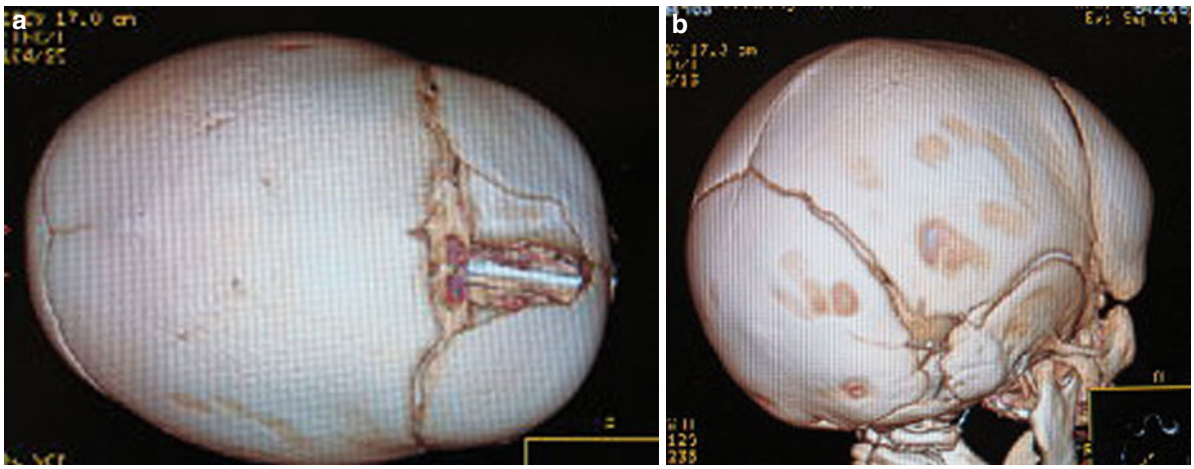

Fig. 2 (**a**, **b**) Three-dimensional CT reconstructions from the same patient shows dolichocephalic skull resulting from premature fusion of the sagittal suture and sagittal ridge

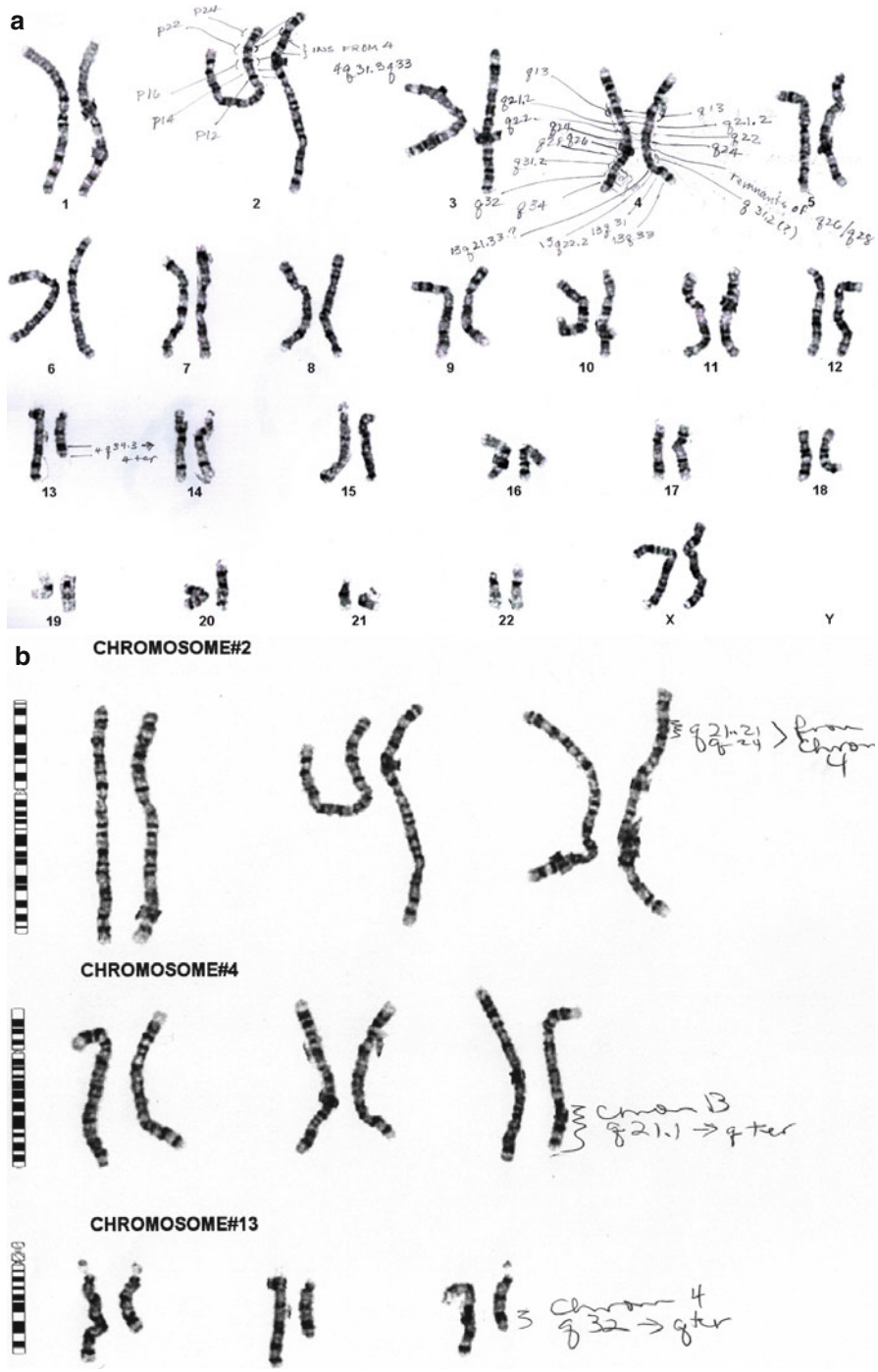

Fig. 3 (**a**, **b**) Her karyotype showed del(4)(q26 → q28.3ter) and del(13)(13q21.2 → q21.31) (Pencil marks are intentionally left here to show the complex chromosome rearrangements)

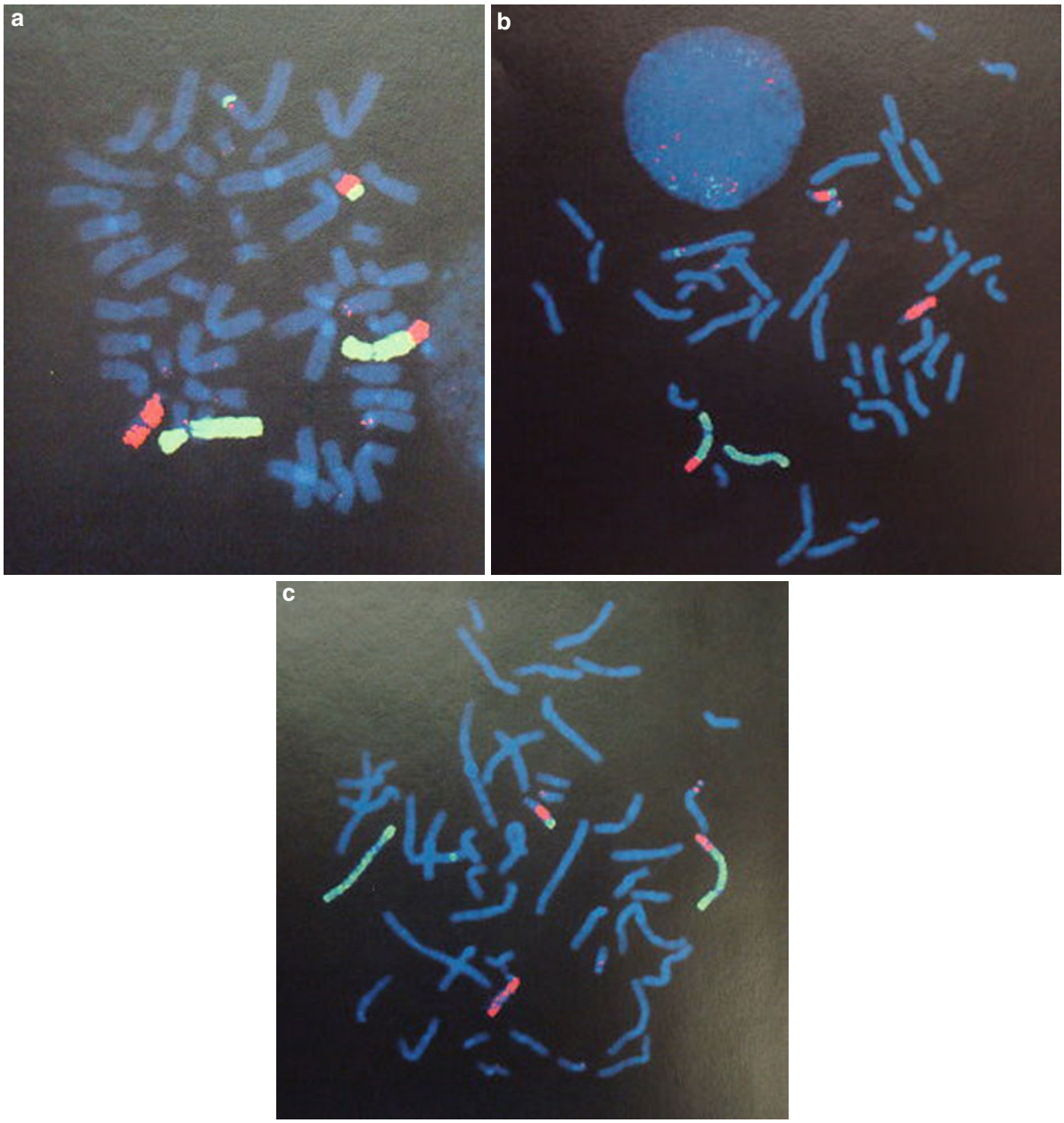

Fig. 4 (**a**–**c**) FISH with wcp2 and wcp4 confirmed an insertion of chromosome 4 material (4q31.2–33) into the short arm of 4q31.1 to 4qter. This translocation was confirmed with FISH subtelomeric probes, showing the qter of the translocation positive for the 13q subtelomere sequences, and the qter of the translocation 13 positive for 4q subtelomere

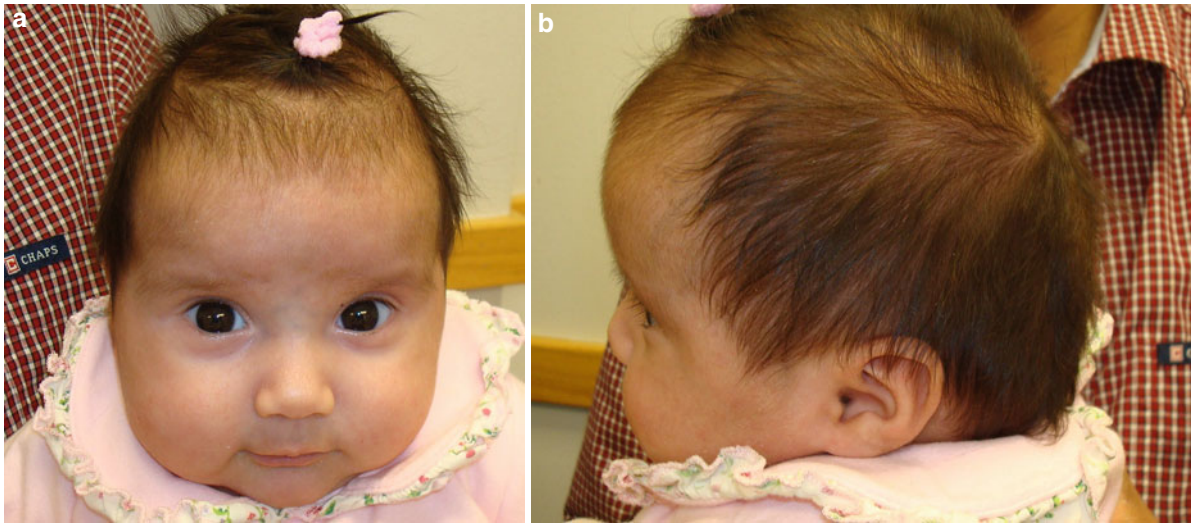

Fig. 5 (**a**, **b**) A 2-month-old infant was evaluated for scaphocephaly (sagittal suture ridge palpable) with Tetralogy of Fallot

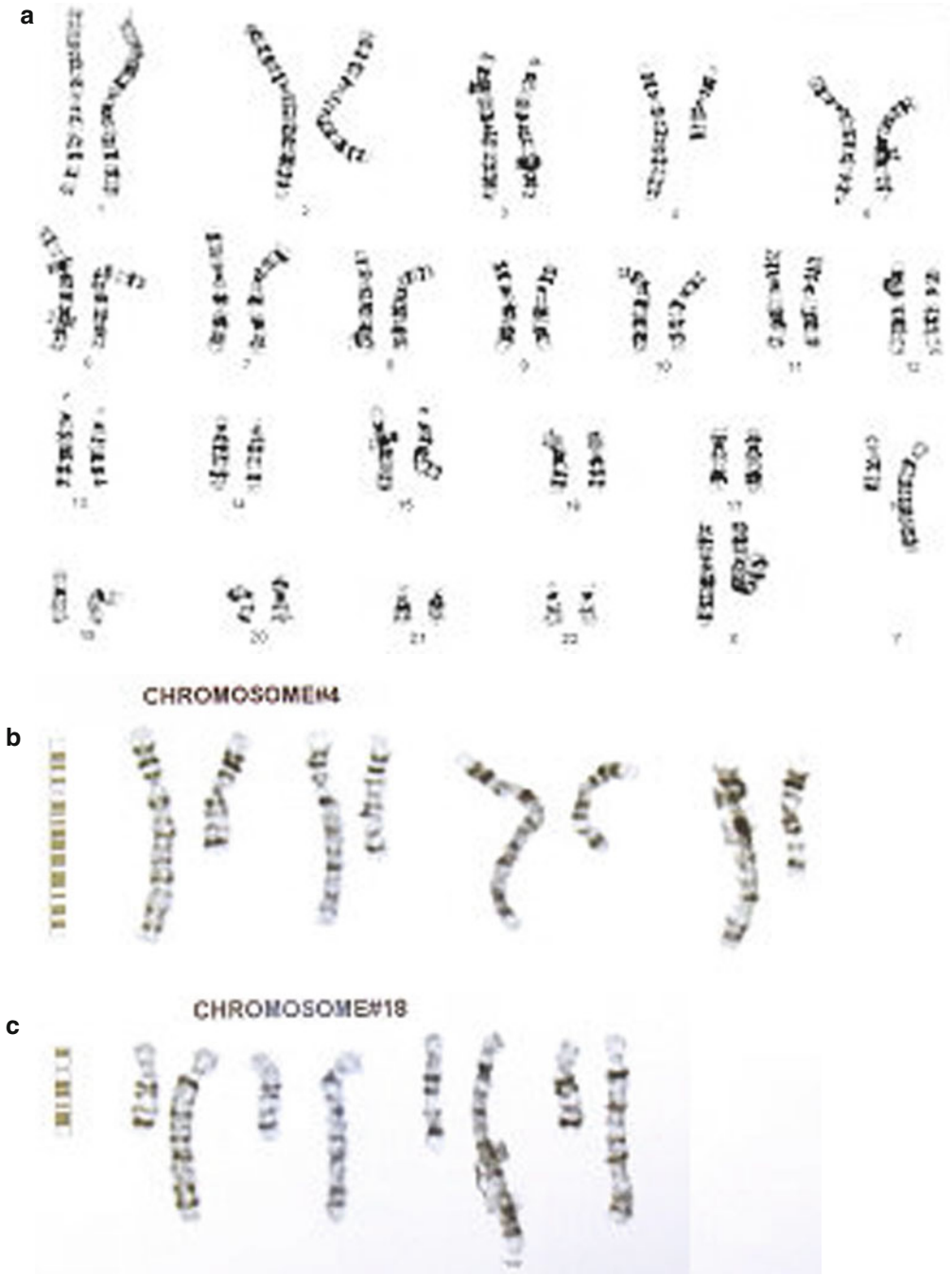

Fig. 6 (**a**–**c**) Her karyotype and ideogram with partial karyotypes showed a balanced translocation t(4;18)(p12;p11.2)

Schizencephaly

Schizencephaly is a rare congenital brain malformation characterized by deep clefts of the cerebral mantle that extend from the cortical surface to the lateral ventricles. The conditions are often associated with convolutional anomalies such as polymicrogyria or nodular subependymal heterotopias.

Genetics/Birth Defects

1. Inheritance
   a. Isolated schizencephaly: mainly sporadic
   b. Rare reports of familial cases
2. Etiology
   a. A developmental defect in the blood vessels supplying the cerebral cortex
      i. Resulting in tissue death and cleft formation due to lack of oxygen (in utero vascular insufficiency)
      ii. With preferential location in the parasylvian regions following the frontoparietal distribution of the middle cerebral artery
   b. Mutations in the homeodomain gene *EMX2* as a possible cause of some cases of schizencephaly
      i. At least some schizencephaly cases result from germline mutations.
      ii. *EMX2*: expressed in restricted areas of the developing mammalian forebrain, including areas that develop into the cerebral cortex
      iii. Discovery of *EMX2* mutations in both sporadic and familial cases of schizencephaly marking an important advance in establishing genetic causes for brain malformations
      iv. Lack of *EMX2* mutations in most schizencephaly patients has increased the likelihood of other genes being involved.
      v. *EMX2* mutations were not confirmed from recent studies on large schizencephaly case series (Tietjen et al. 2007; Merello et al. 2008; Hehr et al. 2010).
   c. Heterozygous mutations in *SIX3* and *SHH* are associated with schizencephaly: a subset of patients with schizencephaly may develop as one aspect of a more complex malformation of the ventral forebrain, directly result from mutations in the *SHH* pathway, and hence be considered as yet another feature of the broad phenotypic spectrum of holoprosencephaly (Hehr et al. 2010)
3. Schizencephaly
   a. Refers to gray matter–lined clefts that extend through the entire hemisphere from the ependymal lining of the lateral ventricles to the pial covering of the cortex
   b. Cleft
      i. A cleft in the cerebral mantle which communicates between the subarachnoid space laterally and ventricular system medially
         a) Unilateral or bilateral cleft
         b) Symmetric or asymmetric cleft
      ii. The sides of clefts generally lined with heterotopic gray matter (an abnormal accumulation of neurons)
   c. Two types of schizencephaly depending on the size of the area involved and the separation of the cleft lips
      i. Type I (closed-lip schizencephaly)
         a) Consisting of a fused cleft

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b) This fused pial-ependymal seam forms a furrow in the developing brain and is lined by polymicrogyric gray matter.

ii. Type II (open-lip schizencephaly): presence of a large defect, a holohemispheric cleft in the cerebral cortex filled with cerebral spinal fluid and lined by polymicrogyric gray matter

d. Associated malformations commonly accompanying schizencephaly

i. Mild hypoplasia of the corpus callosum

ii. Total or nearly total absence of cavum septum pellucidum in 70–90% of patients with schizencephaly. 30–50% of patients show associated optic nerve hypoplasia on clinical examination (septo-optic dysplasia with schizencephaly).

iii. Focal cortical dysplasia

iv. Coloboma of the retina

v. Hydrocephalus

4. Syndromes associated with schizencephaly

a. Septo-optic dysplasia-schizencephaly syndrome

i. Clinical features distinct from isolated septo-optic dysplasia

ii. Significant global developmental delay and spastic motor deficits

iii. Seizures and visual symptoms rather than with endocrine abnormalities

b. Other rare schizencephaly syndromes

i. Prenatal cytomegalovirus infection

ii. Vascular disruption related to twinning

c. Schizencephaly (plus polymicrogyria) as part of multiple congenital anomaly/mental retardation syndromes

i. Adam-Oliver syndrome

ii. Aicardi syndrome

iii. Arima syndrome

iv. Delleman (oculocerebrocutaneous) syndrome

v. Galloway-Mowat syndrome

vi. Micro syndrome

Clinical Features

1. Clinical manifestations depend on the size and location of involved brain.

a. A narrow, unilateral cleft

i. Usually present with seizures and mild focal neurological deficits

ii. Otherwise developmentally normal

b. Bilateral clefts

i. Severe developmental delay

ii. Early intractable epilepsy

iii. Severe motor dysfunction

2. Clinical features

a. Mental retardation (varying degree)

b. Developmental delay: moderate to severe if the defects are large

c. Microcephaly (varying degree)

d. Hydrocephalus in some patients

e. Hypotonia in the postnatal period

f. Motor difficulties

g. Seizures in most patients

h. Generalized spasticity

i. Hemiparesis or quadriparesis

j. Blindness secondary to optic nerve hypoplasia

k. Prognosis depending on the size of the clefts and the degree of neurological deficits

i. Patients with type I abnormalities

a) Almost normal

b) May have seizures and spasticity

ii. Patients with smaller, unilateral clefts (clefts in only one hemisphere)

a) Often paralyzed on one side of the body

b) May have normal intelligence

iii. Patients with type II abnormalities

a) Mental retardation

b) Seizures

c) Hypotonia

d) Spasticity

e) Inability to walk or speak

f) Blindness

iv. Patients with bilateral open-lip schizencephaly generally with the worst clinical symptoms

Diagnostic Investigations

1. Ultrasonography of the brain to demonstrate closed-lip or open-lip brain cleft communicating with lateral ventricle(s)
2. Magnetic resonance imaging (MRI) or computed tomography (CT) of the brain

a. Open-lip or closed-lip schizencephaly

b. Associated absence of the septum pellucidum and hypoplasia of the optic chiasm

3. Potential role of diffusion tensor imaging with tractography in providing insights into the

evaluation of white matter tracts in patients with schizencephaly (Sarikaya 2009)

4. Pathology
   a. Clefts most commonly in the Rolandic fissures
   b. Frequently associated with pachygyria, polymicrogyria, or lissencephaly
5. Molecular genetic testing of *EMX2* mutation for familial schizencephaly: not considered to be appropriate and not available clinically

Genetic Counseling

1. Recurrence risk: low unless germline mutation is present in one of the parent
2. Prenatal diagnosis
   a. Ultrasonography and/or fetal MRI of the brain to demonstrate brain clefts connecting to the lateral ventricles
   b. Differential diagnosis of CSF-containing abnormalities in the fetal brain (Oh et al. 2005)
      i. Developmental lesions
         a) Arachnoid cyst
         b) Ventriculomegaly
         c) Monoventricle in holoprosencephaly
         d) Agenesis of the corpus callosum with an interhemispheric cyst
         e) Schizencephaly
      ii. Destructive lesions
         a) Porencephalic cyst
         b) Ventriculomegaly (infection or bleeding)
         c) Hydranencephaly
   c. *EMX2* mutation analysis on amniocytes or CVS: not considered to be appropriate and not available clinically
3. Management
   a. Physical therapy
   b. Seizure control
   c. VP shunt for hydrocephalus

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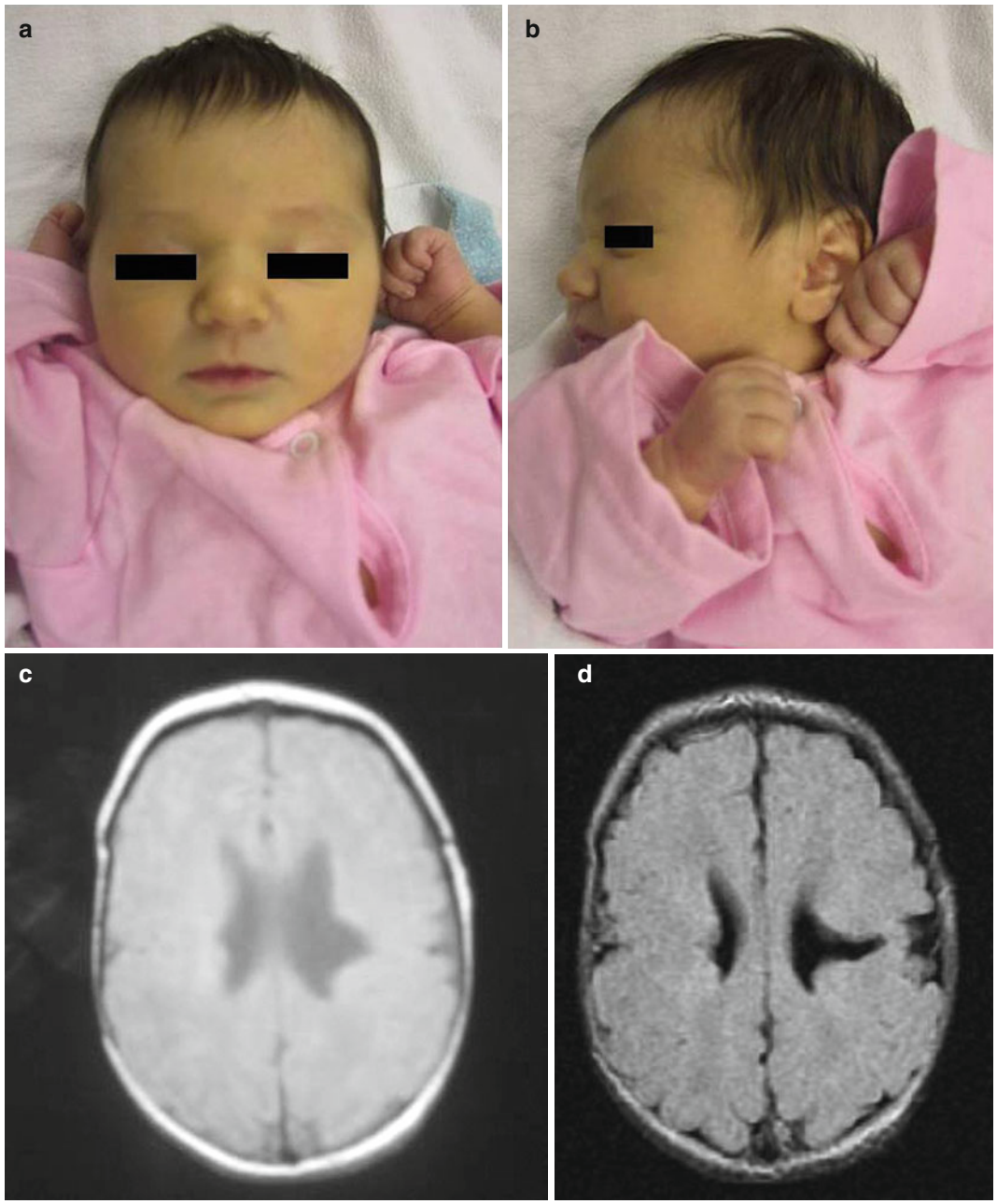

Fig. 1 (**a**–**d**) An infant with asymmetric open-lip parietal schizencephaly, illustrated by MRI

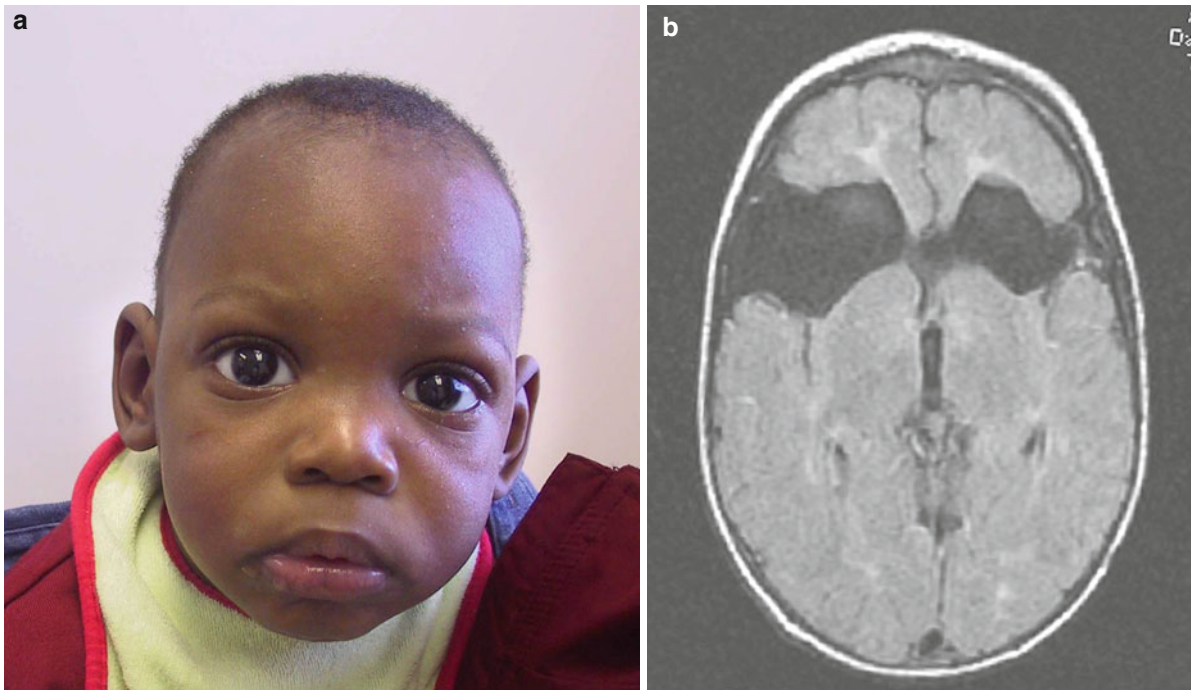

Fig. 2 (**a**, **b**) An infant with schizencephaly with global delay and spastic quadriplegia. His MRI of the brain showed bilateral large open-lip schizencephaly in frontotemporal regions

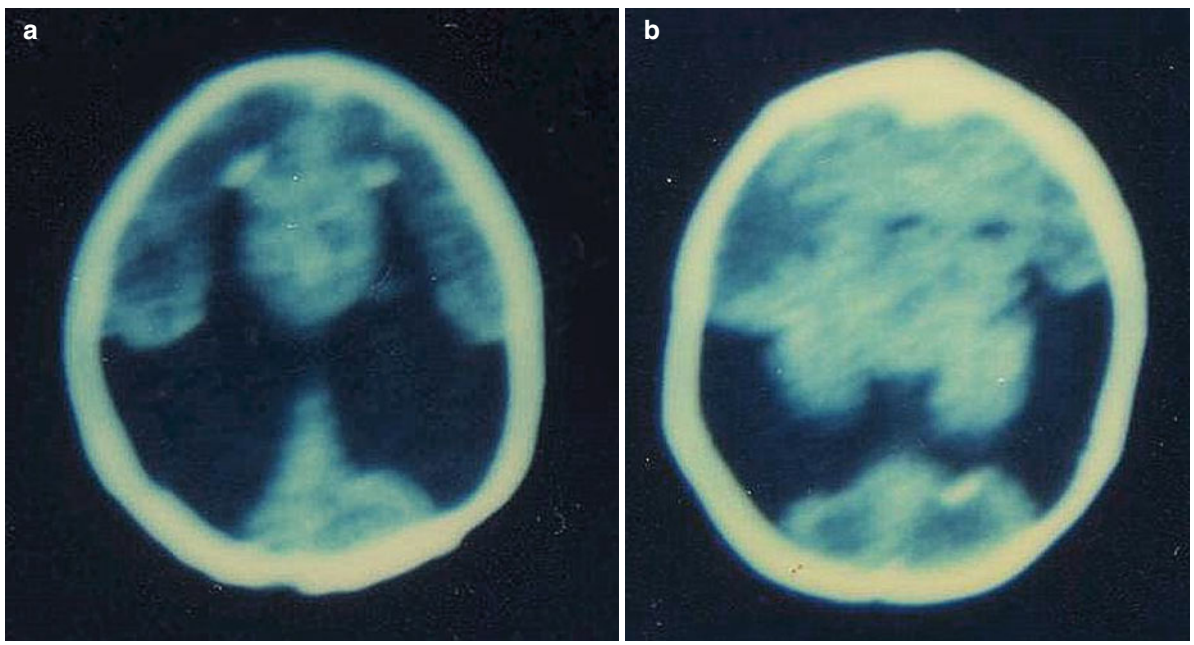

Fig. 3 (**a**, **b**) MRI of the brain of another patient showing bilateral open-lip schizencephaly in the parietal regions in communication with a large cavity filled by cerebrospinal fluid

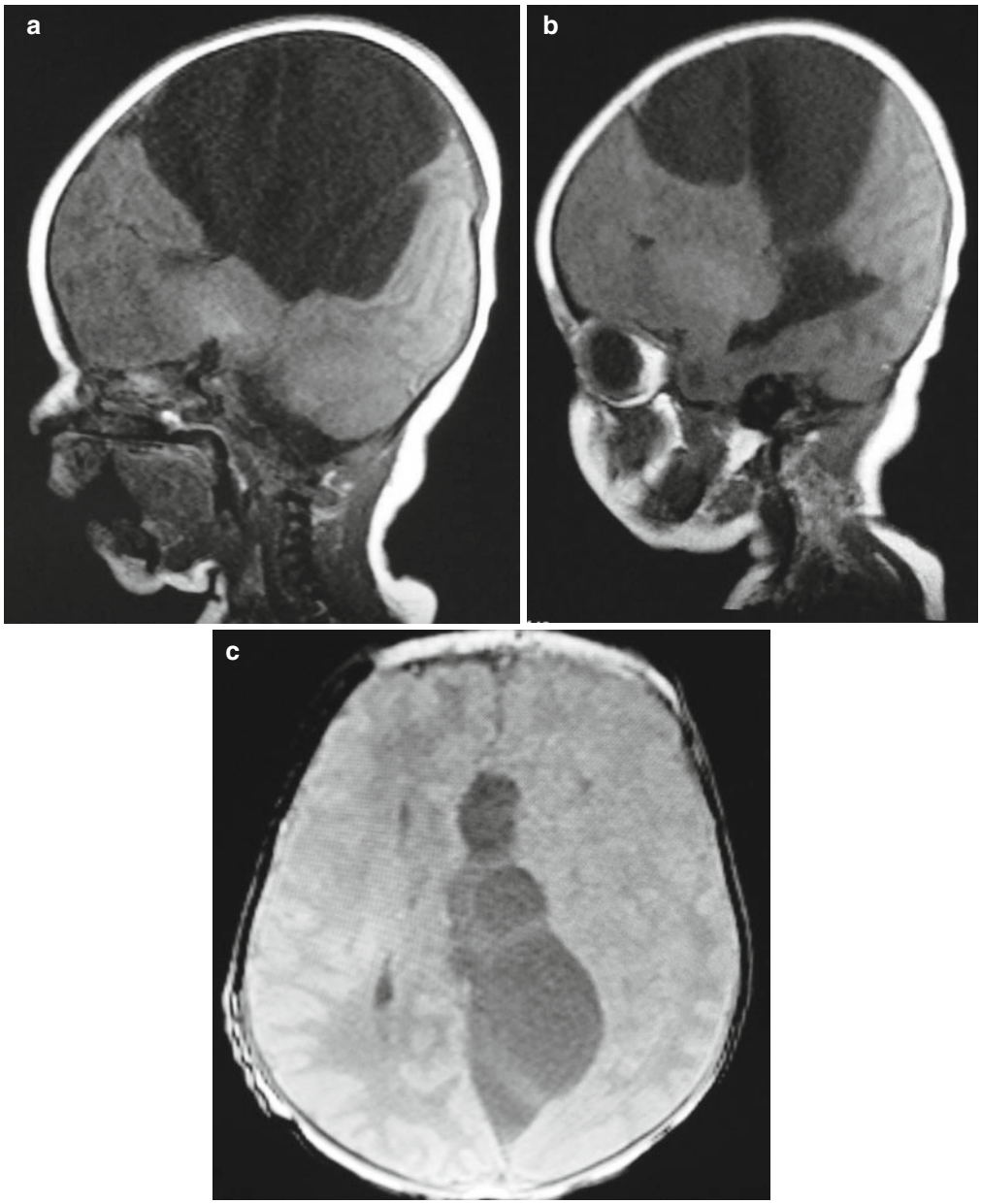

Fig. 4 (**a**–**c**) MRI of the brain of a neonate showed a large open-lip schizencephaly extending to the *right* convexity causing a large gap in the *right* cerebellar hemisphere. There is also absence of the corpus callosum

Schmid Metaphyseal Chondrodysplasia

Schmid metaphyseal chondrodysplasia (SMCD) is a mild hereditary chondrodysplasia resulting from growth plate cartilage abnormalities (Chan et al. 1998).

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant
   b. Variable expression
2. Molecular pathogenesis
   a. SMCD: caused by heterozygous mutations in the gene *COL10A1* (mapped to chromosome 6q21-q22), the gene which encodes α1(X) chains of type X collagen, a short-chain collagen whose expression is largely restricted to the hypertrophic chondrocytes of growth plate cartilage (Bateman et al. 2003)
      i. Most mutations reside in the carboxyl-terminal globular domain (CN1) (Ridanpää et al. 2003)
      ii. Two mutations observed In a putative signal peptide cleavage site
   b. Growth plate abnormalities of SMCD: resulting from collagen X haploinsufficiency, a reduction by 50% in collagen X (Bateman et al. 2003)

Clinical Features

1. Mild to moderate short-limbed dwarfism (Beluffi et al. 1982)
2. Bowed legs
3. Waddling gait, often a presenting sign at second year
4. Coxa vara
5. Genu varum
6. Exaggerated lumbar lordosis
7. Flared anterior rib cage
8. Leg pain during childhood
9. Prognosis
   a. Radiological changes appearing early with a tendency to heal and change slowly with time, giving rise to mildly dwarfed patients
   b. Normal intelligence

Diagnostic Investigations

1. Radiography (Lachman et al. 1988)
   a. Hip
      i. Abnormal acetabular roofs
      ii. Enlarged capital femoral epiphyses
      iii. Coxa vara
      iv. Femoral bowing
      v. Abnormal proximal femoral metaphyses
   b. Knee
      i. Abnormal distal femoral metaphyses
      ii. Abnormal proximal tibial metaphyses
      iii. Abnormal proximal fibular metaphyses
   c. Ankle
      i. Abnormal distal tibial metaphyses
      ii. Abnormal distal fibular metaphyses
   d. Wrist
      i. Abnormal distal radial metaphyses
      ii. Abnormal distal ulnar metaphyses
   e. Ribs: anterior cupping, splaying and sclerosis

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   f. Wide metaphyses with cupping and fraying
   g. Short and stubby long bones
   h. Mild hand involvement: a common feature (Elliott et al. 2005)
      i. Shortening of the tubular bones
      ii. Metaphyseal cupping of the proximal phalanges and metacarpals
   i. Normal spine
2. Histology: variable bone changes (Dimson 1968)
   a. Mild sharp serrations of the metaphyses with increased density of the provisional zone of calcification
   b. Irregularity with flaring and fragmentation and widening of the growth plate
3. Molecular genetic analysis of *COL10A1* mutation (Milunsky et al. 1998)
   a. Mutation analysis
   b. Mutation scanning

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: low recurrence risk unless a parent is affected
   b. Patient's offspring: 50%
2. Prenatal diagnosis by amniocentesis or CVS: can be offered to families at-risk for DMCD with a previously characterized disease-causing *COL10A1* mutation
3. Management
   a. Supportive
   b. Orthopedic management of bowed legs: generally does not require orthopedic surgery

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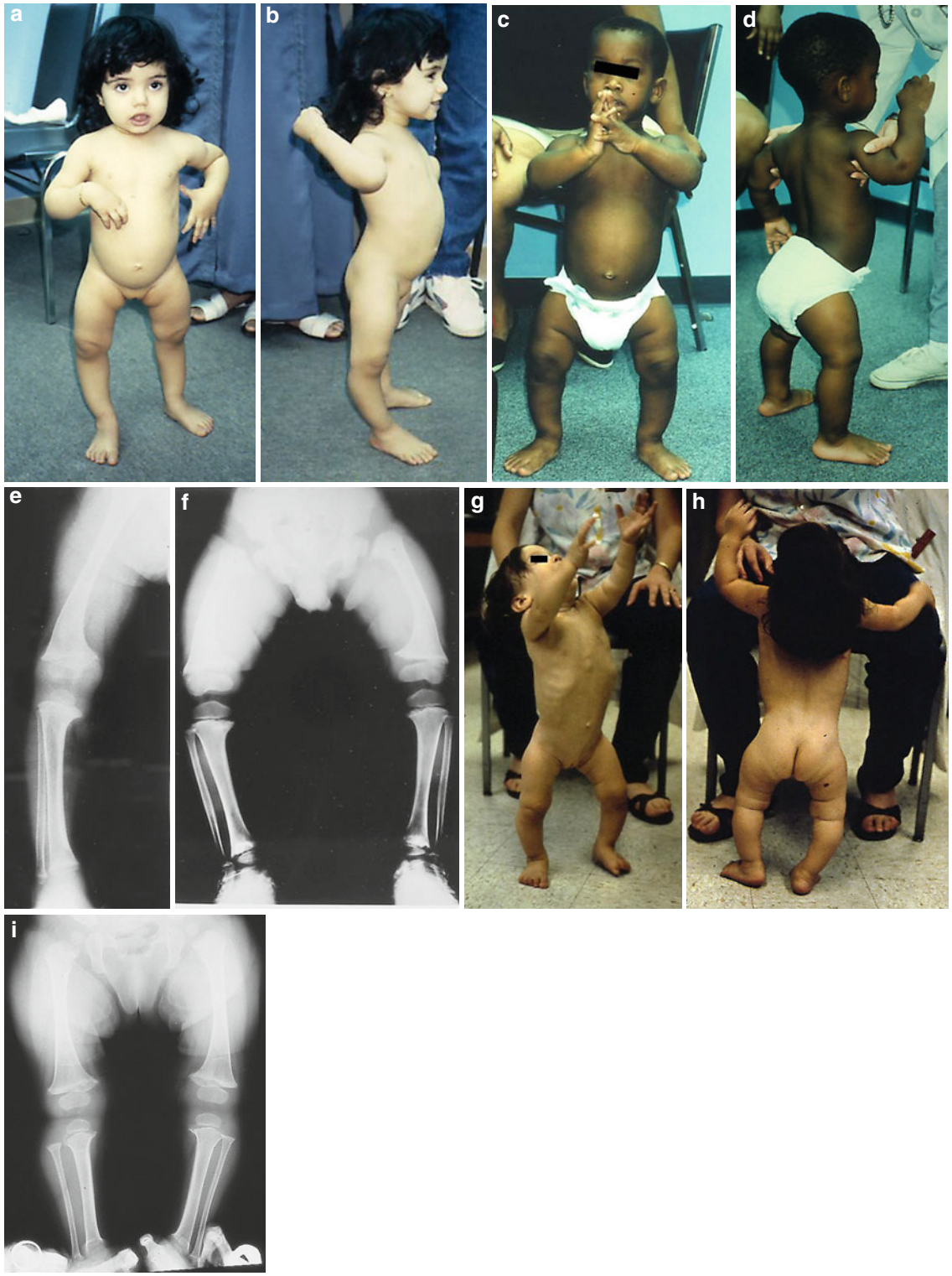

Fig. 1 (**a**–**i**) Three young children with Schmid metaphyseal chondrodysplasia showing short stature, lumbar lordosis, and bowing of the legs. Radiographs showed genu varum and metaphyseal widening with fraying and cupping. Epiphyses are normal

Seckel Syndrome

In 1960, Seckel reported 2 personal cases and 13 cases from the literature of a clinical condition characterized by severe intrauterine and postnatal proportionate dwarfism, severe microcephaly, "bird-headed" profile with receding forehead and chin, large and beaked nose, severe mental retardation, and other anomalies (Majewski and Goecke 1982). Seckel syndrome (SCKL) is a rare heterogeneous type of primordial dwarfism with frequency of less than 1 in 10,000 live births.

Synonyms and Related Disorders

Bird-headed dwarfism; Microcephalic primordial dwarfism; Nanocephalic dwarfism; Seckel-type dwarfism

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Genetic heterogeneity
   a. SCKL1: A gene for Seckel syndrome was mapped to human chromosome 3q22.1–q24 in two inbred Pakistani families originating from the same village (Driscoll 2003).
      i. The gene encoding ataxia-telangiectasia and Rad3-related protein (ATR) maps to the critical region to an interval of 5Mbp between markers D3S1316 and D3S1557.
      ii. A synonymous mutation in affected individuals was identified that alters *ATR* splicing.
      iii. The mutation confers a phenotype including marked microcephaly and dwarfism.
   b. SCKL2: Another gene locus was mapped to chromosome 18p11.31–q11.2 in one inbred Iraqi family (Børglum et al. 2001).
   c. SCKL3: A novel locus at 14q23 by linkage analysis in 13 Turkish families. The novel gene locus SCKL3 is 1.18 cM and harbors ménage a trios 1, a gene with a role in DNA repair (Kilinç et al. 2003).
   d. Caused by mutations of the pericentrin gene (*PCNT*) (mapped to 21q22.3) (Griffith et al. 2008; Rauch et al. 2008; Willems et al. 2009)
      i. The gene encodes cetrosomal protein which plays a key role in the organization of mitotic spindles.
      ii. The mutations also can cause microcephalic osteodysplastic primordial dwarfism type II.
   e. Mutations in *CENPJ*, a gene that has hitherto been linked to primary microcephaly only (Bond et al. 2005; Gul et al. 2006), also can cause Seckel syndrome (Al-Dosari et al. 2009).

Clinical Features

1. Broad interfamilial clinical heterogeneity (Arnold et al. 1999)
2. Growth
   a. Severe proportionate short stature of prenatal onset

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b. Severe postnatal growth deficiency
c. Intrauterine growth retardation
d. Low-birth-weight dwarfism
3. Mental retardation
4. Characteristic craniofacial features
a. Cranial manifestations
i. Severe microcephaly
ii. Premature closure of cranial sutures
b. Receding forehead
c. "Birdlike" face
d. Antimongoloid slant of palpebral fissures
e. Large eyes
f. Beak-like protrusion of the nose
g. Narrow face
h. Receding lower jaw (retrognathia)
i. Micrognathia
j. High-arched or cleft palate
k. Ears
i. Low set
ii. Hypoplastic lobules
l. Dental abnormalities
i. Enamel hypoplasia
ii. Missing permanent teeth
iii. Precocious eruption of teeth
iv. Microdontia
v. Malocclusion
vi. Taurodontism
m. "Dysplastic" ears
5. Associated anomalies
a. Ocular manifestations (Guirgis et al. 2001)
i. Severe myopia and astigmatism
ii. Severe, early onset, bilateral retinal degeneration
iii. Hypotelorism
iv. Bilateral ptosis
v. Microphthalmos
vi. Megacornea
vii. Glaucoma
viii. Retrolental membrane
ix. Macular coloboma
x. Optic hypoplasia
xi. Strabismus
xii. Lens dislocation
b. Skeletal defects
i. Premature closure of cranial sutures
ii. Dislocation of the radial head
iii. Clinodactyly of the 5th fingers
iv. Hip "dysplasia"/dislocation
v. Retardation of ossification
vi. Clubfoot
vii. Hypoplastic patella
viii. Scoliosis
c. CNS anomalies (Shanske et al. 1997)
i. Small cerebrum with simplified, ape-like convolutional pattern (pongidoid micrencephaly)
ii. Dysgenesis of cerebral cortex
iii. Agenesis of corpus callosum
iv. Cerebellar vermis hypoplasia
v. Dorsal cerebral cyst
vi. Arachnoid cyst
vii. Dilated ventricles
viii. Pachygyria
ix. Agyria
x. Intracranial aneurysms
d. Endocrine abnormalities
i. Pituitary gland abnormalities
a) Delayed development
b) Decreased adrenocorticotropic hormone production
c) Decreased growth hormone production
d) Absence of adenohypophysis
e) Hypophyseal hypoplasia
f) Precocious puberty
ii. Adrenal hypoplasia
iii. Hirsutism
e. Hematopoietic abnormalities
i. Acute myelogenous leukemia
ii. Refractory anemia with excess blasts
iii. Pancytopenia
iv. Fanconi anemia
f. Urogenital abnormalities
i. Males
a) Cryptorchidism
b) Hypoplasia of testis
ii. Females
a) Clitoromegaly
b) Hypoplasia of labia majora
g. Features of premature senility
i. Receding hair
ii. Redundant wrinkled skin on the palms
h. Miscellaneous findings
i. Congenital heart defects
a) Patent ductus arteriosus
b) Atrial septal defect
c) Ventricular septal defects
d) Atrioventricular canal defect
ii. Multiple intestinal atresia

6. Seckel-like syndromes (Majewski and Goecke 1982; Arnold et al. 1999)
   a. Microcephalic osteodysplastic primordial dwarfism type I
      i. Distinguished from Seckel syndrome by:
         a) Broad, low "dysplastic" pelvis with poor development of the acetabula
         b) Disproportionately short, broad bowing of humeri and femora with rather unremarkable metaphysis
         c) Agenesis of the corpus callosum and lissencephaly have also been noted.
      ii. Classified as Seckel syndrome by Majewski and Goecke (1982)
   b. Microcephalic osteodysplastic primordial dwarfism type II: differences from the Seckel syndrome include the following (mainly based on X-ray features):
      i. Short limbs with preferential distal involvement (disproportionate shortness of forearms and legs) in the first years of life
      ii. Brachymesophalangy
      iii. Brachymetacarpy I
      iv. Coxa vara
      v. Epiphysiolysis
      vi. Metaphyseal flaring with V-shaped distal femoral metaphyses
   c. Microcephalic osteodysplastic primordial dwarfism type III
      i. Alopecia
      ii. Seckel-like features
         a) Intrauterine growth retardation
         b) Microcephaly
         c) Receding forehead and chin
         d) Large ears
         e) Large prominent nose
         f) Platyspondyly
         g) Long dysplastic clavicles
         h) Hypoplasia of iliac wing and acetabula
         i) Broad femora
      iii. Currently considered to be the same entity as type I (Meinecke et al. 1991)
   d. A variant of osteodysplastic bird-headed dwarfism described by Bangstad et al. (1989)
      i. Progressive ataxia
      ii. Primary gonadal insufficiency
      iii. Endocrine abnormalities
         a) Insulin-resistant diabetes mellitus
         b) Goiter
      e. Chromosome abnormalities
         i. Chromosome instability/breakage (Bobabilla-Morales et al. 2003)
         ii. Deletion 1q22–q24.3
         iii. Interstitial deletion 2q33.3–q34 (Courtens et al. 1997)
         iv. Ring chromosome 4 mosaicism (Anderson et al. 1997)

Diagnostic Investigations

1. Hematological workup indicated in selected patients
   a. Anemia
   b. Pancytopenia
   c. Acute myeloid leukemia
2. Endocrine workup for pituitary and adrenal dysfunction
3. Radiography
   a. Microcephaly with a rather steeply sloping base of the skull
   b. Premature closure of the cranial sutures
   c. Delayed bone age
   d. Hip dysplasia
   e. Elbow dislocation
   f. Dislocation of the radial head
   g. Ivory epiphyses (dense sclerotic areas in the phalanges)
   h. Cone-shaped epiphyses
   i. Disharmonic bone development
      i. Hypoplasia of proximal radii and fibulae
      ii. Absence of epiphyseal ossification centers in fingers and toes
4. Neuropathology and CT/MRI of the brain
   a. Microcephaly
   b. Neuroglial ectopia
   c. Agenesis of the corpus callosum
   d. Micropolygyria
   e. Disproportion of the cerebrum and cerebellum
   f. Dysgenetic cerebral cortex
   g. Hypoplasia of the cerebellar vermis
   h. Dorsal cerebral cyst
5. Growth plate histology
   a. Normal column formation
   b. No structural abnormality of chondrocytes
   c. Decrease in cellularity of chondrocytes

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not likely to have offspring due to severe mental retardation
2. Prenatal diagnosis possible by serial ultrasonography for families at risk for Seckel syndrome
   a. Severe intrauterine growth retardation
   b. Craniofacial abnormalities
      i. Microcephaly
      ii. Receding forehead
      iii. A prominent nose
      iv. Severe micrognathia
   c. Short limbs
3. Management
   a. Symptomatic
   b. Psychosocial support for mental retardation
   c. Dental cares
   d. Orthopedic cares
   e. Treatments for hematological abnormalities

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Fig. 1 (**a**–**c**) A girl with Seckel syndrome showing marked short stature, severe microcephaly, sloping forehead, "bird-headed" face, large eyes, beaked nose, and severe retro/micrognathia

Fig. 2 (**a**–**b**) Two adults with Seckel syndrome showing severe short stature, mental retardation, extreme microcephaly, sloping forehead, a beaked nose, and retro/micrognathia

Severe Combined Immune Deficiency

Severe combined immune deficiency (SCID) is a fatal, heterogeneous group of immune disorder, characterized by T-cell lymphopenia, a profound lack of cellular (T-cell) and humoral (B-cell) immunity, and, in some cases, decreased NK-cell number and function. All infants with SCID develop infections from both common and opportunistic pathogens because protection from maternal antibodies wanes early in life (Buckley et al. 1997; Friedrich et al. 2007). The incidence of SCID is estimated to be 1/100,000 live births, but this may be an underestimate due to some children dying before diagnosis or having unrecognized less severe disease (Stephan et al. 1993; Chan and Puck 2005; McGhee et al. 2005).

Synonyms and Related Disorders

Autosomal recessive SCID (Swiss-type agammaglobulinemia); Bare lymphocyte syndrome; Interleukin (IL)-2 deficient SCID; Janus-associated kinase 3 (JAK3) deficient SCID; Omenn syndrome; Purine nucleoside phosphorylase (PNP) deficient SCID; Reticular dysgenesis; SCID; X-linked SCID; ZAP-70 protein tyrosine kinase (PTK) deficient SCID

Genetics/Basic Defects

1. A heterogeneous syndrome of varied genetic origins (Secord 2009)
   a. X-linked type SCID (X-SCID)
      i. The most common type (50% of all patients with SCIDs), characterized by the absence of the cytokine receptor common γ chain
      ii. A combined cellular and humoral immunodeficiency resulting from lack of T and natural killer (NK) lymphocytes and nonfunctional B lymphocytes
      iii. Caused by a mutation in the X-linked gene *IL2RG*, which encodes the common γ chain, γc (mapped on Xq13), of the leukocyte receptors for interleukin-2 and multiple other cytokines (Fanos et al. 2001)
         a) Significant frequency of de novo mutations accounting for one third of the cases
         b) Occurrence of maternal germ line mosaicism
      iv. Atypical X-SCID: less frequently seen in patients with mutations that result in production of a small amount of gene product or a protein with residual activity
   b. Autosomal recessive type SCID
      i. Formerly known as Swiss-type agammaglobulinemia
      ii. Causes
         a) Adenosine deaminase deficiency (10–20% of all cases of SCID): the *ADA* gene mapped on chromosome 20q13.11 (Arredondo-Vega et al. 1998)
         b) Purine nucleoside phosphorylase (PNP) deficiency: the *PNP* gene mapped on 14q13
         c) Janus-associated kinase 3 (JAK3) deficiency causing autosomal recessive T-B + SCID: the JAK3 gene mapped on 19p13
         d) Interleukin (IL)-2 deficiency
         e) ZAP-70 protein tyrosine kinase (PTK) deficiency: ZAP-70 mapped on 2q12

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f) Bare lymphocyte syndrome
g) Reticular dysgenesis
h) Omenn syndrome

2. Pathophysiology
   a. Varies among various forms of SCID
   b. Common end point in all forms of SCID
      i. Lack of T-cell function
      ii. Lack of B-cell function
   c. Cellular hallmarks differentiating various forms of SCID
      i. X-linked SCID
         a) Absence or near absence of T cells ($CD3^+$) and natural killer (NK) cells leading to lymphopenia
         b) Variable levels of B cells that produce no functional antibodies
      ii. JAK3 deficiency
         a) Absence or near absence of T cells ($CD3^+$) and natural killer (NK) cells leading to lymphopenia
         b) Normal or high levels of B cells that produce no functional antibodies
      iii. ADA deficiency
         a) Death of T and B cells secondary to the accumulation of toxic metabolites in the purine salvage pathway leading to lymphopenia
         b) Decreased or absence of functional antibodies
      iv. PNP deficiency
         a) Death of T cells secondary to the accumulation of toxic metabolites in the purine salvage pathway leading to lymphopenia
         b) Normal number of circulating B cells with poor B-cell function, evidenced by the lack of antibody formation
      v. IL-2 deficiency
         a) Normal or near normal numbers of T cells (both $CD4^+$ and $CD8^+$)
         b) Decreased production of functional antibody
      vi. ZAP-70 PTK deficiency
         a) Absence of $CD8^+$ T cells leading to lymphopenia
         b) No antibody formation
      vii. Bare lymphocyte syndrome
         a) Normal or mildly reduced lymphocyte count
         b) Decreased $CD4^+$ T cells
         c) Normal or mildly increased $CD8^+$ T-cell numbers
         d) Normal or mildly decreased B-cell numbers with decreased antibody production
      viii. Reticular dysgenesis
         a) Absence of myeloid cells in the bone marrow leading to lymphopenia
         b) Presence of functioning red blood cells and platelets
      ix. Omenn syndrome
         a) Presence of normal or elevated T-cell numbers of maternal origin
         b) Usually undetectable B cells
         c) Presence of NK cells
         d) Markedly low total immunoglobulin level with poor antibody production
         e) Elevated eosinophils and total serum immunoglobulin E (IgE) level

3. Molecular defects
   a. X-linked SCID
      i. Mutation of the common gamma chain of the IL receptors (IL-2R, IL-4R, IL-7R, IL-9R, IL-15R) resulting in loss of cytokine function (Cavazzana-Calvo et al. 2000)
      ii. Loss of IL-2R function leading to the loss of a lymphocyte proliferation signal
      iii. Loss of IL-4R function leading to the inability of B cells to class switch
      iv. Loss of IL-7R function leading to the loss of an antiapoptotic signal resulting in a loss of T-cell selection in the thymus and also associated with the loss of a T-cell receptor
      v. Loss of IL-15R function leading to the ablation of NK cell development
   b. JAK3 deficiency
      i. JAK, a protein tyrosine kinase that associates with the common gamma chain of the IL receptors
      ii. Deficiency of JAK3 resulting in the same clinical manifestations as those of X-linked SCID
   c. ADA and PNP deficiencies
      i. Associated with enzyme deficiencies in the purine salvage pathway
      ii. Toxic metabolites responsible for the destruction of lymphocytes that cause the immune deficiency

d. IL-2 deficiency
   i. Molecular defect unknown
   ii. Often associated with other cytokine production defects
e. ZAP-70 PTK deficiency: caused by a mutation in the gene coding for this tyrosine kinase, which is important in T-cell signaling and is critical in positive and negative selection of T cells in the thymus
f. Bare lymphocyte syndrome
   i. Deficiency of major histocompatibility complex (MHC)
   ii. Absent or decreased MHC type I levels
   iii. Decreased MHC type II levels on mononuclear cells
g. Omenn syndrome: believed to be caused by a mutation impairing the function of immunoglobulin and TCR recombinase genes, such as *RAG1* and *RAG2* genes

Clinical Features

1. Age of onset: 3–6 months of life
2. Usual presentation with infections due to lack of T-cell function
   a. Opportunistic organisms
      i. *Pneumocystis carinii* pneumonia
      ii. Systemic candidiasis
      iii. Atypical mycobacterium
      iv. Cryptosporidium
      v. Pneumococcus
   b. Recurrent infections
   c. Persistence of infections despite conventional treatment
3. Failure to thrive
4. Oral or diaper candidiasis
5. Dehydration from chronic diarrhea
6. Fevers
7. Rashes
8. Cough and congestion
9. Increased respiratory rate and effort
10. Absence of tonsils and lymph nodes
11. Absence of lymphadenopathy or increased tonsillar tissue despite serious infections
12. Pneumonias
13. Sepsis
14. Disseminated infections
   a. Salmonella
   b. Varicella
   c. Cytomegalovirus
   d. Epstein-Barr virus
   e. Herpes simplex virus
   f. BCG
   g. Vaccine strain (live) polio virus
15. Recurrent sinopulmonary infections
16. Recurrent skin infections
17. Abscesses
18. Poor wound healing
19. Transplacental transfer of maternal lymphocytes to the infant prenatally or during parturition causing graft-vs-host disease (GVHD), characterized by
   a. Erythematous skin rashes
   b. Hepatomegaly
   c. Lymphadenopathy
20. ADA deficiency and PNP deficiency with later onset and milder or atypical clinical presentation
   a. Diagnosis suspected in patients with
      i. Unexplained T-cell lymphopenia
      ii. Late manifestations of immunodeficiency
         a) Chronic pulmonary insufficiency
         b) History of autoimmunity and neurologic abnormalities
         c) Onset during the first two decades of life and even later
   b. Diagnosis confirmed by finding absent or very low enzyme activity in erythrocytes or in nucleated blood cells
21. Lymphadenopathy or hepatosplenomegaly in Omenn syndrome or bare lymphocyte syndrome
22. Prognosis
   a. Fatal if untreated
   b. Bone marrow transplantation or enzyme replacement to reconstitute the immune system compatible with long survival

Diagnostic Investigations

1. Newborn screening (Adeli and Buckley 2010; Lipstein et al. 2010; Secord 2009)
   a. Newborn screening would not only make the diagnosis at birth but would lead to measures to protect infants from becoming infected before they could receive a transplant.
   b. Newborn screening would also reveal the true incidence of SCID and define the range of conditions characterized by severely impaired T-cell development.

c. Evidence indicates the benefits of early treatment of SCID and the possibility of population-based newborn screening.
d. Better information on optimal treatment and the costs of treatment and screening would benefit policy makers deciding among competing health care priorities.

2. Laboratory workup
   a. X-SCID (Davis and Puck 2005)
      i. Lymphocyte count
         a) Usually very low number of T cells
         b) B cells generally present, but nonfunctional
         c) Low or absent number of NK cells
         d) Typical X-SCID designated as $T^{-}B^{+}NK^{-}$
      ii. Lymphocyte functional tests
         a) Absent antibody responses to vaccines and infections agents
         b) Lacking T-cell responses to mitogens
      iii. Immunoglobulin concentrations
         a) Low serum concentrations of IgA and IgM
         b) IgG generally normal at birth but declines as maternally transferred IgG disappears by 3 months of age
      iv. Thymus: absent thymic shadow on chest radiogram
      v. Molecular genetic testing clinically available: *IL2RF* is the only gene known to be associated with X-SCID.
         a) Sequence analysis
         b) Targeted mutation analysis
   b. Adenosine deaminase deficiency (Hershfield 2009)
      i. Immune function
         a) Lymphopenia, the laboratory hallmark of ADA-deficient SCID, is present at birth. The total blood lymphocyte count is usually lower than 500/μL (normal for neonates: 2,000 to >5,000).
         b) All lymphoid lineages (T-, B-, and NK-cells) are depleted as demonstrated by flow cytometry.
         c) Lower or absent in vitro lymphocyte function, as measured by proliferative response to mitogens and antigens
         d) Low serum immunoglobulins and absence of specific antibody response to infections and immunizations
      ii. Adenosine deaminase (ADA) catalytic activity
         a) Affected individuals who have not been transfused have less than 1% of normal ADA catalytic activity in erythrocyte hemolysates.
         b) Affected individuals who have been recently transfused may require testing of another cell type, such as fibroblasts or leukocytes.
      iii. Biochemical markers of ADA deficiency
         a) Elevated erythrocyte deaminate 2′-deoxyadenosine (dAdo) nucleotides (dAXP): pathognomonic
         b) Reduced erythrocyte S-adenosylhomocysteine hydrolase (AdoHcyase, SAHase) activity (<5% of normal)
         c) Markedly elevated urinary excretion of dAdo
      iv. Molecular genetic testing: *ADA* is the only gene associated with ADA deficiency.
         a) Sequence analysis
         b) Deletion/duplication analysis
   c. ZAP70-related SCID (Capece and Nash 2009)
      i. Lymphocyte counts
         a) T-cell counts: absent or very low CD8+ cells, normal or elevated CD4+ cells, and normal CD3+ cells
         b) B-cell counts: normal B cells and NK cells
      ii. Lymphocyte function
         a) Absence of proliferation of CD4+ cells in response to mitogens (e.g., PHA)
         b) Absence of proliferation of CD4+ cells in response to antigens (e.g., ConA)
         c) Defective $CD4^{+}$ cell-cell activation manifests as impaired Ca^{2+} flux in response to CD3 (OKT3) stimulation.
      iii. ZAP-70 protein expression: absence of ZAP-70 protein in most cases by immunocytochemistry testing of CD4+ T cells
      iv. Immunoglobulin concentrations and function
         a) Severe hypogammaglobulinemia in a majority of affected individuals but normal immunoglobulin levels have been seen
         b) Although functional antibody responses to immunization are present in a few persons, this finding does not indicate that all specific antigenic responses are intact.

v. Molecular genetic testing: Sequence analysis of the *ZAP70* coding region detects missense and nonsense mutations, splice and regulatory region mutations, and insertion mutations.

d. Autosomal recessive SCID (T-B-NK+. *RAG1*/*RAG2*-related): molecular genetic testing of *RAG1*/*RAG2* gene available clinically by sequence analysis or deletion/duplication analysis

3. Chest X-ray
   a. Absent to small thymus shadow
   b. Pneumonia
   c. Typical cupping and flaring of the costochondral junction in patients with ADA deficiency
4. Lymph node biopsy
   a. Paucity of T and B cells
   b. Lack of germinal centers
5. Consider X-SCID in male infants with
   a. Severe recurrent or persistent infections
   b. Infections not responding to ordinary treatment
   c. Infections caused by opportunistic pathogens
   d. Failure to thrive
6. Carrier testing of X-SCID
   a. Testing for known family-specific *IL2RG* mutations
   b. Sequence analysis of the *IL2RG* coding region and splice regions
   c. Southern blot analysis is used to detect large deletions and complex mutations if the family-specific mutation is not known and sequence analysis is uninformative.
   d. X-chromosome inactivation studies on lymphocytes for at-risk females in whom sequence analysis and/or mutation analysis are not an option for carrier testing or are not informative, provided presence of the following two conditions:
      i. Skewed X-chromosome inactivation in lymphocytes
      ii. Non-skewed X-chromosome inactivation in another blood lineage such as granulocytes

Genetic Counseling

1. Recurrence risk
   a. X-SCID
      i. Female germ line mosaicism present if a woman has more than one affected son and the disease-causing mutation in the *IL2RG* gene cannot be detected in her leukocytes
      ii. Over 50% of affected males do not have family history of early deaths in maternal male relatives.
      iii. Patient's sib if the mother is a carrier
         a) Fifty percent of male sibs affected
         b) Fifty percent of female sibs carriers
      iv. Patient's sib is still at increased risk even if the disease-causing mutation has not been identified in the mother's leukocytes since germ line mosaicism has been demonstrated in this condition.
      v. Patient's offspring (offspring of affected males)
         a) Hundred percent of daughters carriers
         b) None of sons affected
   b. Autosomal recessive SCID
      i. Patient's sib: 25%
      ii. Patient's offspring: not increased unless the spouse is a carrier in which case 25% of the offspring will be affected
2. Prenatal diagnosis
   a. X-SCID
      i. Determination on fetal cells obtained by CVS or amniocentesis
      ii. Analysis of DNA from fetal cells for the known disease-causing mutation, provided
         a) Karyotype revealing 46,XY
         b) The disease-causing *IL2RG* mutation has been identified in a family member.
      iii. Fetal blood sampling for immunological evaluation when the family-specific mutation is not known
         a) Lymphocytopenia
         b) Low numbers of T cells
         c) Poor T-cell blastogenic responses to mitogens
   b. Autosomal recessive SCID
      i. JAK3-deficient SCID (Schumacher et al. 1999)
         a) Immunophenotypic evaluation of cord blood cells at 18–20 weeks of gestation
         b) Direct gene analysis using chorionic villus sampling derived DNA in the first trimester
      ii. ADA deficiency
         a) Prenatal diagnosis established by measuring ADA enzyme activity in amniotic cells or chorionic villi (Aitken et al. 1986)
         b) Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the

disease-causing mutations in the family (Hershfield 2009).

3. Management (Secord 2009)
   a. X-linked SCID and JAK3 PTK deficiency
      i. Fatal disease unless cured by bone marrow transplantation (BMT)
         a) The best results achieved by using an HLA-matched sibling as a donor (success rates of 97%)
         b) Using haploidentical T-cell-depleted BMT from a parent (haploidentical family donors resulting in lower success rates of 52%): lifesaving for the majority of X-SCID patients who lack matched sibling
      ii. Monthly intravenous immunoglobulin replacement therapy required if B cells do not engraft
      iii. Report of in utero transplantation of hematopoietic progenitor cells allowing immune reconstitution in a fetus
      iv. Gene therapy (Hacein-Bey-Abina et al. 2010)
         a) Using autologous bone marrow stem/progenitor cells retrovirally transduced with a therapeutic gene
         b) Successful in reconstituting the immune system in patients with X-SCID
         c) Youngest two of the first ten infants treated in a French study developed leukemia due to retroviral insertional mutagenesis.
         d) After nearly 10 years of follow-up, gene therapy was shown to have corrected the immunodeficiency associated with SCID-X1. Gene therapy may be an option for patients who do not have an HLA-identical donor for hematopoietic stem-cell transplantation and for whom the risks are deemed acceptable. This treatment is associated with a risk of acute leukemia.
   b. ADA deficiency
      i. Usually fatal unless
         a) Keeping affected children in protective isolation, or
         b) Reconstituting the immune system by bone marrow transplantation from a human leukocyte antigen (HLA)-identical sibling donor (therapy of choice but only available for a minority of patients)
      ii. Exogenous enzyme replacement primarily with polyethylene glycol-conjugated ADA (PEG-ADA) replacement therapy (Blaese et al. 1995)
         a) Providing noncurative, life-saving treatment for ADA-SCID patients
         b) Increased peripheral T-cell counts providing a source of T cells for gene correction not available without enzyme therapy
         c) Weight gain and decreased opportunistic infections in most patients
         d) Improved T-cell function as measured by in vitro mitogen responses in most patients
         e) Recovery of consistent immune responses to specific antigens in fewer patients
      iii. The first genetic disorder treated by gene therapy: a clinical trial using retroviral-mediated transfer of the adenosine deaminase (*ADA*) gene into the T cells of children with ADA-SCID
         a) Normalization of the number of blood T cells as well as many cellular and humoral immune responses
         b) Successful gene transfer into long-lasting progenitor cells, producing a functional multilineage progeny (Bordignon et al. 1995)
         c) Safe and effective addition to treatment for some patients
      iv. Combined treatment with PEG-ADA and gene therapy
   c. PNP deficiency and bare lymphocyte syndrome: primarily with bone marrow transplantation when an appropriate donor is available
   d. IL-2 production defects
      i. Primarily with intravenous IL-2 replacement
      ii. Alternatively with bone marrow transplantation when an appropriate donor is available
   e. Omenn syndrome
      i. Primarily with bone marrow transplantation when an appropriate donor is available
      ii. Pretreatment ablative chemotherapy necessary because of maternal cell engraftment
   f. Bone marrow transplantation from a related donor: a life-saving and life-sustaining treatment for patients with any type of severe combined immune deficiency, even when there is no HLA-identical donor

g. Two fetuses successfully treated with gene therapy in utero by an injection of haploidentical $CD34^+$ cells for the γ chain deficiency
h. Psychosocial support for the affected family
i. Avoid live vaccines

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Fig. 1 A healthy 9-year-old boy with ADA-deficient SCID who has been receiving biweekly Adagen (pegademase) injections since early infancy

Short Rib–Polydactyly Syndromes

Short rib–polydactyly syndromes (SRPS) are a heterogeneous group of recessively inherited lethal skeletal dysplasia. There are four classic subtypes: type I (Saldino–Noonan) (SRPS I), type II (Majewski) (SRPS II), type III (Verma–Naumoff) (SRPS III), and type IV (Beemer–Langer) (SRPS IV).

Synonyms and Related Disorders

SRPS I (Saldino-Noonan syndrome, polydactyly with neonatal chondrodystrophy type I); SRPS II (Majewski syndrome, polydactyly with neonatal chonddrodystrophy type II); SRPS III (Verma-Naumoff syndrome, polydactyly with neonatal chondrodystrophy type III); SRPS IV (Beemer-Langer syndrome, short rib syndrome, Beemer type)

Genetics/Basic Defects

1. Inheritance: autosomal recessive in all four subtypes
2. Different subtypes of SRPS
   a. A great overlap of anomalies present among different subtypes contributing to diagnostic dilemmas in the short rib–polydactyly syndrome group
   b. Possibly represent a continuous spectrum with variable expressivity, suggested by some reports
3. Ciliary abnormalities due to defects in the retrograde transport protein DYNC2H1 in short rib–polydactyly syndrome (Merrill et al. 2009)
   a. Homozygosity by descent mapping in a consanguineous SRPS family identified a genomic region that contained *DYNC2H1*, a cytoplasmic dynein involved in retrograde transport in the cilium. Affected individuals in the family were homozygous for an exon 12 missense mutation that predicted the amino acid substitution R587C.
   b. Compound heterozygosity for one missense and one null mutation was identified in two additional nonconsanguineous SRPS families.
   c. Cultured chondrocytes from affected individuals showed morphologically abnormal, shortened cilia. In addition, the chondrocytes showed abnormal cytoskeletal microtubule architecture, implicating an altered microtubule network as part of the disease process.
   d. These findings establish SRPS as a cilia disorder and demonstrate that DYNC2H1 is essential for skeletogenesis and growth.
4. DYNC2H1 mutations also cause asphyxiating thoracic dystrophy: ATD and SRP type III are variants of a single disorder belonging to the ciliopathy group (Dagoneau et al. 2009)

Clinical Features

1. SRPS I (Saldino–Noonan)
   a. Constant findings
      i. Severely shortened (flipper-like) limbs with postaxial polydactyly
      ii. Small/narrow thorax with short ribs and hypoplastic lungs
      iii. Protuberant abdomen
      iv. Early neonatal death
   b. Common findings
      i. Hydrops fetalis
      ii. Gastrointestinal abnormalities

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a) Esophageal atresia
b) Short small intestine
c) Malrotation of the bowel
d) Imperforate anus
e) Persistent cloaca
f) Imperforate anus
g) Pancreatic fibrosis and cysts

iii. Cardiac malformations
a) Transposition of the great vessels
b) Coarctation of the aorta or hypoplastic aortic arch
c) Ventricular septal defects
d) Double-outlet left ventricle

c. Occasional findings
i. Oligohydramnios
ii. Renal dysplasia/cystic disease
iii. Abnormal genitalia
a) Cryptorchidism
b) Hypoplastic penis
iv. CNS malformations
a) Cerebellar hypoplasia
b) Dandy–Walker malformation
v. Bifid epiglottis
vi. Bifid tongue
vii. Cleft upper lip

2. SRPS II (Majewski)
a. Constant findings
i. Extremely short limbs with pre-/postaxial polydactyly of the hands and feet
ii. Small/narrow chest with short ribs and pulmonary hypoplasia
iii. Protuberant abdomen
iv. Median cleft lip or pseudocleft of the upper and lower lip or cleft palate
v. Epiglottis and larynx hypoplasia
vi. Short/ovoid tibias with round ends
vii. Presence of premature ossification centers
viii. Early neonatal death

b. Common findings
i. Polyhydramnios
ii. Hydrops fetalis
iii. Ocular hypertelorism
iv. Broad and flat nose
v. Low-set ears
vi. Ambiguous genitalia
vii. Renal cystic disease

c. Occasional findings
i. Short small intestine
ii. Malrotation of the bowel
iii. Cardiac malformations
iv. Dysplastic pancreas

3. SRPS III (Verma–Naumoff)
a. Constant findings
i. Severely shortened limbs with postaxial polydactyly
ii. Small/narrow thorax with short ribs and hypoplastic lungs
iii. Early neonatal death

b. Common findings
i. Hydrops fetalis
ii. Short cranial base
iii. Bulging forehead
iv. Depressed nasal bridge
v. Flat occiput
vi. Renal cystic dysplasia

c. Occasional findings
i. Congenital heart defects
a) Ventricular septal defect
b) Situs inversus
ii. Epiglottic hypoplasia
iii. Intestinal malrotation
iv. Cloacal developmental abnormalities and ambiguous genitalia

4. SRPS IV (Beemer–Langer)
a. Constant findings
i. Severely shortened limbs with or without postaxial polydactyly
ii. Small/narrow thorax with short ribs and hypoplastic lungs
iii. Early neonatal death

b. Common findings
i. Hydrops fetalis
ii. Macrocephaly with frontal bossing
iii. Ocular hypertelorism
iv. Flat nasal bridge
v. Cleft lip and palate
vi. Protuberant abdomen

c. Occasional findings
i. CNS abnormalities
a) Holoprosencephaly/absence of the corpus callosum/hydrocephalus
b) Dandy–Walker cyst and/or arachnoid cyst
c) Hypothalamic hamartomas
ii. Lobulated tongue with hamartomas

iii. Oral frenula
iv. Congenital heart defects
v. Malrotation of the intestine
vi. Renal malformations
  a) Renal cystic dysplasia
  b) Atresia of the ureter with hydronephrosis and hydroureter
vii. Omphalocele
viii. Inguinal hernia

Diagnostic Investigations

1. Radiography
   a. SRPS I (Saldino–Noonan)
      i. Extreme micromelia with severely dysplastic pointed (or ragged) metaphyses of the long tubular bones, and absence of corticomedullary demarcation
      ii. Narrow thorax with short/horizontal ribs
      iii. Deficient ossification in calvarium, vertebrae, pelvis, and bones of the hands and feet
      iv. Small iliac bones with horizontal acetabula
      v. Postaxial polydactyly
      vi. Short tibiae
   b. SRPS II (Majewski)
      i. Extreme micromelia with smooth rounded metaphyses
      ii. Extremely short horizontal ribs
      iii. Normal pelvis and vertebrae
      iv. Disproportionately shortened ovoid-shaped tibiae
      v. Pre- and postaxial polydactyly, syndactyly, and brachydactyly
      vi. Advanced skeletal ossification–advanced maturation of the proximal femora and humeri
   c. SRPS III (Verma–Naumoff)
      i. Extreme micromelia with severely dysplastic widened metaphyses (bones of the legs) and clear corticomedullary demarcation of the long tubular bones
      ii. Extremely shortened and horizontal ribs
      iii. Small and malformed vertebral bodies
      iv. Shortened cranial base
      v. Short iliac bones with horizontal trident lower margin
      vi. Polydactyly
   d. SRPS IV (Beemer–Langer)
      i. Extreme micromelia with smooth metaphyseal margins
      ii. Extremely shortened and horizontal ribs
      iii. Small, poorly ossified vertebrae and increased intervertebral spaces
      iv. High clavicles and small scapulae
      v. Small iliac bones
      vi. Bowed radii and ulnae
      vii. Tibiae: well tabulated and longer than fibulae
      viii. Postaxial polydactyly
2. Histopathology/necropsy
   a. SRPS I (Saldino–Noonan)
      i. Markedly retarded and frequently deranged endochondral ossification. A large island of fibrous tissue may occupy the center of physeal growth zone. A premature ossification center may be seen in the epiphyseal resting cartilage.
      ii. Lungs: hypoplasia which is easily assessed by abnormally small size and low weight
      iii. Identify associated multiple congenital anomalies listed in the clinical features
   b. SRPS II (Majewski)
      i. Markedly retarded endochondral ossification. The chondrocytes in the physeal growth zones are markedly reduced in number and disorderly arranged
      ii. Lungs: hypoplasia as in type I
      iii. Identify associated multiple congenital anomalies listed in the clinical features.
   c. SRPS III (Verma–Naumoff)
      i. Markedly retarded endochondral ossification as in type II. A single patient showed chondrocytic inclusions which are PAS reactive and diastase resistant.
      ii. Lung: hypoplasia as in type I
      iii. Identify associated multiple congenital anomalies which are less common in this type.
   d. SRPS IV (Beemer–Langer)
      i. Physeal growth zones showing a prominent but disorganized zone of hypertrophy. The vascular penetration of physeal cartilage is irregular.
      ii. Lungs: hypoplasia as in type I
      iii. Identify associated multiple congenital anomalies listed in the clinical features.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: The patients will not survive to reproductive age.
2. Prenatal diagnosis: not always possible to differentiate the subtypes
   a. Ultrasonography for SRPS I (Saldino–Noonan)
      i. Short fetal limbs
      ii. Narrow thorax
      iii. Polydactyly
      iv. Pointed metaphyses
      v. Dysplastic cystic kidneys
      vi. Congenital heart defect
      vii. Genital anomalies
   b. Ultrasonography for SRPS II (Majewski)
      i. With a positive family history of Majewski syndrome
         a) Presence of short fetal limbs
         b) Other skeletal findings
      ii. Without a family history
         a) Short fetal limbs
         b) Disproportionately short tibia
         c) Very narrow fetal chest
         d) Short ribs
         e) Bilateral postaxial polydactyly of the hands and feet
         f) Median cleft lip and palate
         g) Polyhydramnios
         h) Hydrops
         i) Marked shortened humerus and femur
         j) Severe bowing and deformity of the bones of the lower leg and forearm
         k) Hypoplastic lungs
         l) Congenital heart defect
         m) Enlarged echogenic kidneys
         n) Genital anomalies
   c. Ultrasonography for SRPS III (Verma–Naumoff)
      i. Short fetal limbs
      ii. Small/narrow thorax
      iii. Short thin ribs
      iv. Polydactyly
      v. Widened metaphyses with marginal spurs
      vi. Micromelia
   d. Ultrasonography for SRPS IV (Beemer–Langer)
      i. Short fetal bones
      ii. Small/narrow thorax
      iii. Short thin ribs
      iv. Polydactyly
   e. Fetoscopy
      i. To identify fetus with SRPS phenotype
      ii. An invasive procedure currently replaced by ultrasonography
3. Management: supportive therapy only for these lethal entities

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Fig. 1 (**a**, **b**) Radiograph of a neonate with Saldino–Noonan syndrome (SRPS I) showing extremely shortened horizontal ribs, very small and dysplastic vertebral bodies and iliac cones, and very short tubular bones with irregular metaphyses

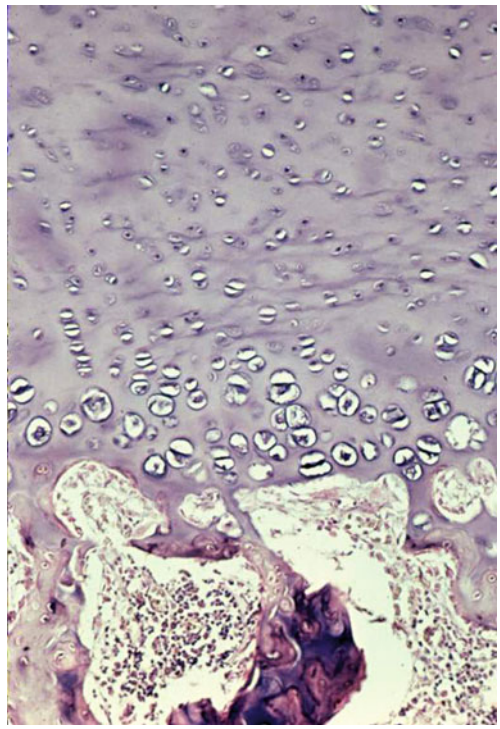

Fig. 2 Photomicrograph of femur (SRPS I) shows markedly retarded and disorganized physeal growth zone

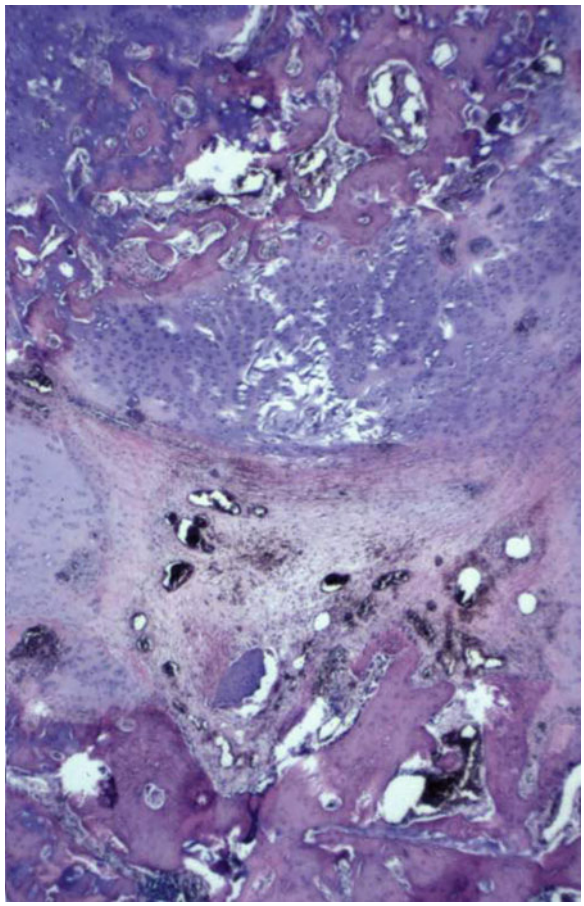

Fig. 3 Photomicrograph of humerus (SRPS I) shows markedly disrupted physeal growth zone by a large cartilage canal-like vascular fibrous tissue. In addition, there is a large premature ossification center (*upper* one third of the picture)

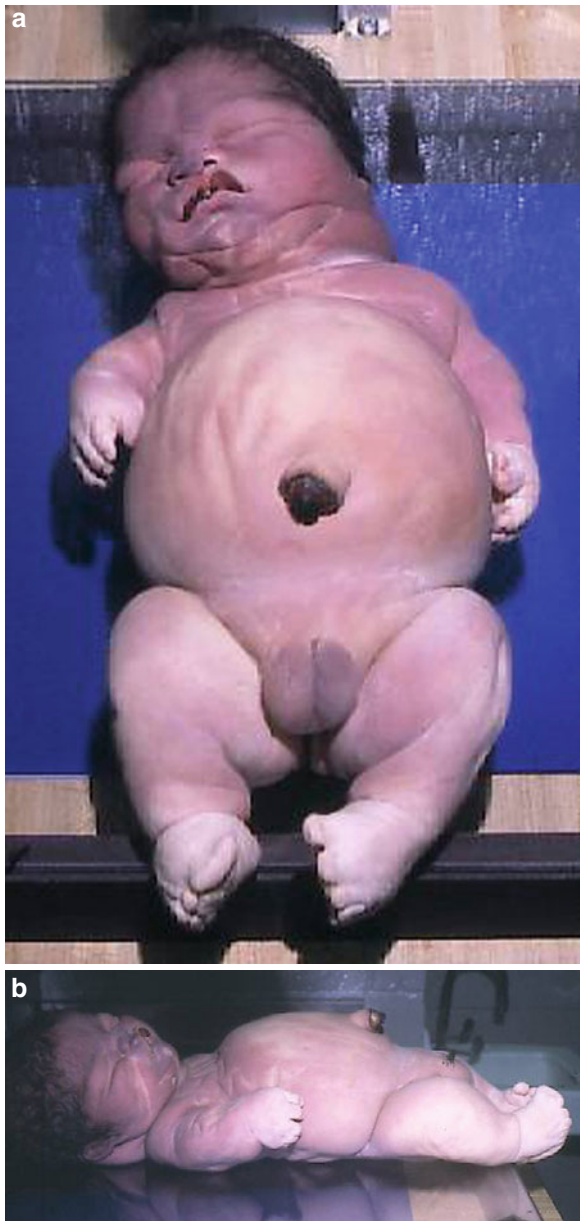

Fig. 4 (**a**, **b**) A neonate with Majewski syndrome (SRPS II) showed hydrops; a large head; hairy forehead; small, malformed, and low-set ears; telecanthus; short nose; a flat nasal bridge; a central cleft of upper and lower lips; short neck; short and narrow chest; markedly distended abdomen with ascites; and extremely short limbs with pre- and postaxial polydactyly, syndactyly, and brachydactyly

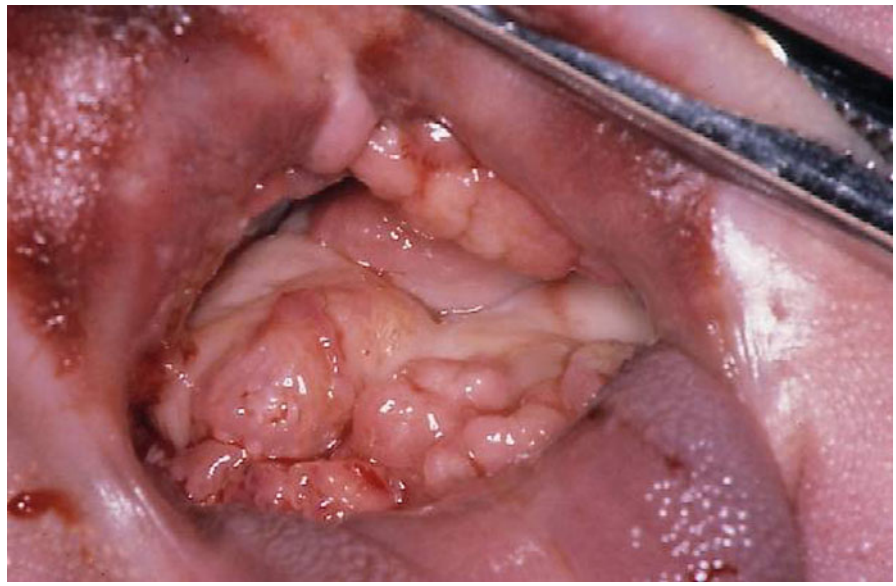

Fig. 5 Mouth of the neonate in Fig. 3 showing lobulated tongue and mucosal frenula

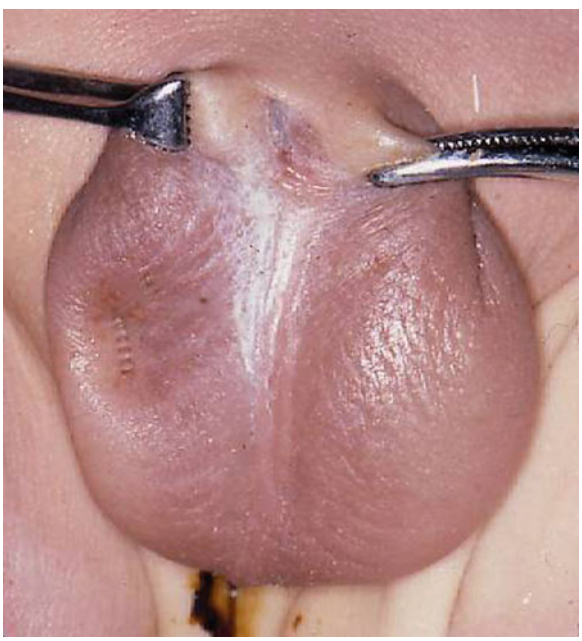

Fig. 6 Ambiguous genitalia with a barely visible micropenis (SRPS II)

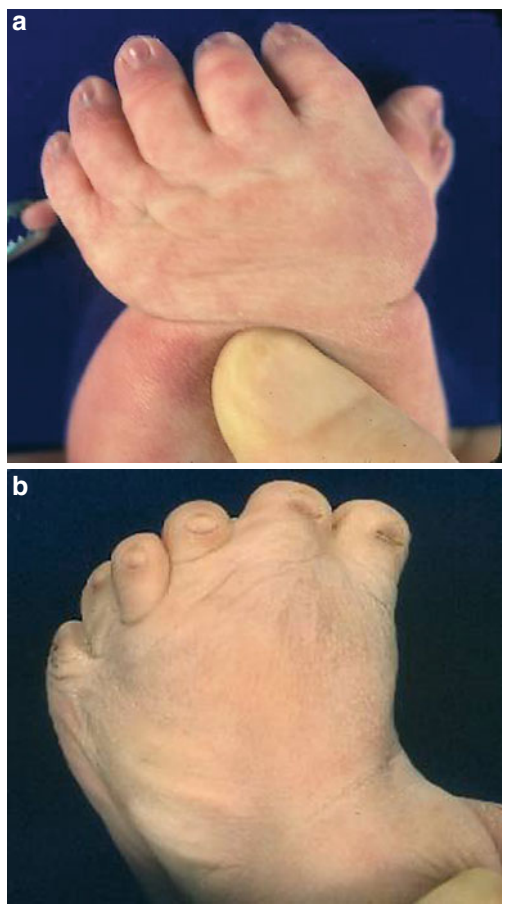

Fig. 7 (**a**, **b**) Hands and feet showed pre- and postaxial polydactyly, syndactyly, and brachydactyly (SRPS II)

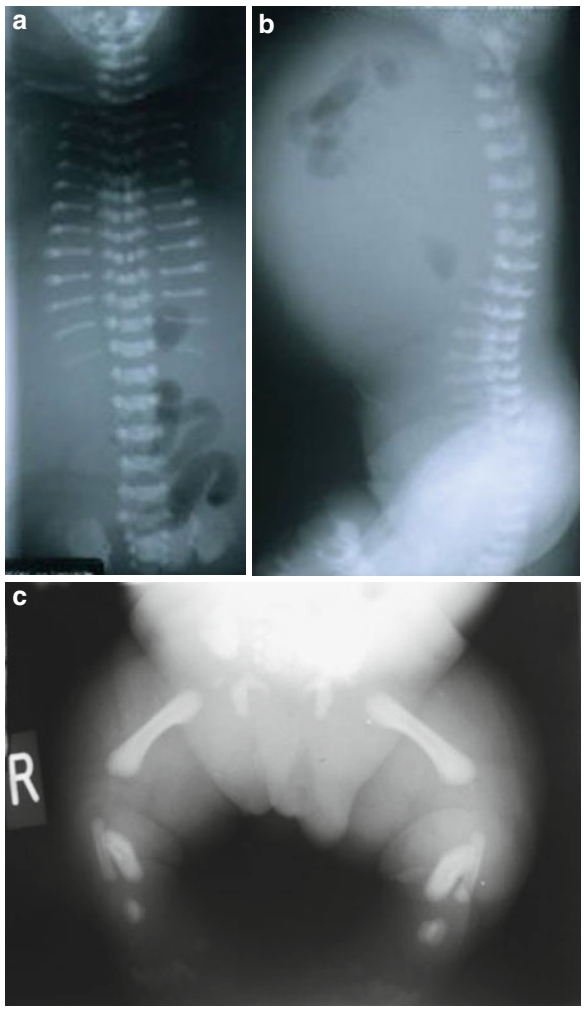

Fig. 8 (**a**–**c**) Radiographs (SRPS II) showing extremely short and horizontal ribs, high clavicles, unremarkable spine and pelvis, and premature ossification of the proximal epiphyses of the humeri, femora, and lateral cuboids. The tubular bones were extremely short, especially the mesomelic segments. The tibiae were disproportionately short and oval in shape

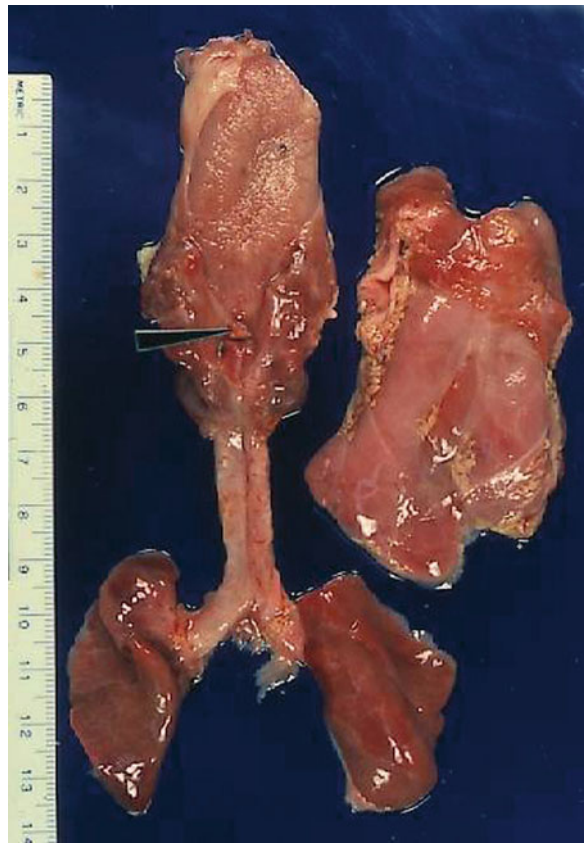

Fig. 9 Respiratory system (necropsy) (SRPS II) showing a small larynx with hypoplastic epiglottis (*arrow*) and remarkably small and hypoplastic lungs. The patient's thymus is juxtaposed for comparison

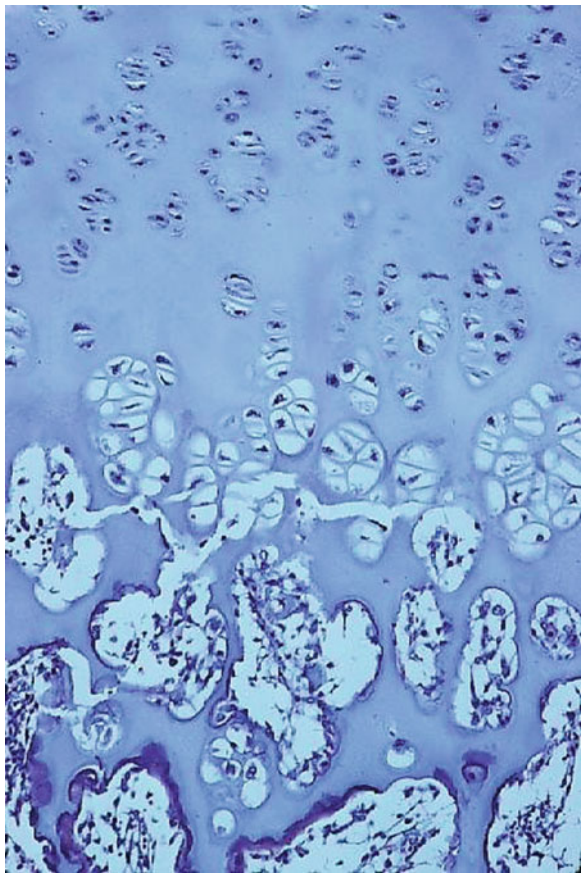

Fig. 10 Photomicrograph of tibia cartilage (SRPS II) (Hematoxylin-eosin, ×108) showing a markedly stunted and disorganized physeal growth zone

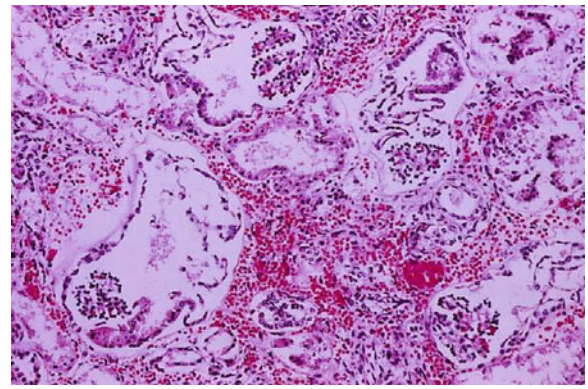

Fig. 11 Photomicrograph of renal cortex showing many dilated glomeruli and mildly cystic renal tubules (SRPS II)

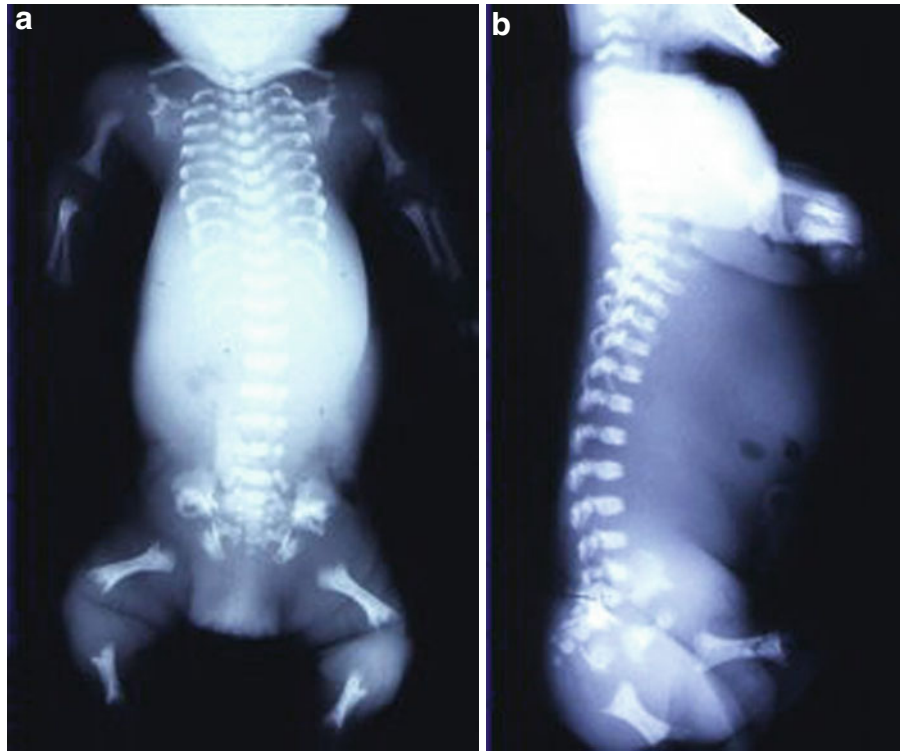

Fig. 12 (**a**, **b**) Radiographs of the skeletal system (SRPS III) showing extremely short and horizontal ribs, small dysplastic vertebral bodies and ilia, short tubular bones with widened metaphyses with longitudinal spurs

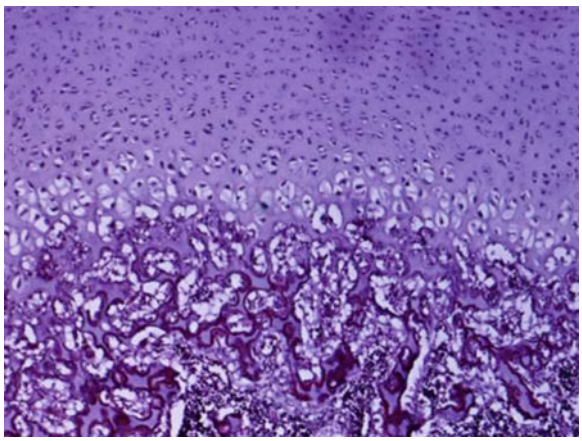

Fig. 13 Photomicrograph of the cartilage of the iliac crest (SRPS III) showing retardation and disorganization of physeal growth zone

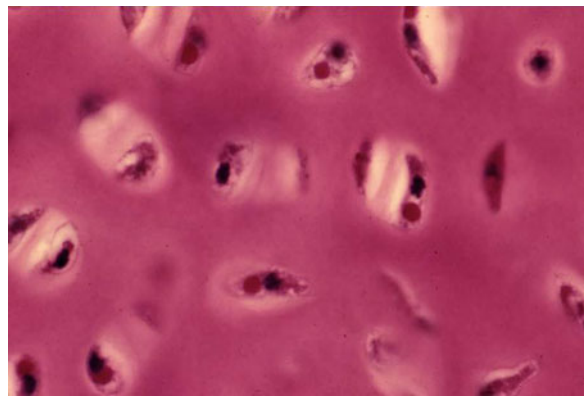

Fig. 14 Higher magnification of the chondrocytes in the resting cartilage and the physeal zone of proliferation frequently show cytoplasmic inclusions (PAS after diastase digestion) (SRPS III)

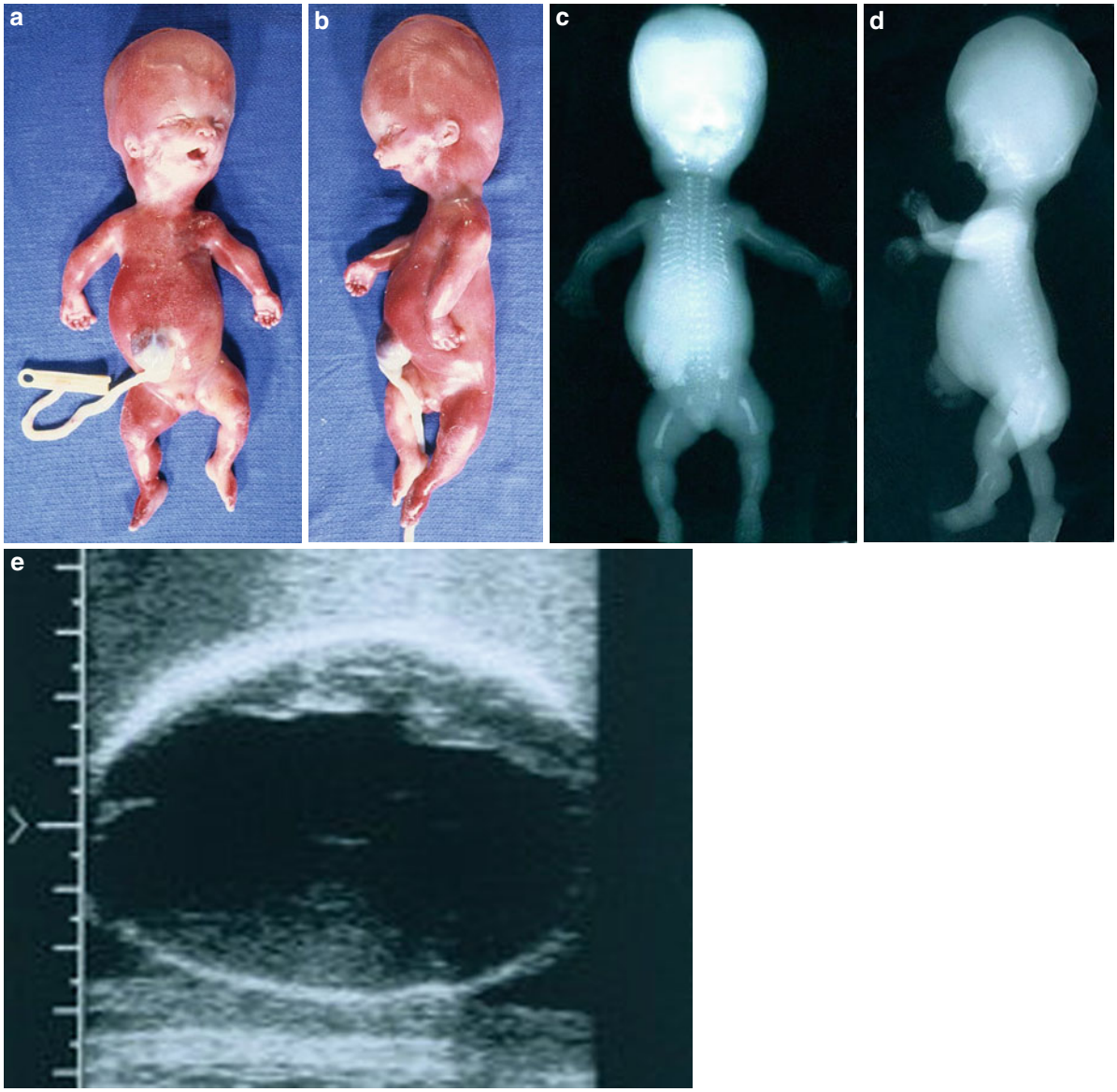

Fig. 15 (**a–e**) A fetus with Beemer–Langer syndrome showing macrocephaly, cystic hygroma, severe micro-/retrognathia with cleft palate, low-set and malformed ears, short limbs, narrow thorax, protuberant abdomen with an omphalocele, and polydactyly. The radiographs show short and horizontal ribs, small scapulae, relatively poorly ossified vertebral bodies, small ilia, short tubular bones with absence of metaphyseal spicules, bowed radii and ulnae, and postaxial polydactyly. The ultrasonography shows porencephalic cyst. The fetus also had a de novo paracentric inversion of chromosome 17q (q12;q25)

Fig. 16 Radiograph of another premature neonate (SRPS IV) showing extremely short and horizontal ribs, small dysplastic vertebral bodies, small iliac wings, and short tubular bone

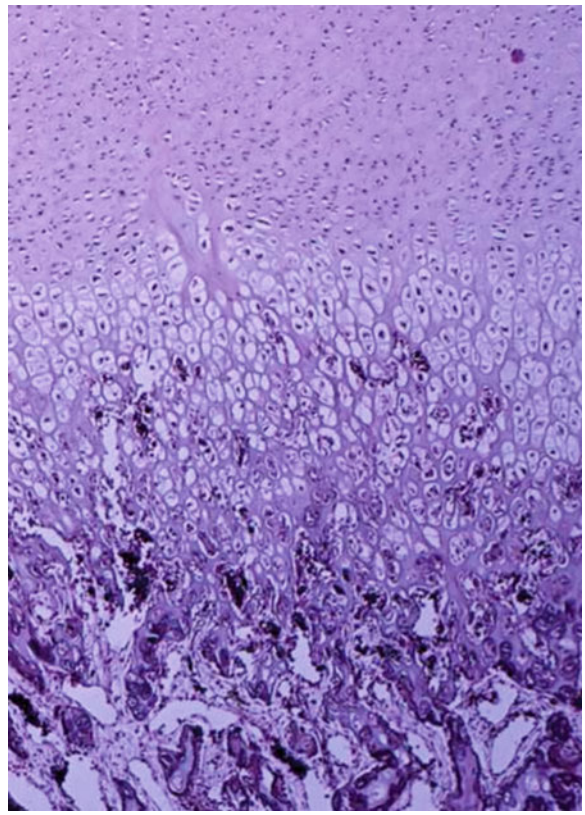

Fig. 17 Physeal growth zone of femur showing prominent but disorganized zone of hypertrophy (SRPS IV)

Sickle Cell Disease

Sickle cell disease (SCD) is the most common single gene disorder in Afro-Americans, affecting approximately 1 in 375 persons of African ancestry. The frequency of sickle cell trait is about 8% in the United States blacks. Sickle blood cells have an increased resistance to malaria. Protection from malaria helps maintain the high prevalence of the sickle gene in areas where malaria is endemic (Fixler and Styles 2002).

Synonyms and Related Disorders

Sickle cell anemia

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Caused by a point mutation at the second nucleotide of codon 6 of the β-globin gene. The base change of A to T causes the amino acid substitution of valine for glutamic acid (GAG to GTG).
   a. Immediate consequence of the mutation: Deoxygenated hemoglobin S polymerizes and distorts the shape of the red blood cell, causing vasoocclusion in the small vessels.
   b. Adverse effects of sickle hemoglobin on the red cell membrane
      i. Oxidative damage
      ii. Cellular dehydration
      iii. Abnormal phospholipid asymmetry
      iv. Increased adherence to endothelial cells
   c. Results of cellular abnormalities
      i. Shortened red cell lifespan causing a lifelong hemolytic anemia
      ii. Intermittent episodes of vascular occlusion causing tissue ischemia and acute and chronic organ dysfunction
3. Sickle cell disease (Lane 1996)
   a. Sickle cell anemia (homozygous sickle cell disease, Hb SS)
      i. Accounts for 60–70% of sickle cell disease in the USA
      ii. The most common form of sickle cell disease
      iii. Caused by inheritance of hemoglobin S from both parents
   b. Other clinically significant sickle cell disorders caused by coinheritance of a sickle gene with a gene for:
      i. β-thalassemia:
         a) The β-thalassemias are divided into β^+-thalassemia (in which some β-globin chains are produced) and β^o-thalassemia (in which there is no β-chain synthesis)
         b) Clinical pictures of patients with hemoglobin S β^+-thalassemia and S β^o-thalassemia resembles sickle cell disease rather than thalassemia, because the sickle β-globin predominates in the presence of underproduction of normal β-globin.
      ii. Hb C
      iii. Hb $D_{\text{Los Angels}}$
      iv. Hb E (HBB Glu25Lys) (Masiello et al. 2007)
         a) One of world's most common hemoglobin variants.
         b) Found primarily in Sri Lanka, Eastern India, Southeast Asia, and Southwest China.

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c) Individuals homozygous for Hb E have mild anemia and microcytosis and are clinically asymptomatic.
d) Compound heterozygotes for Hb S and Hb E are increasingly found throughout the world due to population migrations and racial intermarriages over the last century.
e) Clinical course of adults with Hb SE disease resembles that of Hb S/β^+-thalassemia.
f) Patients who are compound heterozygotes for Hb E and a β-thalassemia mutation have variable phenotypes from mild to severe; the latter is virtually indistinguishable from β-thalassemia major (Fucharoen and Winichagoon 2000).
g) This is because the Hb E mutation creates a cryptic splice site and therefore manifests also as a mild β^+-thalassemia mutation (Orkin et al. 1982).

v. Hb Lepore
vi. Hb O_{Arab}
vii. Hb C_{Harlem}
viii. Hb Quebec-CHORI

4. Pathophysiology of sickle cell disease (Bookchin and Lew 1996)
   a. Hemolysis: The shortened survival of SS red blood cells results from the following two apparently independent properties of Hb S:
      i. Propensity of the concentrated Hb to polymerization resulting in:
         a) Morphologic sickling
         b) RBC dehydration
         c) A marked decrease in RBC deformability
      ii. Hemoglobin S instability
   b. Erythropoiesis
      i. Submaximal erythropoietic response
      ii. Abnormally low affinity for oxygen of SS cells
      iii. Response of the red cells' glycolytic metabolism to hypoxia

Clinical Features

1. Infection
   a. The most immediate risk for infants diagnosed with sickle cell disease
   b. Prone to many bacterial infections, especially from encapsulated organisms, because of lack of splenic function resulting from progressive infarction of the spleen due to sickling of the red cells
2. Hemolysis
   a. Chronic anemia: Hemolytic anemia develops around 3 months of age.
   b. Jaundice (indirect hyperbilirubinemia)
   c. Aplastic crises
      i. Erythrocyte production by the bone marrow may pause temporarily in children with sickle cell disease.
      ii. Human parvovirus B19 infection responsible for 80% of aplastic crises
   d. Cholelithiasis
      i. Prone to develop pigmented gallstones due to large load of bilirubin from hemoglobin breakdown (chronic hemolysis)
      ii. Presenting symptoms: severe recurrent right upper quadrant pain, episode of cholecystitis, common duct obstruction, or pancreatitis
   e. Delayed growth and sexual maturation
3. Vasoocclusion due to occlusion of the microcirculation by rigid red cells and consequent tissue anoxia and infarction
   a. Recurrent acute pain
      i. Dactylitis (hand and foot syndrome) occurs in 25–45% of the patients and can be the earliest manifestation of sickle cell disease. The syndrome is rare after 4 years of age. It is believed to be due to infarction of the red marrow and associated periosteal inflammation. The clinical manifestations are fever and painful swelling of the hands or feet or both.
      ii. Musculoskeletal pain
      iii. Abdominal pain
   b. Functional asplenia (Lane 1996)
      i. The proportion of children with Hb SS who are functionally asplenic: 1 year (28%), 2 years (58%), 3 years (78%), and 5 years (94%)
      ii. At risk for fulminant septicemia and meningitis with pneumococci and other encapsulated bacteria and death during the first 3 years of life in most patients with Hb SS
   c. Splenic sequestration (10–30% of children with Hb SS most commonly between 6 months and 3 years of life)
      i. Sudden massive collection of blood in the spleen due to sickle cells blocking outflow

ii. Rapid enlargement of the spleen causing acute fall of the hemoglobin level of more than 2 g/dL, despite a persistently elevated reticulocyte count
iii. Mild to moderate thrombocytopenia caused by sequestered platelets
iv. Symptoms
a) Acute pallor
b) Lethargy
c) Increased thirst
d) Abdominal fullness
e) Tachycardia
f) Tachypnea
v. May be associated with other complications of sickle cell disease, such as acute chest syndrome, vasoocclusive pain, bacterial infection, stroke, or aplastic crisis
vi. Increased tendency of recurrence (50%)
vii. High mortality (second leading cause of death in children with sickle cell anemia)

d. Acute chest syndrome (Lane 1996)
i. Appearance of a new pulmonary infiltrate on chest radiography
ii. Causes
a) Infection (bacterial pneumonia, atypical bacterial pneumonia by *Mycoplasma* or *Chlamydia*, viral pneumonia, parvovirus B19)
b) Pulmonary vascular occlusion (in situ pulmonary thrombosis, fat embolism, peripheral thromboembolism)
c) Hypoventilation/atelectasis (thoracic bony infarction, abdominal pain, opioids)
d) Pulmonary edema (intravenous fluids, opioids, pulmonary vascular injury)
e) Bronchospasm
iii. Presenting with varying degrees of fever, cough, tachypnea, pleuritic chest pain, and/or hypoxemia
iv. Occurs in more than 50% of pediatric patients with Hb SS
v. The second leading cause for hospitalization
vi. Predispose to chronic restrictive lung disease with pulmonary hypertension and cor pulmonale (important causes of morbidity and mortality in adulthood)

e. Stroke (Lane 1996)
i. Caused by complete occlusion or severe narrowing of large cerebral vessels
ii. Occurs in 7–8% of children with Hb SS after the first year of life, less commonly in children with Hb SC and sickle β-thalassemia
iii. Presenting symptoms
a) Hemiparesis
b) Monoparesis
c) Aphasia
d) Dysphasia
e) Seizures
f) Semicoma
g) Coma
h) Transient ischemic attack
iv. High rate of recurrence (60–90% have a second stroke within 3 years without transfusion therapy)
v. Silent cerebral infarctions in 10–20% of children with Hb SS without clinically apparent neurologic event

f. Chronic nephropathy: an important cause of mortality in adult patients (Molitierno 2003)
i. Hematuria
a) Persistent microscopic (asymptomatic) hematuria: one of the most prevalent features of the disease
b) Gross hematuria
ii. Significant proteinuria (30%)
iii. Papillary necrosis
iv. Hyposthenuria and enuresis: inability to concentrate urine resulting in a high incidence of enuresis
v. Nephrotic syndrome (40%)
vi. Renal infarction
vii. Pyelonephritis
viii. Renal medullary carcinoma
ix. Hypertension (2–6% in patients with Hb SS)
x. Renal failure (5–18%)

g. Priapism (painful erection)
i. Affects about two thirds of male patients
ii. Recurrent attacks eventuate in impotence in 50% of the patients

h. Bone disorders (Smith 1996)
i. Dactylitis (hand and foot syndrome)
ii. Bone infarction: Manifestations include pain, tenderness, and frequently swelling at the involved site(s).
iii. Aseptic necrosis of the long bones: Manifestations include pain or limitation of motion in the hip, shoulder, or other joints, and during walking and climbing stairs.

i. Proliferative retinopathy
j. Leg ulcers
   i. Most common cutaneous complication in sickle cell anemia
   ii. Causing pain, physical disfigurement, social isolation, vocational adversity, and high utilization of health care resources
   iii. Most common in the ankle area over the medial or lateral malleoli, less common over the dorsum of the foot and near the Achilles tendon
   iv. Universal secondary infections (*Staphylococcus aureus* and *Pseudomonas aeruginosa* most common pathogens)
k. Osteomyelitis
   i. *Salmonella* (most common cause)
   ii. *Staphylococcus aureus*
l. Transfusional hemosiderosis

4. Prognosis
   a. Natural history of sickle cell anemia conducted before mandated newborn screening programs: 15% of children die from acute infections or acute anemic events in the first 5 years of life
   b. Hb SC disease
      i. Clinical manifestations milder than Hb SS disease
      ii. Mild hemolytic anemia
      iii. Risk of overwhelming sepsis and death: less than that in Hb SS disease because of the later onset of splenic dysfunction
      iv. Risk of splenic sequestration up to young adulthood
      v. Splenomegaly
      vi. Vasoocclusion
      vii. Proliferative retinopathy
      viii. Aseptic necrosis of femoral head
   c. Early infectious morbidity and mortality in Hb SS and sickle β^o-thalassemia preventable by:
      i. Presymptomatic diagnosis by neonatal screening
      ii. Extensive parental education
      iii. Prophylactic penicillin for infants with Hb SS and Sβ^o-thalassemia (125 mg by mouth twice a day begun between 2 months and 3 years of age and 250 mg twice daily until at least 5 years of age)
      iv. Timely immunizations (all routine immunizations in a timely fashion; new heptavalent conjugated pneumococcal vaccine administered at 2 months of age; influenza virus vaccines yearly after 6 months of age; meningococcal vaccine for children with splenic dysfunction)
      v. Prompt medical evaluation and management of febrile illness
   d. Sickle cell disease and pregnancy: Affected pregnant women are at risk for:
      i. Crisis
      ii. Toxemia
      iii. Pyelonephritis
      iv. Thrombophlebitis
      v. Spontaneous abortion
   e. Progress toward specific therapies
      i. Transfusion therapy
      ii. Bone marrow transplantation
      iii. Hydroxyurea

Diagnostic Investigations

1. Laboratory studies (Lane 1996)
   a. CBC count
      i. CBC and reticulocyte counts to document anemia and brisk marrow response
      ii. Peripheral blood smear to document presence of sickled erythrocytes, target cells, and Howell–Jolly body (indicating functional asplenism)
      iii. Differential white cell count
      iv. Arterial blood gases to reflect the severity of pulmonary crises
      v. Hemoglobin electrophoresis to document Hb SS or Hb S with another mutant hemoglobin in compound heterozygotes
      vi. Liver function tests, BUN, creatinine, and serum electrolytes
      vii. Fetal hemoglobin
2. Imaging studies (Madani et al. 2007)
   a. Radiography
      i. Performed in patients with respiratory symptoms
         a) Pneumonia
         b) Acute chest syndrome: a new focus of opacity (which may be segmental, lobar or multilobar) or collapse with or without a pleural effusion on a chest radiograph, associated with a variable combination of signs and symptoms

including fever, leukocytosis, hypoxia, and chest pain (Charache et al. 1979)
ii. To detect areas of infarction for painful bones
b. MRI to detect areas of avascular necrosis for the femoral and humeral heads and to distinguish osteomyelitis from bony infarction
c. MRI and MR angiography (MRA) of the brain
i. To detect infarction, ischemia and atrophy (44% prevalence), and vasculopathy (55% prevalence) in children with sickle cell disease (Steen et al. 2003)
ii. Moyamoya (Japanese for a "hazy puff of smoke"): an angiographic pattern of large vessel occlusion and telangiectatica collateral circulation, seen in patients with sickle cell disease (Dobson et al. 2002), as well as other conditions, such as tuberous sclerosis, neurofibromatosis, vasculitides, and infection
d. Abdominal sonogram to document spleen size and the presence of biliary stones
e. Transcranial Doppler ultrasonography useful in selecting patients at risk for stroke

3. Sickle cell anemia (Hb SS)
a. Relative clinical severity
i. Markedly severe hemolysis
ii. Markedly severe vasoocclusion
b. Neonatal screening: hemoglobins FS
c. Hemoglobin electrophoresis (Lane 1996)
i. Hb A: 0%
ii. Hb S: 80–95%
iii. Hb F: 2–20%
iv. Hb A_2: <3.5%
v. Hb C: 0%
d. Thin layer isoelectric focusing
i. Gives better resolution of hemoglobins other than Hb A, Hb S, Hb C, and Hb F
ii. Less experience using this method for screening and more costly
e. High-performance liquid chromatography
i. Differentiates many Hbs (Hbs F, A, S, C, D, E)
ii. Hb S + Hb F + Hb A_2 (probable sickle cell disease)
iii. Hb A + Hb S + Hb A_2 (Sickle cell trait)
iv. Hb A + Hb C (Hb C trait)
v. Hb C (Hb C disease)
vi. Hb S + Hb C (sickle C disease)
vii. Is quantitative (can differentiate sickle trait from sickle β-thalassemia and identify β-thalassemia)
f. Sickle prep
i. Does not distinguish between heterozygote and homozygote
ii. Easy for mass screening
iii. Inappropriate for newborn screening
g. Solubility test
i. Hb S detected by precipitation/turbidity
ii. Does not distinguish sickle cell anemia from other sickle diseases
iii. May give false negative if Hb is low
iv. May give false positive if lipidemia is present
v. Easy to use for mass screening if only the presence of Hb S is desired
vi. Inappropriate for newborn screening
h. DNA diagnosis

4. Sickle β^o-thalassemia
a. Relative clinical severity
i. Moderate severe hemolysis
ii. Moderate severe vasoocclusion
b. Neonatal screening: hemoglobin FS
c. Hemoglobin electrophoresis
i. Hb A: 0%
ii. Hb S: 80–92%
iii. Hb F: 2–15%
iv. Hb A_2: 3.5–7.0%
v. Hb C: 0%

5. Sickle hemoglobin C disease (Hb SC)
a. Relative clinical severity
i. Mild hemolysis
ii. Mild vasoocclusion
b. Neonatal screening: hemoglobins FSC
c. Hemoglobin electrophoresis
i. Hb A: 0%
ii. Hb S: 45–50%
iii. Hb F: 1–5%
iv. Hb A_2: Quantity of A_2 cannot be measured in the presence of Hb C.
v. Hb C: 45–50%

6. Sickle β^+-thalassemia
a. Relative clinical severity
i. Mild to moderate hemolysis
ii. Mild to moderate vasoocclusion
b. Neonatal screening: hemoglobins FSA or FS
c. Hemoglobin electrophoresis

i. Hb A: 5–30%
ii. Hb S: 65–90%
iii. Hb F: 2–10%
iv. Hb A_2: 3.5–6.0%
v. Hb C: 0%

7. Sickle cell trait
   a. Relative clinical severity: normal phenotype
   b. Neonatal screening: hemoglobins FAS
   c. Hemoglobin electrophoresis
      i. Hb A: 50–60%
      ii. Hb S: 35–45%
      iii. Hb F: <2%
      iv. Hb A_2: <3.5%
      v. Hb C: 0%
8. Normal
   a. Relative clinical severity: normal phenotype
   b. Neonatal screening: hemoglobins FA
   c. Hemoglobin electrophoresis
      i. Hb A: 95–98%
      ii. Hb S: 0%
      iii. Hb F: <2%
      iv. Hb A_2: <3.5%
      v. Hb C: 0%
9. Newborn hemoglobinopathy screening
   a. Provided in all 50 states in the USA
   b. The most commonly used screening method: electrophoresis and high-performance liquid chromatography
   c. Fetal hemoglobin present predominantly in young infants
   d. Positive results to be followed by fetal hemoglobin electrophoresis for confirmation
   e. Results with only Hb F and S: suggest the infant has either sickle cell anemia or sickle β^o-thalassemia
   f. Results with Hb F, S, and C: suggest the infant has hemoglobin SC disease
   g. Results with Hb F, S, and A and the infant has not been transfused
      i. Hb S > Hb A: most likely sickle β^+-thalassemia
      ii. Hb A > Hb S: presumed sickle cell trait
      iii. Hb A ≈ Hb S
         a) Study the parents to determine if one of them has the thalassemia trait
         b) Repeat Hb electrophoresis after several months
10. Molecular genetic testing
   a. Carrier testing
      i. Most commonly accomplished by high-performance liquid chromatography
      ii. Isoelectric focusing
      iii. DNA-based assays
   b. Prenatal diagnosis: most commonly use DNA-based assays for the detection of the Hb S mutation
   c. Testing methods
      i. Targeted mutation analysis
         a) Hb S (E6V)
         b) Hb C (E6K)
         c) Hb D (E121Q)
         d) Hb O-Arab (E121K)
      ii. Sequence analysis for Hb mutations

Genetic Counseling

1. Recurrence risk
   a. Homozygous sickle cell disease (Hb SS): The child inherits a sickle (S) gene from each parent.
      i. Risk to patient's sibs: 25%
      ii. Risk to patient's offspring: not increased unless the spouse is a carrier
   b. Sickle hemoglobin C disease (Hb SC): The child inherits an S gene from one parent and a C gene from the other parent.
      i. Risk to patient's sibs: 25% if Hb AS in one parent and Hb AC in other parent
      ii. Risk to patient's offspring: not increased unless the spouse is either Hb AS or Hb AC carrier
   c. Sickle β-thalassemias: The child inherits an S gene from one parent and a β-thalassemia gene from the other parent.
      i. Risk to patient's sibs: 25% if sickle cell carrier in one parent and β-thalassemia carrier in other parent
      ii. Risk to patient's offspring: not increased unless the spouse is a carrier for either Hb S or β-thalassemia gene
2. Prenatal diagnosis
   a. Possible by analysis of DNA extracted from fetal cells obtained by amniocentesis or CVS

b. Both disease-causing hemoglobin alleles of the carrier parents must be identified before prenatal testing.
c. Formal genetic counseling needed when the mother is a known carrier and the father is unknown and/or unavailable for testing.

3. Preimplantation genetic diagnosis (PGD) (El-Toukhy et al. 2010)
   a. PGD for SCD has been performed using PCR and RFLP for detection of the SCD mutation with linked markers (Kuliev et al. 1998, 2005; De Rycke et al. 2001)
   b. The A > T point mutation at codon 7 of the β-globin gene, responsible for SCA can be easily identified by the *Ddel* or *MstII* restriction enzymes
4. Management
   a. Preventive care
      i. Immunizations
         a) *Hemophillus influenzae* type b (Hib) vaccine
         b) 7-valent pneumococcal conjugate vaccine
         c) 23-valent pneumococcal polysaccharide vaccine
         d) Consider quadrivalent meningococcal polysaccharide vaccine
         e) Influenza immunization recommended yearly
      ii. Prophylactic medications
         a) Penicillin prophylaxis: effective in preventing 80% of life-threatening episodes of childhood *Streptococcus pneumoniae* sepsis
         b) Erythromycin prophylaxis: an alternative for individuals allergic to penicillin
         c) Consider folic acid supplementation
      iii. Other preventive strategies
         a) Transcranial Doppler to screen the presence of abnormal velocity of arterial blood flow (at risk for stroke)
         b) Screening for pulmonary hypertension, proteinuria, retinopathy, osteonecrosis, neurocognitive dysfunction, liver disease, growth failure, nutritional deficiency, and gallbladder disease
   b. Acute illness
      i. Infection/fever
         a) Broad-spectrum antibiotics (e.g., ceftriaxone) pending culture results
         b) Vancomycin only for proven or suspected meningitis or other severe illness
      ii. Painful crisis
         a) Oral hydration
         b) Oral analgesics including narcotics, acetaminophen, and ibuprofen
         c) Hospitalization for more severe pain episodes with parental analgesics and hydration
      iii. Splenic sequestration
         a) Emergency transfusion indicated when the signs of cardiovascular instability are present
         b) Splenectomy for multiple or severe episodes of splenic sequestration
      iv. Acute chest syndrome
         a) Treat aggressively with oxygen, analgesics, and antibiotics
         b) Simple transfusion
         c) Exchange transfusion
      v. Stroke
         a) Monitor neurologic status
         b) Aggressive treatment of increased intracranial pressure and seizures
         c) Exchange transfusion generally indicated with the goal of decreasing Hb S percentage to <30% of the total hemoglobin
         d) A preventive chronic transfusion protocol initiated after a CNS event to prevent a second stroke
         e) Prophylactic transfusion with folic acid replacement shown to decrease the incidence of vasoocclusive crisis during pregnancy
      vi. Priapism
         a) Hydration
         b) Analgesia administration
         c) Aspiration and irrigation by a urologist
   c. Surgical care, limited to treat complications
      i. Skin graft to help heal chronic leg ulcers
      ii. Hip replacement or other orthopedic procedures to treat avascular necrosis
      iii. Surgical draining of the penile corpora for resistant priapism
      iv. Cholecystectomy for gallstones
   d. Disease-modulating therapy
      i. Hydroxyurea
         a) Principle: The most prescribed therapy causes myelosuppressive-induced Hb F synthesis by decreasing terminal

differentiation of erythroid stem cells, resulting in decreased sickling and improved red cell survival.

b) Effects of therapy: Patients treated have fewer acute episodes of pain crisis and acute chest syndrome, decreased need for transfusion, and improved survival.

c) Not effective for cerebrovascular complications of sickle cell disease

ii. Other medications that increase the percentage of Hb F, currently under investigation

a) Short-chain fatty acids, such as butyrate or valproic acid

b) 5-azacytidine

iii. Chronic red blood cell transfusion

a) To prevent stroke in patients with an abnormal transcranial Doppler and stroke recurrence

b) To treat chronic debilitating pain and pulmonary hypertension

c) Goal: to maintain the percentage of Hb S between 30% and 50%

d) Complications: iron overload, alloimmunization, and infection

iv. Bone marrow transplant: a curative option for patients with sickle cell disease and other hemoglobinopathies (Bolaños-Meade and Brodsky 2009)

a) Bone marrow transplant from a nonaffected donor, usually a human lymphocyte antigen (HLA)-matched sibling, is the only known curative therapy (Walters et al. 1996, 2000; Vermylen et al. 1998; Bernaudin et al. 2007)

b) Proposed selection criteria: Patients should be less than 16 years of age, have an HLA-identical related donor, and have at least one of the following signs or symptoms: stroke or central nervous system event lasting for more than 24 h, acute chest syndrome, recurrent severe pain episodes, impaired neuropsychological function with an abnormal MRI scan, stage I or II sickle lung disease, sickle nephropathy, bilateral proliferative retinopathy, osteonecrosis of multiple joints, or red blood cell alloimmunization during long-term transfusion therapy (Walters et al. 1996)

v. Gene therapy

a) Principle: A single nucleotide substitution in the pathogenesis of sickle cell disease makes the presence of the sickle cell allele an ideal candidate for gene therapy.

b) Question of the safety of this type of approach: development of leukemia in two patients participating in a clinical trial of gene therapy for X-linked severe combined immunodeficiency disease

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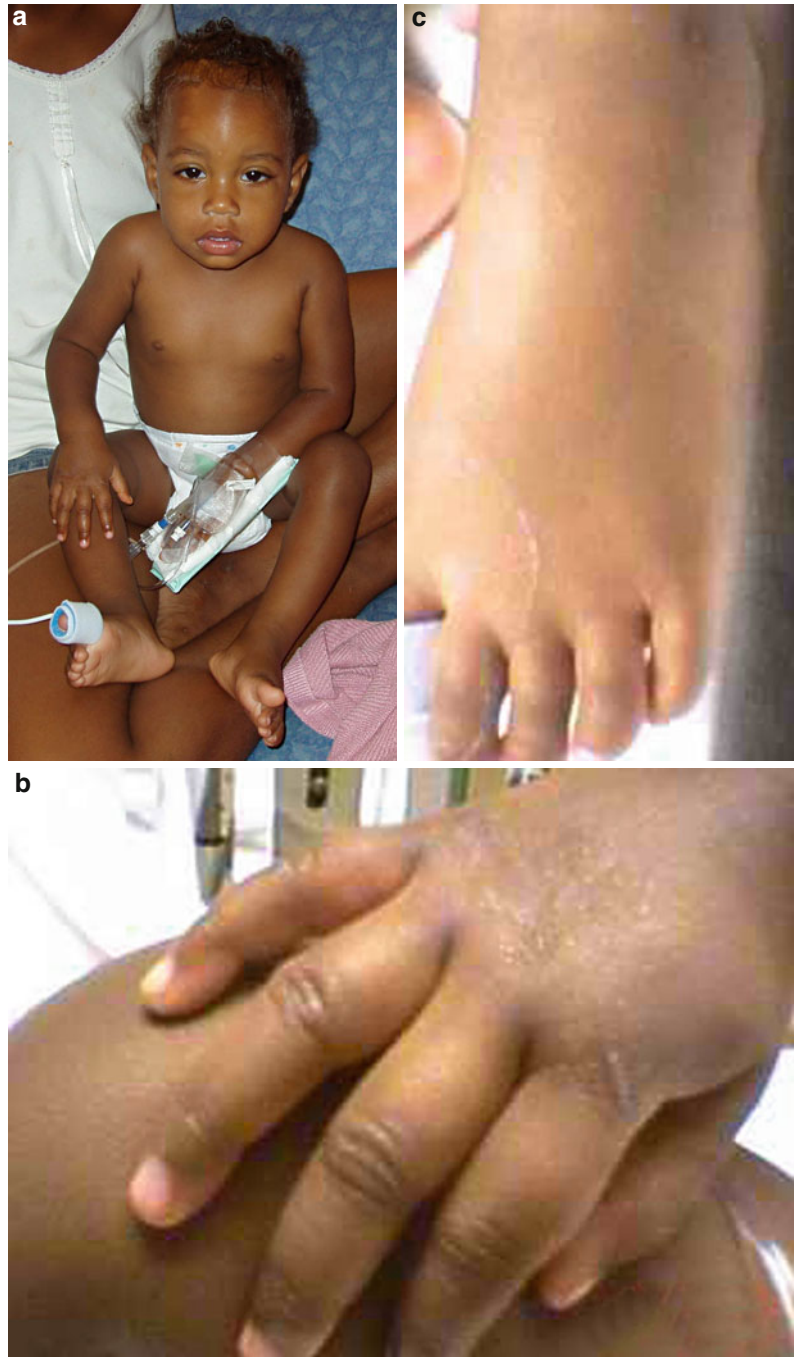

Fig. 1 (**a**–**c**) A young child with sickle cell anemia showing hand and foot syndrome (dactylitis)

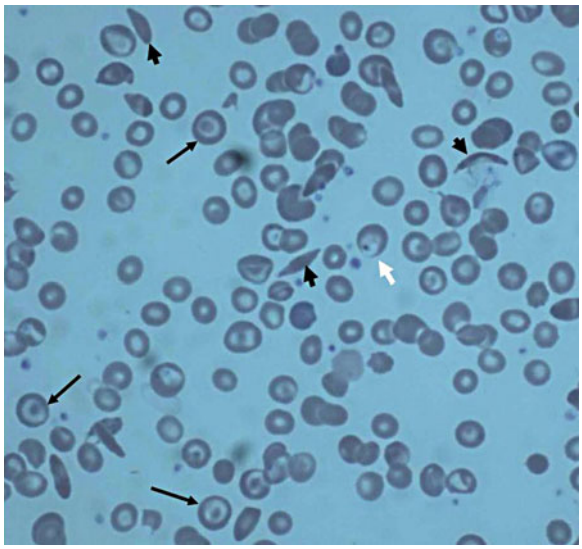

Fig. 2 Peripheral blood smear from a 28-year-old man with hemoglobin SS disease showing several sickle cells (drepanocytes) (*short arrows*), Howell–Jolly body (*white arrow*), and target cells (*long arrows*)

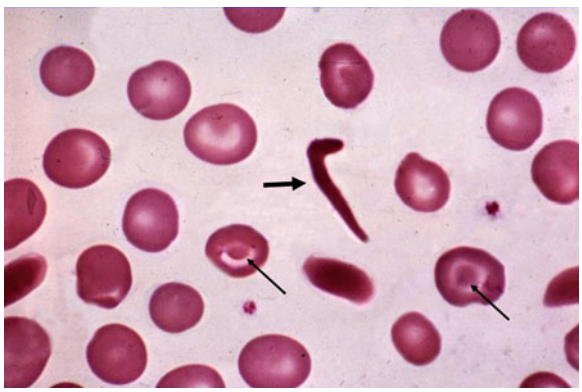

Fig. 3 Peripheral blood smear from another patient with sickle cell disease showing a sickle erythrocyte (*short arrow*) and target cells (*long arrows*) (Wright–Giemsa stain, × 1,000)

Fig. 4 A 3-year-old black male with sickle cell anemia with a history of meningitis at 3 months and splenic sequestration and pain crisis, resulting in splenectomy at 8 months of age

Silver–Russell Syndrome

Silver–Russell syndrome (SRS) is a clinically and genetically heterogeneous disorder, characterized by severe prenatal/postnatal growth retardation, characteristic facies, skeletal asymmetry, and other congenital anomalies. The incidence is estimated as 1:50,000–1:100,000 live births.

Synonyms and Related Disorders

Russell-Silver syndrome; Silver-Russell dwarfism

Genetic/Basic Defects

1. Inheritance (Duncan et al. 1990; Preece 2002)
   a. Sporadic occurrence in majority of cases
   b. 19% of cases with more than one affected individuals in the family, providing evidence for a genetic cause
   c. A genetically (and clinically) heterogeneous disorder
      i. Autosomal recessive (17.4%)
      ii. Autosomal dominant (8.7%)
      iii. X-linked dominant (74%)
2. Chromosomal basis (Preece 2002)
   a. Small number of cases with Silver–Russell syndrome reported in association with numerous chromosomal abnormalities
      i. R(15) and deletion of 15q
      ii. Diploid-triploid mixoploidy
      iii. 45,X/46,XY
      iv. XXY
      v. Trisomy 18 mosaicism
      vi. Del(8)(q11-q13)
      vii. Del(18p)
      viii. Dup(1)(q32.1-q42.1)
      ix. Dup(7p12.1-p13)
      x. Distal chromosome 17q (Hitchins et al. 2002)
         a) Balanced translocation (17;20)(q25;q13) inherited from clinically normal father
         b) De novo translocation (1;17)(q31;q25) with breakpoint recently cloned and localized to 17q23.3-q24
         c) Heterozygous deletion of the chorionic somatomammotropin hormone 1 (*CSH1*) gene located within the growth hormone and CSH gene cluster on 17q24.1. The deletion was inherited from the father who appeared clinically normal but had short stature.
   b. Maternal uniparental disomy (UPD) for chromosome 7 (about 7–10% of cases) (Eggermann et al. 2001; Hitchins et al. 2001)
      i. Inheritance of both chromosome 7 from the mother
      ii. A possible novel imprinted region at 7p12-p14, 7q32, and 7q31-ter: UPD can disrupt the balance between imprinted genes and thereby lead to phenotypic manifestations.
      iii. Strong evidence of disruption of imprinted gene expression rather than mutation of a recessive gene underlying the Silver–Russell phenotype in these cases
   c. Genetic and epigenetic disturbances can meanwhile be detected in approximately 50% of patients with typical SRS features (Eggermann et al. 2010).
      i. Nearly one tenth of patients carry a maternal uniparental disomy of chromosome 7 (UPD (7)mat).

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ii. More than 38% show a hypomethylation in the imprinting control region 1 in 11p15.
iii. More than 1% of patients show (sub)microscopic chromosomal aberrations.
iv. Interestingly, in ~7% of 11p15 hypomethylation carriers, demethylation of other imprinted loci can be detected.

Clinical Features

1. Diagnostic criteria: presence of three major features plus one or more minor features is generally required for a positive diagnosis.
   a. Major criteria
      i. Low birth weight (intrauterine growth retardation)
      ii. Proportionate short stature (postnatal growth retardation): mature height about −3.6 standard deviation scores in both sexes (Davies et al. 1988)
      iii. Small triangular face
      iv. Fifth finger clinodactyly
   b. Minor criteria
      i. Relative macrocephaly due to sparing of cranial growth
      ii. Ear anomalies
      iii. Skeletal asymmetry (face, limb, or body)
      iv. Brachydactyly of the fifth fingers
      v. Bilateral camptodactyly with terminal interphalangeal contractures
      vi. Syndactyly
      vii. Transverse palmar crease
      viii. Downward-slanting corner of the mouth
      ix. Muscular hypotrophy/hypotonia
      x. Motor/neurological delay
      xi. Irregular spacing of the teeth
      xii. Café-au-lait spots
      xiii. Precocious puberty
      xiv. Squeaky voice
      xv. Genital abnormalities
      xvi. Speech delay
      xvii. Feeding difficulties
2. Other manifestations
   a. Significant cognitive impairment (50%)
   b. Gastrointestinal symptoms (77%)
      i. Gastroesophageal reflux disease (34%)
      ii. Esophagitis (25%)
      iii. Food aversion (32%)
      iv. Failure to thrive (63%)
   c. Skeletal anomalies
      i. Large anterior fontanelle (delayed closure)
      ii. Absence of asymmetry
      iii. Syndactyly of the toes
   d. Genitourinary anomalies
      i. Hypospadias
      ii. Posterior urethral valves
   e. Cardiac defects
   f. Various tumors
      i. Craniopharyngioma
      ii. Testicular seminoma
      iii. Hepatocellular carcinoma
      iv. Wilms tumor
   g. Essentially normal pattern of puberty and adolescent growth
   h. Fertility not necessarily impaired, at least in females
   i. Other features
      i. Blue sclera
      ii. Café-au-lait spots
      iii. Excessive sweating
      iv. Hypoglycemia
3. Clinical characterization (Hannula et al. 2001; Binder et al. 2008; Bruce et al. 2009; Eggermann et al. 2010)
   a. Phenotype of maternal UPD7 carriers is generally milder.
   b. 11p15 epimutation (*H19* imprinting control region hypomethylation) carriers usually present the typical picture of SRS.

Diagnostic Investigations

1. Increased serum or urinary gonadotropin levels in the prepubertal age
2. Hypoglycemia
3. Growth hormone studies
4. Metabolic acidosis due to renal tubular acidosis in a few patients
5. Radiography
   a. Delayed bone age
   b. Limb asymmetry
   c. Ivory epiphyses of the distal phalanges
   d. Clinodactyly of the fifth fingers
   e. Short fifth middle phalanges
   f. Pseudoepiphyses at the base of the second metacarpal

6. Chromosome analysis to define chromosome basis
   a. Mosaic trisomy 7 (Flori et al. 2005; Font-Montgomery et al. 2005)
   b. Interstitial deletion of chromosome 7q [del(7)(q21.1q21.3)] (Courtens et al. 2005)
7. Molecular genetic testing (Eggermann et al. 2009; Saal 2007)
   a. Maternal uniparental disomy (UDP) of chromosome 7 (7–10%) clinically available: both maternal isodisomy and heterodisomy have been reported (Bernard et al. 1999; Price et al. 1999).
   b. Genetic or epigenetic mutations in the imprinted region on chromosome 11p15.5: methylation analysis of *H19* (35%) clinically available
   c. 11p15 epimutation and UPD (7) mat carriers do not always show the unambiguous SRS phenotype.
   d. In addition to patients with the classical SRS phenotype fulfilling the SRS-specific scores, genetic testing for the 11p15 epimutation and/or UPD (7) mat should also be considered in case of SRS-like phenotypes, for example, mild IUGR and PNGR (more than −2 SD) associated with a prominent forehead and triangular face or asymmetry as the only clinical signs.
   e. In particular, the lack of IUGR in patients with an SRS-like phenotype should not automatically result in exclusion from molecular testing.

Genetic Counseling

1. Recurrence risk (Saal 2007)
   a. Multiple etiologies of SRS
      i. Maternal uniparental disomy for chromosome 7: both parents are predicted to be unaffected.
      ii. Possible mutations or epigenetic changes that modify expression of genes in the imprinted region of chromosome 11p15.5
      iii. Autosomal dominant inheritance
      iv. Autosomal recessive inheritance
   b. Patient's sibs
      i. Not increased in a nongenetic sporadic case or as the result of maternal uniparental disomy for chromosome 7 (both parents are predicted to be unaffected)
      ii. Increased depending on the inheritance pattern
   c. Patient's offspring
      i. Not increased in a nongenetic sporadic case and probably low in case of maternal uniparental disomy for chromosome 7
      ii. Increased depending on the inheritance pattern
2. Prenatal diagnosis
   a. Ultrasonography of fetus at risk by family history
      i. Delayed fetal skeletal growth may not be evident until the late second trimester.
      ii. Asymmetry of fetal limbs may not be evident until the third trimester
   b. Usually not possible because most occurrences are in a single individual in a family; therefore, most pregnancies are not identified to be at increased risk for recurrence (Saal 2007)
3. Management
   a. Growth deficiency
      i. Optimize caloric intake
      ii. Consider nasogastric or gastrostomy feeding for severe gastroesophageal reflux and failure to thrive
      iii. Consider growth hormone treatment in patients with documented growth hormone deficiency
   b. Dental cares for overcrowding of teeth
   c. Orthopedic management for asymmetry of legs
   d. Early intervention programs including physical therapy for developmental delay due to hypotonia
   e. Special education for learning disabilities
   f. Psychological counseling related to body image and peer relationship

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Fig. 1 An infant with Silver–Russell syndrome showing prenatal and postnatal growth deficiency, triangular face, and asymmetry of legs

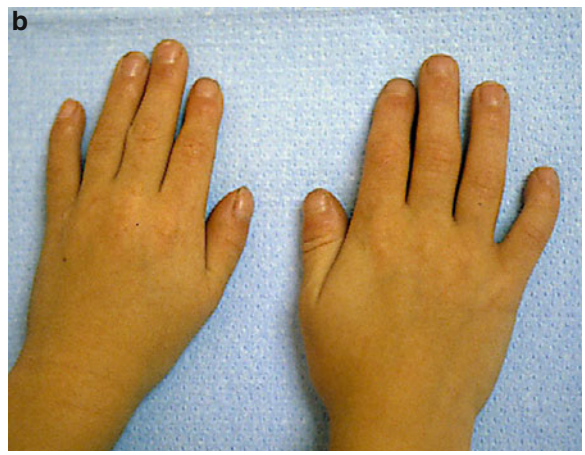

Fig. 2 (**a**, **b**) A girl with Silver–Russell syndrome showing prenatal and postnatal growth deficiency, triangular face, and clinodactyly of the fifth fingers

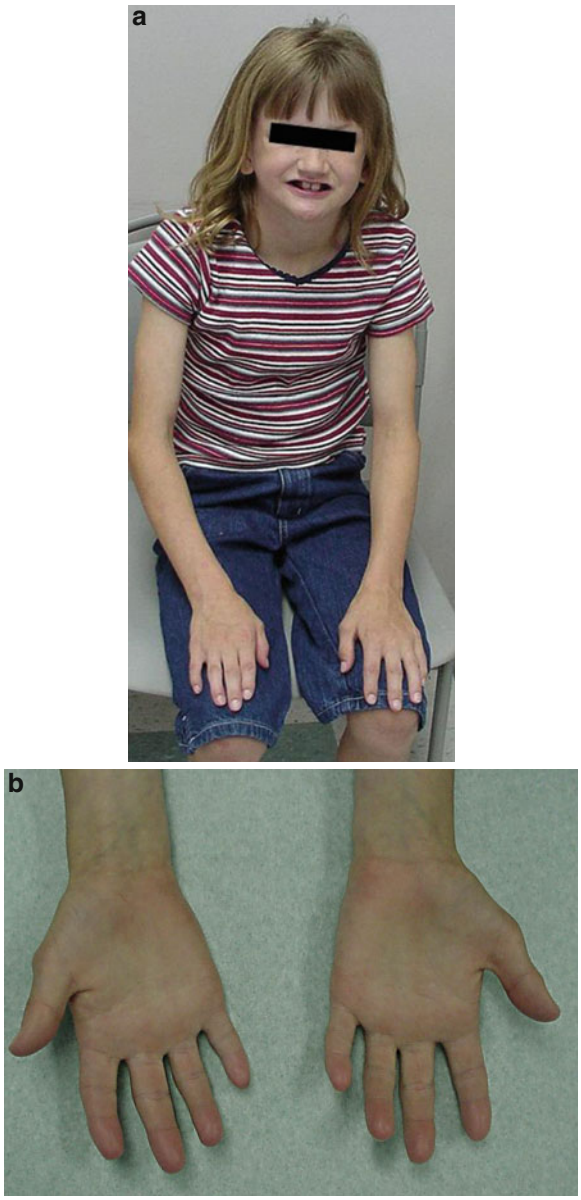

Fig. 3 (**a**, **b**) A girl with Silver–Russell syndrome showing prenatal and postnatal growth deficiency with brachydactyly and clinodactyly of the fifth fingers

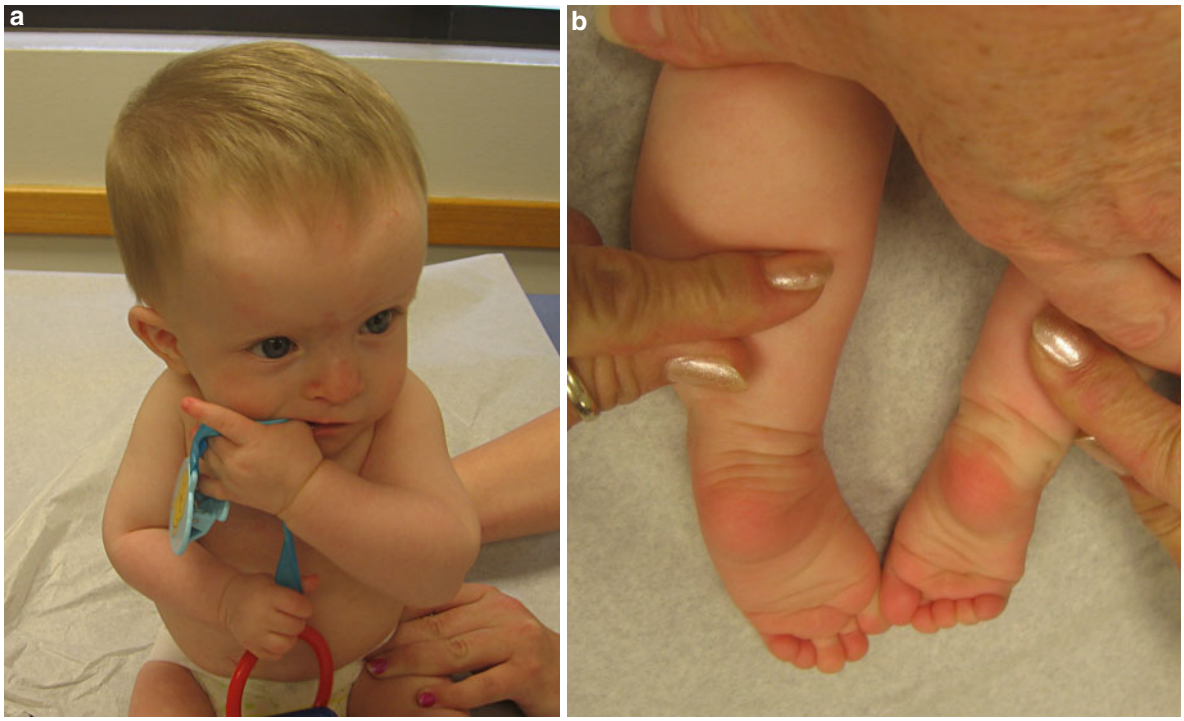

Fig. 4 (**a**, **b**) A 6-month-old male infant was evaluated for intrauterine growth retardation, postnatal growth retardation, a relatively large head, a triangular face, and left side of the body larger than the right. Clinically, he was suspected to have Silver–Russell syndrome. Molecular genetic testing detected loss of methylation at differentially methylated region 1 (DMR1), upstream of the *H19* gene at 11p15. This result is consistent with a diagnosis of Silver–Russell syndrome due to hypomethylation of DMR1

Sirenomelia

Sirenomelia is a rare malformation sequence characterized by a partial or complete fusion of the lower limbs associated with urogenital, anal, lower spine, and other anomalies. The term sirenomelia comes from "siren" or "mermaid" because of the characteristic fusion of the lower extremities. Because of its physical resemblance to the mythical mermaid, the topic of sirenomelia has fascinated public for centuries. Sirenomelia occurs in approximately 1 in 60,000 births.

Synonyms and Related Disorders

Sirenomelia sequence; Sirenomelia mermaid syndrome

Genetics/Basic Defects

1. Sporadic occurrence
2. Incidence of sirenomelia in monozygotic twins markedly increased over dizygotic twins or singletons
3. Cause obscure
   a. Malformations as developmental field defects, probably arising during blastogenesis. Previously considered a vascular disruption anomaly, sirenomelia is a quintessential primary defect of blastogenesis affecting multiple midline primordia during the final stages of granulation at the caudal eminence.
   b. The fusion theory: the lower extremities develop in lateral contact to each other and subsequently become fused.
   c. The classical theory: deficiency of the caudal axial area in the embryo allows the approximation of the side plates where the limbs develop.
   d. The single umbilical artery theory: resulting vascular insufficiency does not allow the normal process of lower limb development.
   e. The vascular steal theory: the sirenomelic malformations result from diversion of the blood flow from caudal structures of the embryo to the placenta. The tissues distal to the diversion receive diminished vascular supply; consequently, the development is arrested at some stage during fetal life.
   f. The extrinsic theory: any mechanical pressure on the caudal portion of the embryo may impede normal rotation of the limb buds as it has been observed in chick embryos exposed to such influences.
   g. The neural tube distention theory: overdistention of the neural tube in the caudal region expands the roof plate of the tube, displacing and laterally rotating the mesoderm, which allows the fusion of the limb buds.

Clinical Features

1. Fusion of the lower limbs
   a. The most striking feature of the syndrome
   b. Fusion of the lower limbs and abnormalities of the feet creating the appearance of a mermaid
   c. Often with rotated feet
   d. Posteriorly located patella
2. Sirtori's classification into three types according to the number of the feet (Sepulveda et al. 1998; Heflin 2007)
   a. Sympus apus (absence of both feet)
      i. The most common form of sirenomelia

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   ii. Characterized by a completely fused single lower extremity with one femur, no fibulae, and one or two tibia
   iii. Both feet may be absent or rudimentary feet may be present
  b. Sympus unipus or monopus (presence of only one foot)
   i. Characterized by a single fused lower extremity with two femora, two tibia, and two fibulae
   ii. Only one foot is present with a varying number of toes (up to ten) on the single foot.
  c. Sympus dipus (presence of both feet)
   i. Characterized by a single fused lower extremity
   ii. Presence of two distinct feet that appear like a fin or flipper
3. Stocker's more detailed classification into seven subtypes according to the fused bones (Stocker and Heifetz 1987)
  a. Type I: paired femora, tibiae, and fibulae
  b. Type II: a single, fused fibula
  c. Type III: absent fibula
  d. Type IV: partially fused femora and a single fibula
  e. Type V: partially fused femora and absent fibulae
  f. Type VI: a single femur and tibia
  g. Type VII: a single femur and absent tibiae and fibulae
4. Oligohydramnios
5. Single umbilical artery
  a. With hypoplasia of the aorta below the origin of the umbilical artery
  b. Presents virtually in every case of sirenomelia
6. Vascular anomalies
  a. Single umbilical artery
  b. Persistent vitelline artery
  c. Hypoplastic distal aorta
  d. Aberrant femoral arteries
7. Urogenital anomalies
  a. Unilateral or bilateral renal agenesis (the most common finding)
  b. Renal cystic dysplasia
  c. Fusion of the renal pelvis
  d. Absent bladder
  e. Urethral atresia
  f. Ectopic urethra
  g. Posterior urethral valves
  h. Male
   i. Absent external genitalia
   ii. Small/rudimentary phallus
   iii. Absent testis
  i. Females
   i. Absent/ambiguous external genitalia
   ii. Absent ovaries
   iii. Anomalous/rudimentary uterus
   iv. Anomalous vagina
8. Gastrointestinal anomalies
  a. Meckel's diverticulum
  b. Duodenal atresia
  c. Absent gallbladder
  d. Annular pancreas
  e. Omphalocele
  f. Intestinal malrotation
  g. Blind-end colon/rectum
  h. Colon duplication
  i. Absent spleen
  j. Imperforate anus
  k. Limb-body wall complex
9. Cardiac anomalies
  a. Tetralogy of Fallot
  b. Totally anomalous pulmonary venous return
  c. Ventricular septal defect
  d. Atrial septal defect
  e. Truncus arteriosus
  f. Hypoplastic ventricles
  g. Mitral atresia
  h. Transposition of the aorta
  i. Coarctation of the aorta
  j. Hypoplastic left heart
  k. Acardius amorphus
10. Pulmonary anomalies
  a. Pulmonary hypoplasia
  b. Tracheoesophageal fistula
  c. Laryngeal stenosis and tracheal atresia
  d. Cystic adenomatoid malformation
  e. Diaphragmatic hernia
  f. Abnormal lung lobation
  g. Pulmonary agenesis associated with acardius amorphus
11. CNS anomalies
  a. Craniorachischisis
  b. Holoprosencephaly
  c. Hydrocephalus
  d. Arnold-Chiari malformation

e. Absent corpus callosum
f. Meningomyelocele
12. Pelvis/sacral anomalies
a. Dysplastic pelvis
b. Sacral agenesis/dysplasia
13. Vertebral anomalies
a. Hemivertebrae
b. Spina bifida
c. Kyphoscoliosis
14. Upper limb anomalies
a. Absent radius
b. Abnormal thumb
c. Absent limb
d. Preaxial polydactyly
15. Face
a. Potter facies
i. Large, floppy low-set ears
ii. Flat nose
iii. Micrognathia
b. Skin tags
16. Prognosis
a. Generally lethal
i. Stillborn in more than half of cases
ii. Remainder of cases most likely die shortly after birth due to severe associated visceral anomalies, incompatible with life
b. Occasional long term survival possible

Diagnostic Investigations

1. Radiography
a. Classification based on osseous findings
i. Type I (all bones of thigh and lower leg present and unfused)
ii. Type II (fused fibulae)
iii. Type III (absent fibulae)
iv. Type IV (partially fused femora and fused fibulae)
v. Type V (partially fused femora)
vi. Type VI (fused femora and fused tibiae)
vii. Type VII (fused femora and absent tibiae)
b. Rotation of the legs and feet
c. Abnormalities of the vertebrae, especially sacral bones
d. Deficient bony pelvis
2. Angiography for vascular anomalies
3. Chromosome analysis: normal in most cases

Genetic Counseling

1. Recurrence risk
a. Patient's sibs: negligible
b. Patient's offspring: affected individuals do not expect to survive to reproduce.
2. Prenatal diagnosis
a. Ultrasonography
i. Inability to demonstrate separate lower limbs
ii. Identification of varying degree of a single or "fused" lower limb
iii. Lower spine agenesis/dysgenesis
iv. CNS, cardiac, GI, and other abnormalities
v. A single umbilical artery
vi. Oligohydramnios associated with urogenital anomalies, especially renal agenesis/dysgenesis
vii. Prenatal diagnosis of sirenomelia difficult to make because of the associated anhydramnios
b. Color Doppler imaging (Sepulveda et al. 1998)
i. A simple, noninvasive method to detect vascular abnormalities associated with sirenomelia
ii. Two vascular hallmarks of the syndrome in utero
a) Persistence of the vitelline artery: a single large artery arising from the high abdominal aorta to become the single umbilical artery, leaving an atretic or absent distal aorta. Such a vascular abnormality is thought to be responsible for a vascular steal phenomenon and poor perfusion distal to the anomalous artery, leading to the sirenomelia sequence.
b) Absence of renal vessels
c. Prenatal diagnosis by ultrasonography of fetus made as early as first trimester (Monteagudo et al. 2002; Schiesser et al. 2003; van Keirsbilck et al. 2006; Contu et al. 2009)
3. Management (Guidera et al. 1991)
a. Orthopedic treatment of patients with less severe spectrum of caudal regression
i. Soft tissue release
ii. Osteotomies
iii. Separation of the lower limbs. Long term functional results of the separation are unknown.
iv. Orthotics

b. Anticipate extensive reconstruction in the event of survival
c. Goal of orthopedic intervention: proper seating and standing, achievable without amputation
d. Severe form of sirenomelia: a lethal condition

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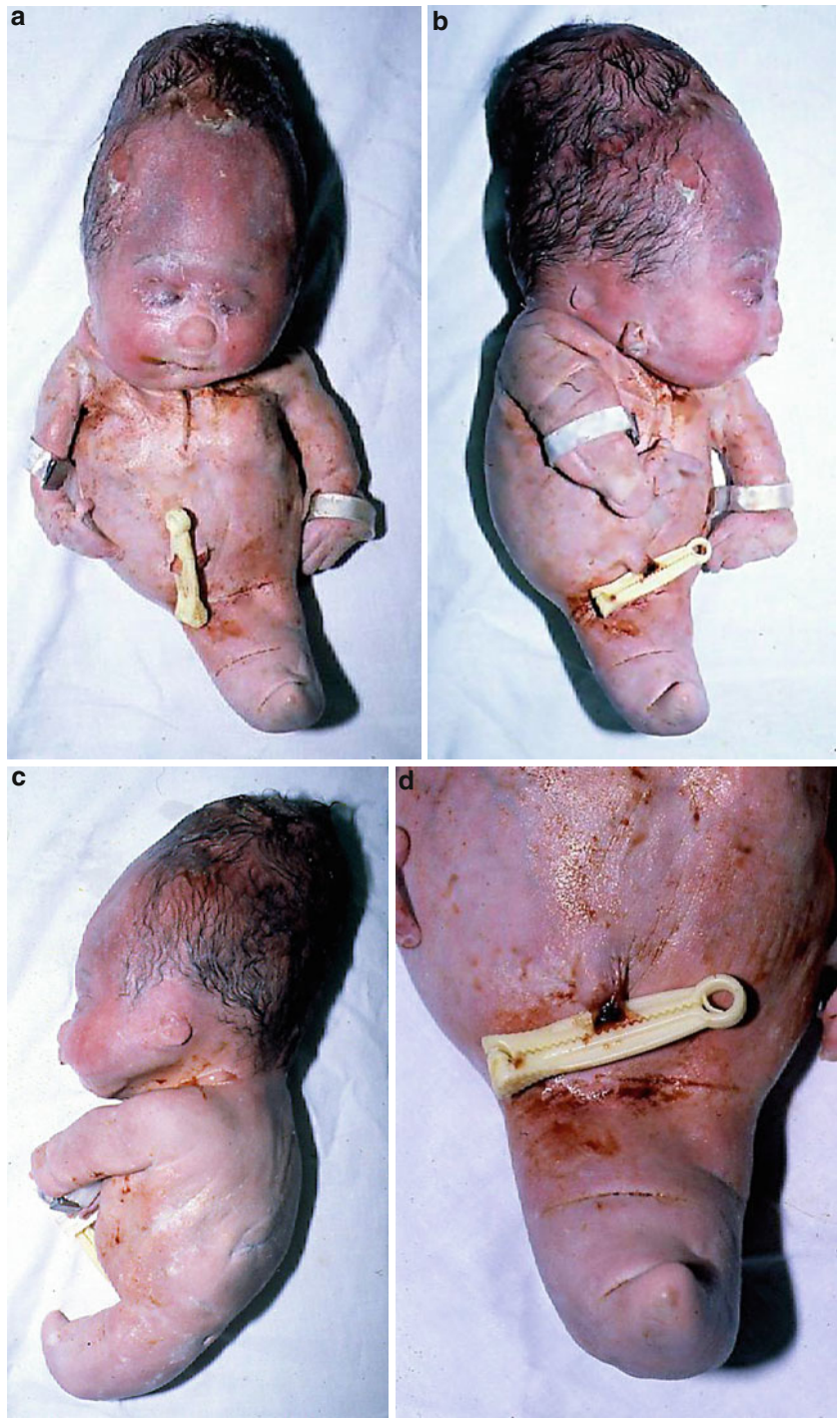

Fig. 1 (**a**–**d**) A stillborn with sirenomelia showing Potter facies, short neck, absent external genitalia, and fused single lower limb with absent feet. This infant also had holoprosencephaly

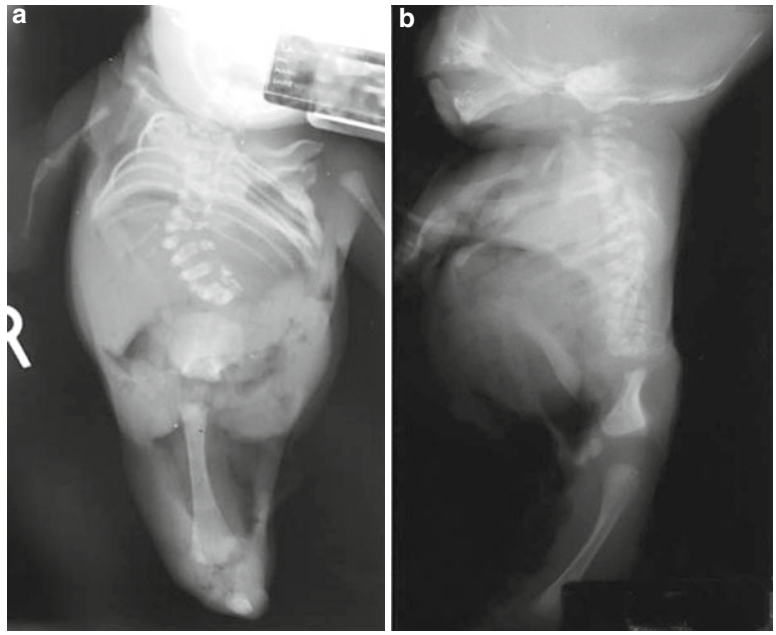

Fig. 2 (**a**, **b**) Radiographs of the previous infant showed vertebral segmentation defects, malformed ribs, absent sacrum, dysplastic pelvic bones, a single femur, and absent tibiae/fibulae/tarsal/metatarsals/phalanges

Fig. 3 A female stillborn (35 weeks gestation) with sirenomelia (monomelia). The infant had a single femur with one bone below knee; agenesis of urinary system (ureters, bladder, and urethra); ectopic rudimentary renal tissue; absence of uterus, vagina, and external genitalia; and imperforate anus

Fig. 4 A male premature neonate with sirenomelia showing fused lower extremities and posterior alignment of the knees and feet. The *left* foot was malformed. Other major anomalies included absence of external genitalia; bilateral renal agenesis; agenesis of the ureters, bladder, urethra, and prostate; esophageal atresia with TE fistula; imperforate anus with absence of the rectum; intestinal malrotation; persistent *left* superior vena cava; bifid cardiac apex; and scoliosis with two hemivertebrae

Smith-Lemli-Opitz Syndrome

In 1964, Smith, Lemli, and Opitz reported three patients with a common distinctive facial appearance, microcephaly, broad alveolar ridges, hypospadias, a characteristic dermatoglyphics pattern, severe feeding disorder, and global developmental delay. The incidence of the Smith-Lemli-Opitz syndrome is estimated to be approximately 1 in 10,000–1 in 40,000 births based on clinical diagnosis and 1 in 60,000–1 in 100,000 births based on biochemical testing. There appears to be strikingly different incidences among various ethnic groups.

Synonyms and Related Disorders

Rutledge multiple congenital anomaly syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Basic defect
   a. Caused by a defect of cholesterol biosynthesis.
   b. Underlying biochemical defect: deficiency of 7-dehydrocholesterol reductase (DHCR7), an enzyme catalyzing the last step of the Kandutsch-Russell cholesterol biosynthesis pathway, resulting in generalized cholesterol deficiency.
   c. Mutations of *DHCR7* gene lead to deficient activity of 7-dehydrocholesterol reductase (DHCR7), the final enzyme of the cholesterol biosynthesis pathway. Functional null alleles of the *DHCR7* locus result in lethal form of Smith-Lemli-Opitz syndrome.
   d. Human *DHCR7* gene has been cloned and localized to 11q12-13.
   e. An example of metabolic deficiency as a cause of a dysmorphic syndrome.
3. Clues pointing to an underlying biochemical defect of cholesterol metabolism
   a. Holoprosencephaly, microcephaly, pituitary agenesis, limb defects, and genital anomalies produced by in utero exposure of rat and mouse pups to chemical inhibitors of the cholesterol biosynthetic pathway
   b. Large adrenal glands with complete absence of lipid in adrenal cortex of patients with Smith-Lemli-Opitz syndrome
   c. Abnormalities of the pituitary-adrenal axis
   d. Suppressed fetal estriol production in pregnancies affected with Smith-Lemli-Opitz syndrome
   e. Neonatal liver disease in severe Smith-Lemli-Opitz syndrome associated with low serum cholesterol level
   f. Male pseudohermaphroditism not caused by dihydrotestosterone receptor defects
   g. Observation of two patients with Smith-Lemli-Opitz syndrome with low plasma cholesterol and elevated levels of 7-dehydrocholesterol (7DHC), the immediate precursor of cholesterol in the Kandutsch-Russell biosynthetic pathway, suggesting that this multiple malformation was caused by a simple Garrodian enzymatic defect
4. Rutledge multiple congenital anomaly syndrome (Rakheja et al. 2003)
   a. Considered a variant of Smith-Lemli-Opitz syndrome

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b. Biochemical abnormality of excess 7-dehydrocholesterol and low cholesterol identified in the liver tissue

5. Five additional related human syndromes resulting from impaired cholesterol synthesis (Kelly 2000; Porter 2002)
   a. Desmosterolosis
      i. Autosomal recessive inheritance.
      ii. Caused by mutations in 24-dehydrocholesterol reductase (*DHCR24*) gene.
      iii. Elevated plasma desmosterol.
      iv. Report of a female infant with a lethal syndrome of macrocephaly, thick alveolar ridges, gingival nodules, cleft palate, total anomalous pulmonary venous drainage, ambiguous genitalia, short limbs, and generalized osteosclerosis was found to have markedly increased tissue levels of desmosterol.
      v. Another report of a child with microcephaly, short stature, and delays in speech and psychomotor development was found to have an increased plasma level of desmosterol and markedly increased levels of desmosterol in cultured lymphoblasts.
   b. X-linked dominant chondrodysplasia punctata type 2 (CDPX2) (Conradi-Hünermann syndrome)
      i. Typically in females with a variable combination of bilateral and asymmetric shortening of long bones, punctate calcification of epiphyses, trachea, and larynx, segmental cataracts, and patches of ichthyotic skin that typically follow the lines of Blaschko
      ii. Caused by function-impairing mutations in the sterol-Δ^8 Δ^7-isomerase gene, which maps to Xq11.2-3
      iii. Lethal to males early in gestation
   c. CHILD syndrome (*c*ongenital *h*emidysplasia with *i*chthyosiform erythroderma/nevus and *l*imb *d*efects)
      i. X-linked dominant inheritance
      ii. Cutaneous and bony abnormalities similar to CDPX2
      iii. Report of a patient with classic CHILD syndrome
         a) Manifests the characteristic sterol abnormality of CDPX2
         b) Carries a mutation creating a stop codon in the same sterol-Δ^8-isomerase associated with CDPX2
   d. Greenberg dysplasia (hydrops-ectopic calcification-moth-eaten skeletal dysplasia)
      i. Autosomal recessive inheritance
      ii. A lethal skeletal dysplasia characterized by hydrops fetalis, short-limbed dwarfism, postaxial polydactyly, and abnormal chondro-osseous mineralization
      iii. Radiologic abnormalities
         a) Moth-eaten appearing long bones
         b) Ectopic epiphyseal calcification
         c) Laryngeal and tracheal calcification
         d) Platyspondyly
      iv. Steroid-Δ^{14}-reductase deficiency
   e. Antley-Bixler syndrome (Opitz et al. 2002)
      i. A skeletal abnormality syndrome primarily affecting head and limbs
      ii. Also known as multisynostotic osteodysgenesis with long bone fractures
      iii. A high incidence of genital ambiguity, an anomaly unlikely due to the *FGFR2* mutation, suggesting possible disordered steroidogenesis in early pregnancy
      iv. Elevated two primary precursors of steroid hormones, pregnenolone and progesterone, as are the classical diagnostic metabolites for 17- and 21-hydroxylase deficiencies, suggesting attenuated steroid hydroxylation (including 17,20-lyase activity) at least in the form not associated with *FGFR2* mutations (Shackleton et al. 2004)

Clinical Features

1. General.
   a. Postnatal growth retardation
   b. Failure to thrive
   c. Feeding difficulties requiring gavage feeding in many cases
   d. Abnormal intestinal motility
      i. Pyloric stenosis
      ii. Vomiting
      iii. Gastroesophageal reflux
   e. Feeding intolerance

f. Gastrointestinal irritability
g. Allergy
h. Initial hypotonia/later hypertonia
i. Recurrent otitis media and pneumonias
j. Photosensitivity
k. Adrenal insufficiency uncommon

2. Craniofacial features.
   a. Congenital microcephaly: very common
   b. Metopic prominence and bitemporal narrowing
   c. Capillary hemangioma over the glabella
   d. Eyes
      i. Epicanthal folds
      ii. Ptosis (more than 50% of patients, often with asymmetrical or unilateral ptosis)
      iii. Congenital cataracts
      iv. Optic nerve hypoplasia
   e. Broad nasal bridge and short nasal root with anteverted nares
   f. Micrognathia
   g. Oral
      i. Cleft lip/palate
      ii. High-arched/narrow hard palate
      iii. Broad/ridged alveolar ridges
      iv. Redundant sublingual tissues
      v. Long philtrum
   h. Low-set and posteriorly rotated ears
3. CNS anomalies.
   a. Global psychomotor retardation
   b. Microcephaly (almost universal finding)
   c. Agenesis/hypoplasia of corpus callosum
   d. Cerebellar hypoplasia
   e. Enlarged ventricles
   f. Decreased size of frontal lobes
   g. Pituitary lipoma
   h. Cerebellar hypoplasia with hypoplasia or aplasia of the vermis
   i. Holoprosencephaly sequence (5% of cases)
   j. Seizures
4. Limb anomalies.
   a. Bilateral or unilateral postaxial polydactyly in the hands or feet
   b. Short/proximally placed thumb
   c. Short first metacarpals
   d. Hypoplastic thenar eminences
   e. Subtle "zigzag" alignment of the phalanges of the index finger
   f. Characteristic Y-shaped cutaneous syndactyly of the second–third toes
5. Genital anomalies.
   a. Male (range from normal to the appearance of complete sex reversal)
      i. External genitalia: normal, hypospadias, female appearing, or ambiguous
      ii. Internal genitalia: gonads varying from normal testes to ovotestes to normal ovaries or missing gonads; sex reversal including blind vaginal pouch and rudimentary or bicornuate uterus
   b. Female
      i. Hypoplasia of labia minora
      ii. Hypoplasia of labia majora
6. Congenital heart defects (about 50% of cases).
   a. Endocardial cushion defect (AV canal)
   b. Septal defect
   c. Hypoplastic left heart syndrome
   d. Patent ductus arteriosus
   e. Aortic coarctation
   f. Anomalous pulmonary venous return
   g. Hypertrophic cardiomyopathy
   h. Hypertension
7. Renal anomalies (about 25% of cases).
   a. Renal hypoplasia/aplasia with oligohydramnios sequence
   b. Horseshoe kidney
   c. Renal cortical cysts
   d. Hydronephrosis
   e. Renal ectopia
   f. Ureteral duplication
   g. Fetal lobation
   h. Hypoplastic bladder and ureters
8. Adrenal anomalies.
   a. Adrenal hyperplasia
   b. Adrenal hypoplasia
9. Respiratory tract anomalies.
   a. Laryngomalacia
   b. Tracheomalacia
   c. Sleep apnea
   d. Abnormal pulmonary lobation
   e. Pulmonary hypoplasia
10. Gastrointestinal/hepatic anomalies.
    a. Pyloric stenosis (prominent clinical problem)
    b. Poor feeding/sucking
    c. Gastroesophageal reflux
    d. Constipation
    e. Malrotation
    f. Hirschsprung disease
    g. Cholestatic liver disease

11. Skin.
    a. Photosensitivity
    b. Cutis marmorata
    c. Dry skin/eczema
12. Behavioral disorders.
    a. Hypersensitivity with tactile defensiveness (oral, hands, and feet)
    b. Unusual hyperresponsivity to auditory and visual stimuli
    c. Aggressiveness and self-injury
    d. Severe sleep disturbance
    e. Autistic behavior
13. Prognosis.
    a. Many survive to adulthood.
    b. Many affected children died in the first year from failure to thrive and infections.
14. So-called Smith-Lemli-Opitz syndrome type II, a lethal syndrome resembling the original Smith-Lemli-Opitz syndrome.
    a. Autosomal recessive disorder
    b. Lethal in the newborn period from internal malformations
    c. Most 46, XY "males" with severe hypogenitalism or female appearing external genitalia
    d. Same sterol pattern in most patients
    e. Differences in severity between type I and type II Smith-Lemli-Opitz syndrome: due to severity of the mutations according to subsequent molecular genetic studies
    f. Possibility of genetic heterogeneity of the Smith-Lemli-Opitz syndrome
15. Clinical criteria for the revised severity score (revised Bialer score) by Kelly and Hennekam (2000). The severity score is obtained based on categories of cerebral, ocular, oral, skeletal, and genital defects identified. Based on the severity score, Smith-Lemli-Opitz syndrome phenotype can be divided into three categories: mild (<20), classical (20–50), and severe (>50). Severity score can be correlated with biochemical parameters and provides a basis for establishing a genotype-phenotype correlation.
    a. Brain
        i. Score 1: seizures; qualitative MRI abnormality
        ii. Score 2: major CNS malformations; gyral defects
    b. Oral
        i. Score 1: bifid uvula or submucous cleft
        ii. Score 2: cleft hard palate or median cleft lip
    c. Acral
        i. Score 0: non-Y-shaped minimal toe syndactyly
        ii. Score 1: Y-shaped 2–3 toe syndactyly; clubfoot; upper or lower polydactyly; other syndactyly
        iii. Score 2: any two of the above
    d. Eye
        i. Score 2: cataract; frank microphthalmia
    e. Heart
        i. Score 0: functional defects
        ii. Score 1: single chamber or vessel defects
        iii. Score 2: complex cardiac malformation
    f. Kidney
        i. Score 0: functional defect
        ii. Score 1: simple cystic kidney disease
        iii. Score 2: renal agenesis; clinically important cystic disease
    g. Liver
        i. Score 0: induced hepatic abnormality
        ii. Score 1: simple structural abnormality
        iii. Score 2: progressive liver disease
    h. Lung
        i. Score 0: functional pulmonary disease
        ii. Score 1: abnormal lobation; pulmonary hypoplasia
        iii. Score 2: pulmonary cysts; other major malformations
    i. Bowel
        i. Score 0: functional GI disease
        ii. Score 1: pyloric stenosis
        iii. Hirschsprung disease
    j. Genitalia
        i. Score 1: simple hypospadias
        ii. Score 2: ambiguous or female genitalia in a 46, XY; frank genital malformation in a 46, XX

Diagnostic Investigations

1. Diagnostic biochemical hallmarks of the syndrome
    a. Low serum cholesterol levels (10% of patients with DHCR7 deficiency have normal levels of cholesterol)
    b. Markedly elevated serum levels of 7-dehydrocholesterol (cholesta-5,7-dien-3beta-ol; 7DHC), precursor of cholesterol
2. DHCR7 enzyme assay
3. Analysis of sterol biosynthesis in cultured cells

4. *DHCR7* mutation testing
   a. Sequence analysis
   b. Targeted mutation analysis
   c. Seven most frequent mutations described to date, representing two-thirds of the mutation in analyzed alleles (Jira et al. 2003)
      i. IVS8-1 G > C (31.5%)
      ii. T93M (11.2%)
      iii. R404C (10.7%)
      iv. W151X (6.4%)
      v. V326L (6.3%)
      vi. R352W (3.2%)
      vii. E448K (3.2%)

Genetic Counseling

1. Recurrence risk: Carrier frequency (2%, a reasonable estimate for risk assessment) is relatively high (Porter 2008).
   a. Patient's sibs: 25%
   b. Patient's offspring: not increased
2. Prenatal diagnosis.
   a. Prenatal screening as part of routine triple marker screen for Down syndrome and neural tube defects: abnormally low maternal serum level of unconjugated estriol observed in pregnancies affected with Smith-Lemli-Opitz syndrome (Schoen et al. 2003).
   b. Second trimester ultrasonography. (Goldenberg et al. 2004)
      i. Nuchal edema
      ii. Renal malformation
      iii. Polydactyly
      iv. Ambiguous genitalia
      v. Cerebral malformation
      vi. Cardiac malformation
      vii. Intrauterine growth retardation
   c. Prenatal diagnosis (Jezela-Stanek et al. 2006) can be established by:
      i. Detection of elevated 7-dehydrocholesterol concentrations or SLOS-causing mutations in the DHCR7 gene by analysis in chorionic villus samples or amniocytes
      ii. Amniotic fluid sterol analysis
      iii. Serial measurements of estriol, pregnanetriol, 7-dehydropregnanetriol, and 8-dehydroestriol concentrations in maternal urine samples obtained between 9 and 20 weeks of gestation
   d. Preimplantation genetic diagnosis has been made for SLOS with successful blastomere diagnosis with mutations in the *DHCR7* gene, allowing transfer of mutation-free embryos and successful pregnancies (Liss et al 2008).
3. Management (Porter 2000; Jira et al. 2003).
   a. Therapeutic trials using dietary supplementation of cholesterol
      i. Used to treat complications related to the biochemical disturbance. Clinical benefits of this therapy are limited by presence of developmental problems.
      ii. Currently, most patients being treated with pharmaceutical-grade cholesterol suspended in either soybean oil or Ora-Plus syrup or alternatively with egg yolks.
      iii. Multiple benefits of dietary cholesterol supplementation.
         a) Improved nutrition and growth
         b) Decreased irritability
         c) Increased alertness
         d) Increased sociability
         e) Decreased self-abusive and aggressive behavior
         f) Decreased tactile defensiveness
         g) Decreased photosensitivity
         h) Decreased infections
         i) Improved hearing
         j) Improved muscle tone and strength
      iv. Use of bile acids shown no clear benefit
   b. An alternative therapeutic strategy of treating with simvastatin (an oral HMG-CoA reductase inhibitor) for a median period of 2 years with impressive overall biochemical effect
      i. A decrease of 7DHC and 8DHC
      ii. An increase of cholesterol
      iii. Promising clinical improvement
   c. Fresh frozen plasma, which contains cholesterol-rich lipoproteins, used to provide cholesterol supplementation in very sick patients and the fetuses (Porter 2000)

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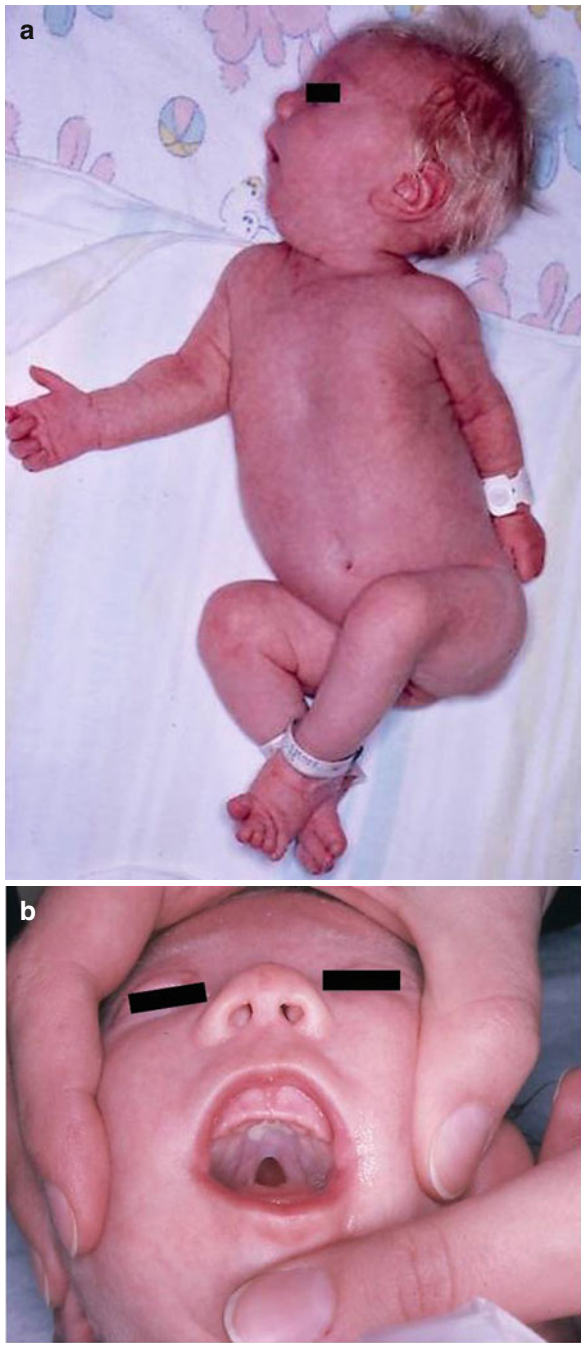

Fig. 1 (**a**, **b**) An infant with Smith-Lemli-Opitz syndrome showing failure to thrive, ptosis, cleft palate, thick alveolar ridge, upturned nares, micrognathia, transverse palmar crease, and syndactyly between the second and third toes

Fig. 2 (**a**–**f**) A boy with Smith-Lemli-Opitz syndrome showing characteristic facial features (epicanthal folds, ptosis of the eyelids, broad nose with upturned nares, and thick alveolar ridges), ambiguous genitalia (hypospadias), umbilical hernia, transverse palmar crease, and talipes equinovarus

Smith-Magenis Syndrome

Smith-Magenis syndrome (SMS) is a complex multiple congenital anomaly and mental retardation syndrome caused by an interstitial deletion of chromosome 17p11.2.

Synonyms and Related Disorders

Chromosome 17p11.2 deletion syndrome

Genetics/Basic Defects

1. Inheritance.
   a. Autosomal dominant inheritance in virtually all cases of SMS occurring de novo
   b. Rare familial chromosome complex rearrangements leading to deletion(17)(p11.2) and SMS
2. Caused by an interstitial deletion of 17p11.2 in the majority of cases (Potocki et al. 2003).
   a. A common deletion size observed in the majority of patients, derived from nonallelic homologous recombination between low-copy repeat gene clusters during either maternal or paternal gametogenesis
   b. Either smaller or larger sized deletions in about 20–25% of patients
3. Considered a contiguous gene syndrome.
   a. Haploinsufficiency of multiple functionally unrelated genes located in close proximity is responsible for the phenotype.
   b. Deletion of a common interval spanning an estimated 4–5 Mb in majority of patients.
4. Sterol regulatory element-binding protein 1 (SREBF1) has been mapped to 17p11.2 within the SMS critical region. Therefore, the patients are hemizygous for the gene encoding SREBP1 leading to hypercholesterolemia.
5. Rare nondeletion cases (Potocki et al. 2003; Truong et al. 2010).
   a. Report of additional patients without a microdeletion, each harbors a mutation in *retinoic acid induced 1* gene (*RAI1*), which maps within the SMS critical region (Slager et al. 2003).
   b. Haploinsufficiency of *RAI1* results in developmental delay, mental retardation, sleep disturbance, self-abusive behaviors, and most features commonly seen in SMS.
   c. Although *RAI1* is the primary gene responsible for most features of SMS, other genes within 17p11.2 contribute to the variable features and overall severity of the syndrome (Girirajan et al. 2006).
   d. *MYO15* clearly associated with a specific phenotypic feature (sensorineural hearing impairment) in a patient with SMS who harbored a recessive mutation on the nondeleted allele.

Clinical Features

1. Infantile hypotonia (Smith et al. 2010)
2. Feeding difficulties
3. Failure to thrive
4. Developmental delay
5. Distinctive craniofacial features
   a. Brachycephaly
   b. Broad square-shaped face
   c. Prominent forehead
   d. Synophrys

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e. Epicanthal folds
f. Upslanted palpebral fissures
g. Deep-set eyes
h. Broad nasal bridge
i. Marked midfacial hypoplasia
j. Short full-tipped nose with reduced nasal height
k. Micrognathia in infancy changing to relative prognathia with age
l. Distinctive appearance of the mouth, with fleshy everted upper lip with a "tented" appearance

6. Otolaryngologic anomalies
   a. Speech delay
   b. Hoarse voice
   c. Velophalangeal insufficiency
   d. Tracheobronchial problems
7. Ocular anomalies
   a. Iris anomalies
   b. Microcornea
   c. Retinal detachment
8. Skeletal abnormalities
   a. Short stature
   b. Scoliosis
   c. Brachydactyly
   d. Flat feet
9. Characteristic neurobehavioral phenotype (Boddaert et al. 2004)
   a. Mental retardation (most patients in moderate range)
   b. Speech delay
   c. Signs of peripheral neuropathy
   d. Inattention
   e. Hyperactivity
   f. Maladaptive behaviors including frequent outbursts and temper tantrums
   g. Attention seeking
   h. Attention deficit
   i. Impulsivity
   j. Distractibility
   k. Disobedience
   l. Aggression
   m. Toileting difficulties
   n. Decreased sensitivity to pain
   o. Self-injurious behaviors
      i. Self-hitting
      ii. Self-biting
      iii. Skin picking
      iv. Inserting foreign objects into body orifices
      v. Yanking fingernails and/or toenails (onychotillomania)
   p. Stereotypic behaviors
      i. Specific to SMS
         a) Spasmodic upper-body squeeze or "self-hug"
         b) Hand licking and page flipping ("lick and flip")
      ii. Additional stereotypes
         a) Mouthing objects or insertion of hand in mouth
         b) Teeth grinding
         c) Body rocking
         d) Spinning or twirling objects
   q. Significant sleep disturbance potentially due to circadian rhythm abnormalities of melatonin (Potocki et al. 2003)
10. Other features
    a. Cardiac defects
    b. Renal and urinary tract abnormalities
    c. Thyroid function abnormalities
    d. Cleft lip/palate
    e. Hearing loss
    f. Seizures
    g. Immune function abnormalities, especially low IgA

Diagnostic Investigations

1. Cytogenetic studies for detection of an interstitial deletion of 17p11.2
   a. G-banded karyotype: may not detect small deletion especially when the indication of cytogenetic study is other than SMS
   b. Molecular cytogenetic analysis by FISH using a DNA probe specific for the SMS critical region
2. Molecular genetic testing of RAI1, the only gene known to account for the majority of features in SMS: available only on a clinical basis
3. Blood chemistry
   a. Hypercholesterolemia
   b. Hypertriglyceridemia
   c. Qualitative immunoglobulins
   d. Thyroid function tests
4. Renal ultrasound for possible renal and urologic anomalies
5. Echocardiogram for possible cardiac defects
6. Radiography of the spine for scoliosis and other vertebral anomalies
7. EEG for clinical seizures

8. MRI and PET imaging (Boddaert et al. 2004)
   a. A significant decrease of grey matter concentration in the insula and lenticular nuclei
   b. A significant hypoperfusion in the same regions
9. Diagnostic strategies (Elsea and Girirajan 2008)
   a. Fluorescent in situ hybridization (FISH): classical methods used to detect the SMS 17p11.2 microdeletion (90% of cases).
   b. Molecular identification (sequence analysis) of a mutation in *RAI1* (remaining 10% of cases).
   c. Whole genome chromosome microarray studies (CGH) will also identify 17p11.2 deletion involving *RAI1*.
   d. Multiplex ligation-dependent probe amplification (MLPA) and real-time quantitative PCR are the newer cost-effective and high-throughput technologies.

Genetic Counseling

1. Recurrence risk (Smith et al. 2010; Smith et al. 2002).
   a. Patient's sib (Elsea and Girirajan 2008)
      i. Less than one percentage if parental chromosome analysis is normal, taking account of possible presence of parental germ line mosaicism
      ii. An increased risk, provided a parent carries a chromosome rearrangement and dependent upon the specific chromosome rearrangement or if mosaicism for either a deletion or *RAI1* mutation is present in either parent (Mosaicism in a parent of an affected child is estimated at 3–5%)
   b. Patient's offspring
      i. Unlikely to have offspring due to severe phenotype
      ii. Theoretically, a 50% risk of having offspring with SMS
2. Prenatal diagnosis: available for pregnancies at risk using a combination of routine cytogenetic studies and FISH.
   a. Amniocentesis
   b. CVS
3. Preimplantation genetic diagnosis may be available for families in which the disease-causing deletion or mutation has been identified.
4. Management.
   a. Early childhood intervention programs.
   b. Special education.
      i. Speech and language
      ii. Physical and occupational
      iii. Sensory integration
   c. Vocational training in later years.
   d. Psychotropic medications to increase attention and decrease hyperactivity.
   e. Behavioral modification.
   f. Administration of β_1-adrenergic antagonist and melatonin helps to manage hyperactivity, enhances cognitive performance, and reduces sleep disorders (de Leersnyder, 2003).
   g. Psychosocial support for the family.

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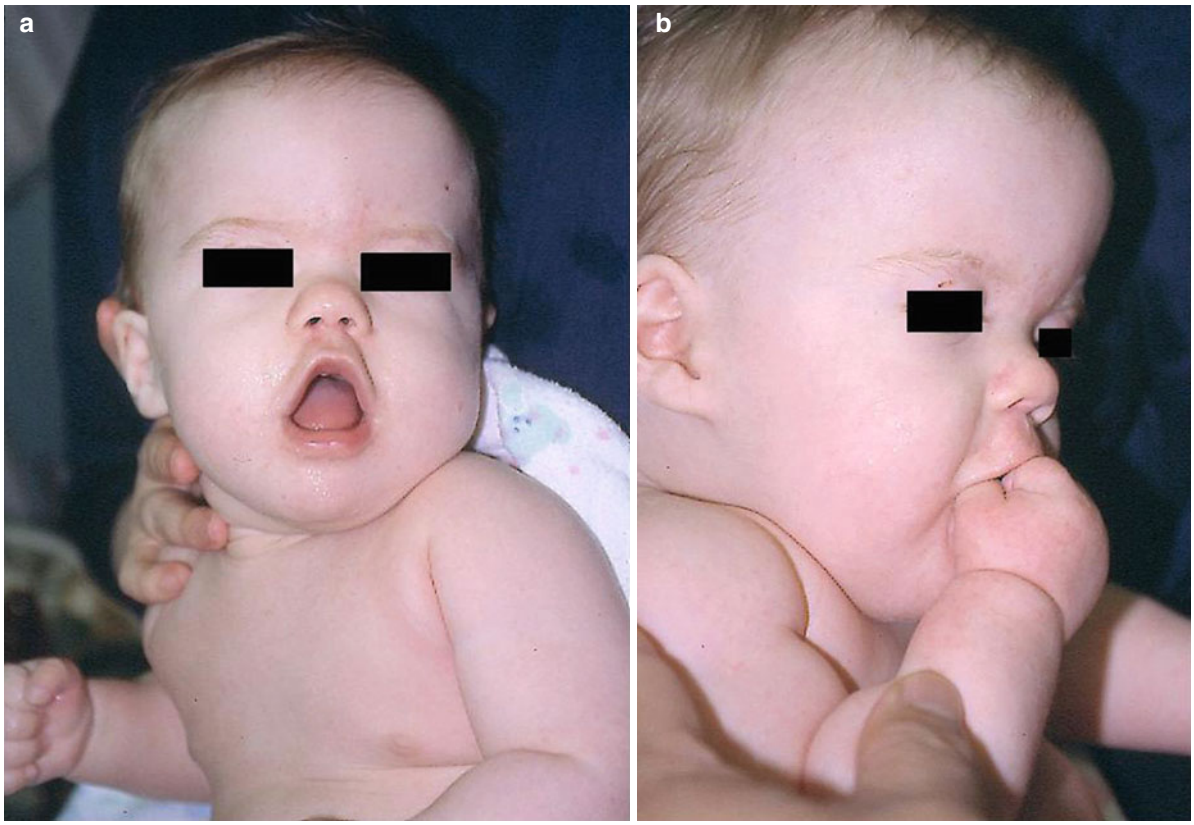

Fig. 1 (**a**, **b**) An infant with Smith-Magenis syndrome showing prominent forehead, broad square-shaped face, synophrys, short full-tipped nose, and fleshy everted upper lip with a "tented" appearance. Chromosome analysis showed an interstitial deletion of 17p11.2

Sotos Syndrome

Sotos syndrome was described by Sotos in 1964 and is relatively common among overgrowth syndromes. It is also known as cerebral gigantism.

Synonyms and Related Disorders

Cerebral gigantism

Genetics/Basic Defects

1. Inheritance: genetically heterogeneous (Visser and Matsumoto 2003)
   a. Sporadic in majority of cases (>98%)
   b. Autosomal dominant inheritance reported in a few families
   c. Autosomal recessive inheritances postulated in some families
2. Discovery of human *n*uclear receptor *S*ET *d*omain-containing protein 1 (*NSD1*) gene (Hőglund et al. 2003)
   a. Report of a patient with Sotos syndrome who had t(5;8)(q35;q24.1).
   b. Discovery of a partial genomic sequence homologous to mouse *NSD1* near the breakpoint by constructing a BAC/PAC/cosmid contig covering the breakpoint.
   c. Human *NSD1* gene was subsequently isolated and characterized.
3. Molecular defect
   a. The major cause of Sotos syndrome: haploinsufficiency of the *NSD1* gene at 5q35, because the majority of patients had either a common microdeletion including *NSD1* or a truncated type of point mutation in *NSD1*
   b. *NSD1* gene mutations and deletions (Rio et al. 2003)
      i. Japanese patients (66%)
         a) Point mutations (48.5%)
         b) Deletions (18.2%)
      ii. British patients (78%)
         a) Point mutations (70%)
         b) Large deletions (8%)
   c. Size of the deletion correlates with severity of the phenotype.
4. No satisfactory explanation for the overgrowth

Clinical Features

1. Prenatal and postnatal overgrowth (major clinical features)
   a. Large for gestational age at birth
   b. Excessive growth velocity, particularly in the first 3–4 years
   c. Advanced bone age by 2–4 years over chronological age during childhood
   d. Large hands and feet
   e. Excessive heights in some adult patients
2. Performance
   a. Developmental retardation
   b. Mental deficiency of varying degree
   c. Lack of fine motor control
   d. Difficulties in neonatal adaptation and/or feeding
3. Characteristic craniofacial appearance
   a. Dolichocephalic large head
   b. Prominent forehead

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   c. Ocular hypertelorism
   d. Downslanting of the palpebral fissures
   e. High-arched palate
   f. Premature teeth eruptions
   g. Pointed chin (prominent mandible)
4. CNS manifestations
   a. Hypotonia
   b. Seizures
   c. Clumsy gait
   d. Mildly enlarged ventricles
   e. Increased subarachnoid spaces
   f. Agenesis/hypoplasia of the corpus callosum
   g. Agenesis of the septal pellucidum
   h. Hypoplasia/atrophy of the cerebellar vermis
   i. Large cisternal magna
   j. Abnormal Sylvian fissure
5. Neoplasms (3.9%)
   a. Benign tumors
      i. Multiple hemangiomas
      ii. Osteochondroma
      iii. Large hairy nevus
      iv. Giant-cell granulomas of the mandible
   b. Malignant tumors
      i. Wilms tumor
      ii. Neuroblastoma
      iii. Hepatocellular carcinoma
      iv. Epidermoid carcinoma of the vagina
      v. Small-cell carcinoma of the lung
6. Other features
   a. Strabismus
   b. Lax joints
   c. Pes planus
   d. Kyphoscoliosis
   e. Asymmetric leg length
   f. Syndactyly
   g. Congenital heart defects
      i. Septal defects
      ii. Persistent ductus arteriosus
      iii. Ebstein malformation
   h. Functional megacolon
   i. Urinary anomalies
      i. Hypoplastic kidney
      ii. Hydronephrosis
      iii. Vesicoureteric reflux
   j. Recurrent hernias
   k. Abnormal dermatoglyphics
7. Social and behavioral difficulties
   a. Emotional immaturity
   b. Poor motor control
   c. Temper tantrums
   d. Good social skills in some patients
8. Weaver syndrome: the major differential diagnosis (Douglas et al. 2003)
   a. Seen less commonly than Sotos syndrome
   b. Caused by *NSD1* mutations in a significant number of patients
   c. Cardinal features
      i. Accelerated growth
      ii. Distinctive facies with micrognathia and a deep horizontal chin crease
      iii. Advanced bone age
      iv. Developmental delay
   d. Additional features
      i. A hoarse low-pitched cry
      ii. Metaphyseal flaring of the femurs
      iii. Deep-set nails
      iv. Prominent finger pads
      v. Camptodactyly

Diagnostic Investigations

1. Glucose intolerance (14%)
2. Radiography: advanced bone age
3. CNS lesions by CAT scan and/or MRI of the brain
   a. Ventricles
      i. Ventriculomegaly
      ii. Prominent trigone of the lateral ventricles
      iii. Prominent occipital horn
   b. Extracerebral fluid
      i. Increased supratentorial space
      ii. Increased posterior fossa space
   c. Midline anomalies
      i. Persistent cavum septum pellucidum
      ii. Persistent cavum vergae
      iii. Cavum velum interpositum
      iv. Macrocisterna magna
      v. Agenesis of corpus callosum
      vi. Hypoplasia (thinning) of corpus callosum
   d. Periventricular leukomalacia
   e. Macrocerebellum
   f. Open operculum
4. Cytogenetic testing
   a. Most affected individuals do not have a cytogenetic abnormality.
   b. Rare cytogenetic abnormality such as a translocation involving 5q35 results in Sotos syndrome (Kurotaki et al. 2003).

5. DNA analysis: NSD1 abnormalities, such as truncating mutations, missense mutations in functional domains, partial gene deletions, and 5q35 microdeletions encompassing NSD1, are identifiable in the majority (49%) of Sotos syndrome cases (Tatton-Brown and Rahman 2007; Cole et al. 2009).
   a. Intragenic sequence analysis/mutation scanning
   b. Deletion/duplication analysis
      i. 5q35 microdeletion analysis/*NSD1* whole gene deletion analysis
      ii. *NSD1* exonic/multiexonic gene deletions

Genetic Counseling

1. Recurrence risk (Tatton-Brown and Rahman 2007)
   a. Patient's sib
      i. Most individuals with Sotos syndrome are the result of de novo mutations.
      ii. No affected siblings of unaffected parents have been reported, indicating that the incidence of germ line mosaicism must be low.
      iii. Therefore, the recurrence risk of unaffected parents approximates to the population risk, which is estimated to be ~1:15,000.
   b. Patient's offspring: a 50% risk as for other autosomal dominant conditions
2. Prenatal diagnosis of fetuses at risk for Sotos syndrome
   a. Ultrasonography in the third trimester
      i. Macrocephaly
      ii. Ventriculomegaly
      iii. Hypoplasia of the corpus callosum
      iv. An enlarged cisterna magna
      v. Overgrowth
      vi. Unilateral hydronephrosis
      vii. Polyhydramnios
   b. Prenatal diagnosis possible by molecular mutation analysis of fetal DNA obtained from amniocytes or CVS of previously identified disease-causing *NSD1* gene: available on a clinical basis
   c. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified.
3. Management:
   a. No specific therapy exists.
   b. Supportive management for cardiac abnormalities, seizures, renal problems, and scoliosis
   c. Referral to appropriate specialist for learning/behavior/speech difficulties

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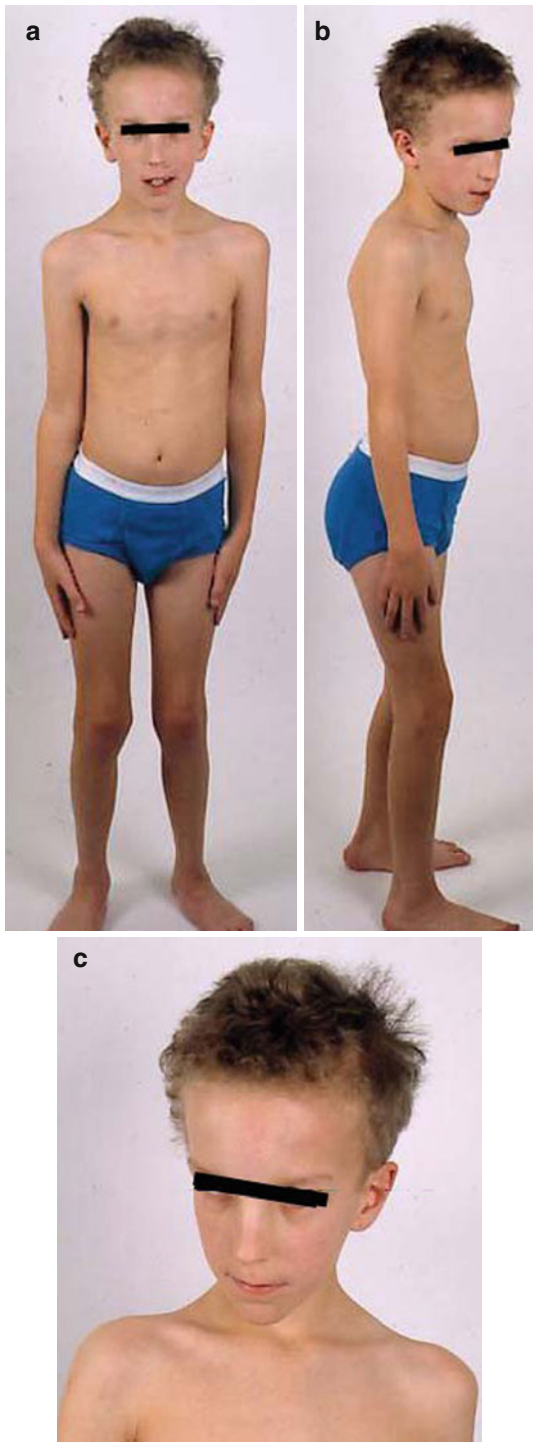

Fig. 1 (**a**–**c**) A child with Sotos syndrome showing excessive growth, a large dolichocephalic head, prominent forehead, downslanting palpebral fissures, and a pointed chin

Fig. 2 The radiograph of the hand from a 20-month-old, showing advanced bone age (3 years)

Fig. 3 (**a**–**c**) A 5-year-old girl with Sotos syndrome showing gigantism, large head, prominent forehead, large hands and feet, and MRI findings of enlarged subarachnoid spaces, mild ventriculomegaly, thinning of the corpus callosum, and mild polymicrogyria

Fig. 4 (**a**–**c**) An adult with Sotos syndrome showing excessive height (compared with other family members), prominent forehead, hypertelorism, a pointed chin, and large hands and feet (compared to normal adult). Chromosome analysis by FISH showed duplicated 4p15.2 and deleted 4q32. Both parents have normal chromosomes

Fig. 5 (**a**–**c**) A 2-year-old girl with Sotos syndrome has excessive height, weight, and head circumference; advanced bone age; and delayed development. The skull is characterized by dolichocephaly, frontal bossing, and deep-set eyes. Molecular study showed two variants of unknown significance: c.1515 T > C(p.N505N) and c.1515 T > C) (p.L1956P). There were no apparent deletions or duplications within the coding region of NSD1

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a disorder characterized by degeneration of lower motor neurons and occasionally bulbar motor neurons leading to progressive limb and trunk paralysis as well as muscular atrophy. It is a clinically and genetically heterogeneous group of neuromuscular diseases. It is the second most common lethal autosomal recessive disorder after cystic fibrosis in Caucasian populations with an overall incidence of 1 in 10,000 live births and a carrier frequency of approximately 1 in 50 (Biros and Forrest 1999).

Synonyms and Related Disorders

Adult SMA; Arthrogryposis multiplex congenita-SMA; Congenital axonal neuropathy; Dubowitz disease; Kugelberg-Welander disease; Werdnig-Hoffman disease

Genetics/Basic Defects

1. Inheritance
   a. Autosomal recessive in most cases (SMA1, SMA2, SMA3)
   b. Autosomal dominant in both juvenile and adult form, representing 2% of infantile and about 30% of adult SMA
2. Caused by mutation or deletion of *Survival Motor Neuron-1* (*SMN1*)
3. Mutation in all three forms (SMA1, SMA2, and SMA3) mapped to chromosome 5q13 (SMA critical region)
4. SMN deletions
   a. High frequency of *SMN* deletions in SMA patients (92.8%) provides a direct and accurate genetic test for:
      i. Diagnostic confirmation of SMA
      ii. Prenatal prediction of SMA
   b. Homozygous deletion of *SMN* observed in:
      i. Atypical forms of SMA associated with congenital heart defects
      ii. Arthrogryposis
      iii. Some cases of congenital axonal neuropathy
      iv. Some patients affected with adult form of SMA
   c. Rare cases of homozygous *SMN* exon 7 deletion or conversion reported in asymptomatic relatives of haploidentical type II or III SMA patients
   d. Absence of deletion of the *SMN* gene or linkage to chromosome 5q in:
      i. SMA associated with diaphragmatic involvement
      ii. SMA with olivopontocerebellar atrophy
      iii. Autosomal dominant form of SMA
      iv. Amyotrophic lateral sclerosis
      v. Post-polio syndrome
5. Molecular-phenotype correlation (Lorson et al. 2010; MacKenzie 2010)
   a. Phenotype of SMA associated with disease-causing mutations of the *SMN* gene spans a continuum without a clear delineation of subtypes.
   b. The severity of the SMA phenotype inversely correlated with:
      i. *SMN2* copy number: The greater the *SMN2* copy number (both in infants and children

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with spinal muscular atrophy and in mouse models), the milder the disease.
ii. The level of full-length SMN protein produced by *SMN2* (~10–15% compared with *SMN1*)

Clinical Features

1. Existing classification system based on age of onset of symptoms: useful for prognosis and management
   a. Congenital axonal neuropathy
      i. Prenatal onset of SMA
      ii. Decreased fetal movement
      iii. Maternal polyhydramnios
      iv. Severe muscle weakness (hypotonia)
      v. Absence of movement
      vi. Joint contractures
      vii. Facial diplegia
      viii. Ophthalmoplegia
      ix. Respiratory failure requiring immediate endotracheal intubation and ventilation
      x. Death from respiratory failure within days
   b. Arthrogryposis multiplex congenita-SMA
      i. Prenatal onset of SMA
      ii. Decreased fetal movement
      iii. Maternal polyhydramnios
      iv. Breech presentation
      v. Severe muscular weakness (hypotonia)
      vi. Arthrogryposis multiplex congenita
      vii. Absence of movement except for extraocular and facial movement
      viii. Death from respiratory failure before 1 month of age
   c. SMA1 (acute spinal muscular atrophy, Werdnig-Hoffman disease)
      i. Represents about 30% of all SMA cases
      ii. Onset before 6 months of age
      iii. The most severe form with fatal outcome
      iv. Severe generalized muscular weakness (hypotonia)
      v. Lack of motor development
      vi. Mild joint contractures at the knees and rarely at the elbows
      vii. Most severely affected neonates
         a) Difficulty in sucking and swallowing
         b) Abdominal breathing
      viii. Facial muscles spared completely with a bright, normal expression
      ix. Ocular muscles and the diaphragm not involved until late in the course of the disease
      x. Fasciculation of the tongue seen in most but not all cases
      xi. Intercostal paralysis with severe collapse of the chest: the rule
      xii. Affected children unable to sit without support
      xiii. Absence of tendon reflexes (areflexia)
      xiv. Normal intelligence
      xv. Usually die within 2 years due to the following:
         a) Feeding difficulty
         b) Breathing difficulty
   d. SMA2 (chronic infantile spinal muscular atrophy, Dubowitz disease)
      i. Represent about 45% of SMA cases
      ii. Onset between 6 and 12 months
      iii. The intermediate form (a more slowly progressive generalized disease with a variable prognosis)
      iv. Poor muscle tone at birth or within first 2 months of life
      v. Slow attainment of motor milestones
         a) Not sitting independently by age 9–12 months
         b) Not standing by 1 year of age
      vi. Frequent tongue fasciculations and atrophy
      vii. Common finger trembling and general flaccidity
      viii. Diminished or absent deep tendon reflexes
      ix. Intact sensation
      x. Loss of the ability to sit independently by the mid-teens
      xi. Slow or arrest of clinical progression
      xii. Severe scoliosis if untreated
      xiii. Defect in respiratory ventilation
      xiv. Highly variable life expectancy, ranging up to adult life in some cases
   e. SMA3 (juvenile spinal muscular atrophy, Kugelberg-Welander disease)
      i. Represents abut 8% of all SMA cases
      ii. Childhood onset after 12 months (usually after 18 months to 30 years of life)
      iii. The mild chronic form

iv. Motor milestones
  a) Ability to walk but frequent fall on walking
  b) Trouble walking upstairs and downstairs at age 2–3 years
v. Muscle weakness
  a) Proximal muscle weakness associated with muscle atrophy
  b) Legs more severely affected than the arms
vi. Normal sensation
vii. No evidence of upper motor neuron involvement
viii. Hypertrophy of the calves in about 25% of cases
ix. Prognosis generally correlates with the maximum motor function attained.

f. SMA4 (adult SMA)
  i. Adult onset (after 20 or 30 years of age)
  ii. Muscle weakness (after 30 years of age)
  iii. Clinical features similar to those described for SMA3 with evidence of lower motor neuron involvement
    a) Tongue fasciculations
    b) Muscle atrophy
    c) Depressed deep tendon reflexes
    d) Normal sensation

2. Consider diagnosis of SMA in infants presenting with the following clinical features:
  a. During neonatal period
    i. Severe hypotonia
    ii. Absent movement
    iii. Contractures, usually of a mild degree
    iv. Evidence of anterior horn cell (i.e., lower motor neuron) involvement
      a) Tongue fasciculations
      b) Absence of deep tendon reflexes
    v. Respiratory failure
    vi. Variable cranial nerve involvement usually apparent late in the course
      a) Ophthalmoplegia
      b) Facial diplegia
  b. After neonatal period
    i. Poor muscle tone
    ii. Symmetric muscle weakness
      a) Sparing the ocular muscles
      b) Involving the facial muscles and diaphragm late in the course of the disease
    iii. Delayed acquisition of motor skills
    iv. Evidence of anterior horn (i.e., lower motor neuron) involvement
      a) Tongue fasciculations (seen in only 65% of patients)
      b) Absence of deep tendon reflexes
    v. Normal reaction to sensory stimuli
    vi. Normal intelligence

3. Natural history (Lorson et al. 2010; MacKenzie 2010)
  a. Clinical features of the disease are caused by specific degeneration of α-motor neurons in the spinal cord, leading to muscle weakness, atrophy, and, in the majority of cases, premature death.
  b. Most afflicted infants and children, while largely neurologically and completely cognitively intact, grow progressively weaker over time, with many ultimately succumbing to respiratory failure at a young age.
  c. The natural history of SMA has been altered over the past several decades, primarily through supportive care measures, but an effective treatment does not presently exist.

4. Other forms of severe spinal muscular atrophy not linked to *SMN* gene (Wang et al. 2007)
  a. Scapuloperoneal spinal muscular atrophy
    i. Autosomal dominant (gene mapped on 12q24.1-q24.31)
    ii. Clinical presentations
      a) Congenital absence of muscles
      b) Progressive weakness of scapuloperoneal and laryngeal muscles
  b. Pontocerebellar hypoplasia with spinal muscular atrophy
    i. Autosomal recessive
    ii. Clinical presentations
      a) Onset at 0–6 months
      b) Cerebellar and brainstem hypoplasia
      c) Absent dentate nucleus
      d) Neuronal loss in basal ganglia
      e) Cortical atrophy
  c. X-linked infantile spinal muscular atrophy with arthrogryposis
    i. X-linked (gene mapped on Xp11.3-q11.2)
    ii. Clinical presentations
      a) Onset at birth or infancy
      b) Contractures
      c) Death before 2 years of age

d. Spinal muscular atrophy with respiratory distress type 1
   i. Autosomal recessive (gene mapped on 11q13.2-q13.4)
   ii. Clinical presentations
      a) Onset within the first 3 months of age
      b) Eventuation of the right or both hemidiaphragms
      c) Finger contractures
      d) Pes equines foot deformities

Diagnostic Investigations

1. Increased serum creatine phosphokinase (CK) activity in about half of the patients with type III SMA
2. Electromyography (EMG)
   a. During voluntary effort
      i. Spontaneous discharge activity in resting muscle
      ii. Increased amplitude
      iii. Prolonged duration of motor unit potentials
   b. Severe denervation commonly found in older patients
   c. Nerve conduction velocity
      i. Generally considered normal
      ii. Some decrease in velocity in severe case
3. Muscle histology
   a. Denervation changes with small groups of atrophic muscle fibers associated with markedly hypertrophied fibers.
   b. Small angular fibers randomly intermixed with normal-sized fibers
   c. Atrophic fibers arranged in groups
      i. Usually of uniform fiber type based on the myosin ATPase reaction
      ii. Considered as an extensive collateral reinnervation of previously denervated muscle fibers by sprouts from surviving motor neurons
   d. In SMA type III, but not in infantile SMA (type I or II)
      i. Markedly hypertrophic fibers
      ii. Excessive variation in fiber size
      iii. Internal nuclei
      iv. Observation of degenerative changes with necrosis and regenerative fibers associated with proliferative interstitial connective tissue
         a) Interpreted as "pseudomyopathic" changes
         b) Usually found in patients with high serum levels of CK activity suggesting the presence of a myopathic process secondary to neurogenic process
         c) These pseudomyopathic changes not observed in other human neurogenic diseases, suggesting that they can be specific to the molecular mechanism resulting in or associated with juvenile SMA
4. Neuropathologic features found at autopsy of SMA patients
   a. Loss of the large anterior horn cells of the spinal cord (most striking feature)
   b. Severe degree of central chromatolysis in the remaining surviving motor neurons, appearing as large ballooned cells without stored substances
   c. Other anterior horn cells
      i. Pyknotic
      ii. Presence of occasional figures of neuronophagia associated with astrogliosis
      iii. Small anterior roots
5. Molecular diagnosis of SMA (Prior and Russman 2011)
   a. The following relatively simple DNA tests enable confirmation of a suspected clinical diagnosis of SMA or prediction of the outcome of a pregnancy in families with a history of SMA (Biros and Forrest 1999).
      i. SSCP analysis
      ii. PCR followed by restriction enzyme digestion
   b. Mutation analysis of *SMN1* available on clinical basis
      i. Used to detect deletion of exons 7 and 8 of *SMN1*
      ii. Homologous deletions of exon 7 of *SMN1* in 95% of cases with clinical diagnosis of SMA
      iii. Compound heterozygotes for deletion of *SMN1* exon 7 and an intragenic mutation of *SMN1* in 2–5% of patients with a clinical diagnosis of SMA
   c. Sequence analysis of all *SMN1* exons and intron/exon borders available on clinical basis
      i. Used to identify the intragenic *SMN1* mutations present in the 2–5% of patients who are compound heterozygotes
      ii. Limitations
         a) Cannot determine whether the point mutation is in the SMN1 gene or the SMN2 gene, unless one of these genes is absent

b) Does not detect exonic duplications
c) Cannot detect deletions of whole exons if more than one SMN gene copy is present

d. Duplication analysis to determine *SMN2* copy number
i. *SMN2* copy number ranges from 0 to 5
ii. Quantitative PCR: currently used for accurate determination of *SMN2* copy number

e. SMA carrier testing (gene dosage analysis) available clinically
i. Mutation analysis not reliable for carrier detection since it does not quantitate the number of *SMN1* gene copies
ii. A PCR-based dosage assay (called SMA carrier testing or *SMN* gene dosage analysis) allows for the determination of the number of *SMN1* gene copies, thus permitting highly accurate carrier detection.
iii. Dosage analysis to differentiate carriers from non-carriers

f. Linkage analysis available on clinical basis
i. Available to families in which direct DNA testing is not informative
ii. May be used for confirmation of carrier testing results and prenatal testing results

6. Newborn screening: An effective technology exists for newborn screening of SMA (Prior et al. 2010).

Genetic Counseling

1. Recurrence risk
a. Patient's sib
i. Autosomal recessive inheritance: 25%
ii. Autosomal dominant inheritance: not increased unless a parent is affected

b. Patient's offspring: only milder forms of SMA likely to reproduce
i. Autosomal recessive inheritance
a) All offspring: carriers
b) Recurrence risk not increased unless the spouse is affected or a carrier
ii. Autosomal dominant inheritance: 50%

2. Prenatal diagnosis
a. Possible to detect fetuses at 25% risk when the disease-causing *SMN* mutations in both parents are known
b. Mutation analysis on fetal DNA obtained from CVS or amniocentesis
c. Linkage analysis
i. Many diagnostic laboratories still perform linkage analysis in addition to direct SMN^T mutation analysis in families where the previously affected child lacks both copies of SMN^T, since there are people in the normal population who lack both copies of SMN^T but not clinically affected.
ii. The only option available to the families where no deletion has been observed but the clinical findings are consistent with 5q SMA

d. Preimplantation genetic diagnosis: available clinically for families in which the disease-causing mutations have been identified in an affected family member

3. Management (Iannaccone 2007; Sendtner 2010)
a. Treat and prevent complications of weakness and maintain quality of life.
b. Several organ systems affected by weakness
i. Respiratory (restrictive lung disease)
a) Noninvasive ventilation support using new technology for patients with sufficient orofacial muscle strength. Long-term ventilatory support is not usually considered.
b) A new awareness of the importance of identifying sleep-disordered breathing
c) A new multidisciplinary approach to standard of care
ii. Gastrointestinal (dysphagia): feeding gastrostomy for children with difficult in sucking and swallowing
iii. Orthopedic (progressive deformities)
a) Orthosis to allow to sit upright rather than bedridden
b) Option of surgical repair for the severe scoliosis

c. Therapy development
i. Previous therapy approaches have focused on upregulation of SMN expression from a second SMN (*SMN2*) gene that gives rise to low amounts of functional SMN protein.
ii. Drug development to target disease-specific mechanisms at cellular and physiological levels is in its early stages, as the pathophysiological processes that underlie the main disease symptoms are still not fully understood.
iii. Human induced pluripotent stem cell technology for generation of large numbers of

human motor neurons could help to fill this gap and advance the power of drug screening.

iv. In parallel, advances in oligonucleotide technologies for engineering *SMN2* pre-mRNA splicing are approaching their first clinical trials, whose success depends on improved technologies for drug delivery to motor neurons.

v. If this obstacle can be overcome, this could boost therapy development, not only for SMA but also for other neurodegenerative disorders.

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Fig. 1 A 2 1/2-week-old white male died of respiratory failure associated with congenital spinal muscular atrophy (Werdnig–Hoffman disease). There was generalized muscle atrophy including respiratory muscle

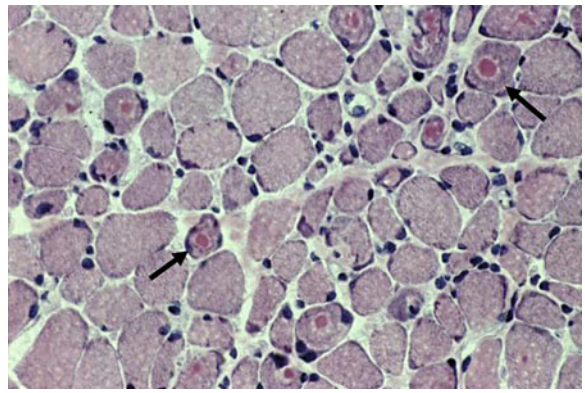

Fig. 3 Residual muscle seen in a 14-year-old female showed chronic denervative change with presence of scattered target fibers (*arrows*) (H & E ×400)

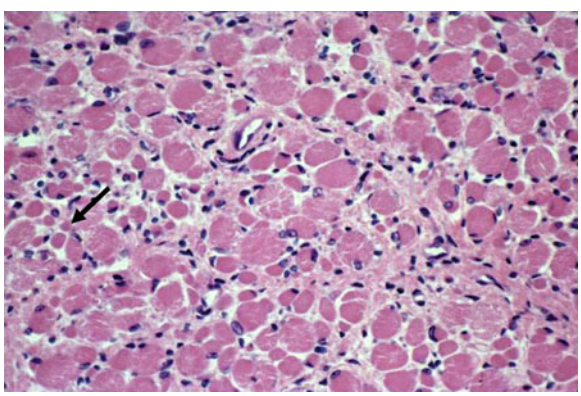

Fig. 2 Quadriceps muscle shows many exceedingly atrophic muscle fibers which tend to be in groups (*arrow*). No degenerative muscle fibers are present (H & E, ×100)

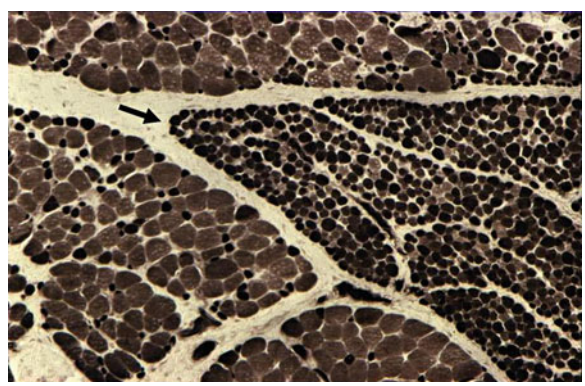

Fig. 4 Biopsy of quadriceps muscle from a 10-month-old girl shows a group atrophy involving several entire fascicles (*arrow*). Both type I (light-stained) and type II (dark-stained) fibers are affected. This is accompanied by an enervative phenomenon (the large muscle fibers all stain pale) (Myosin ATPase, at 9.4, ×50)

Fig. 5 (**a**, **b**) A 3-month-old infant boy with Werdnig-Hoffman disease showing generalized hypotonia. He had a small chest with diaphragmatic breathing, fasciculation of the tongue, and absence of deep tendon reflexes. Molecular genetic analysis revealed homozygous exon 7 deletion and homozygous exon 8 deletion for the survival motor neuron genes (*SMN*)

Fig. 6 A 27-month-old girl with SMA1. She could not stand holding or independently and had foot drops, absence of deep tendon reflexes, and muscle weakness. She was confined to a wheelchair. Molecular genetic analysis revealed homozygous exon 7 deletion and homozygous exon 8 deletion for the *SMN* gene

Fig. 7 A 5-year-old girl with SMA showing tongue fasciculation

Fig. 8 A 30-year-old man with Kugelberg-Welander disease showing muscle weakness and had been confined to a wheelchair for some time. He had trouble standing and began to walk at 6 years of age. Molecular genetic diagnosis revealed homozygous exon 7 deletion and homozygous exon 8 deletion

Spondyloepiphyseal Dysplasia

Spondyloepiphyseal dysplasia (SED) refers to a group of disorders with primary involvement of the vertebrae and epiphyseal centers resulting in a short-trunk disproportionate dwarfism. Two major types (congenita and tarda) will be discussed here.

Synonyms and Related Disorders

SED congenita; SED tarda

Genetics/Basic Defects

1. Genetic basis of SED
   a. SED congenita
      i. Autosomal dominant inheritance
      ii. Spondyloepiphyseal dysplasia congenita gene mapped to chromosome 12q13
      iii. Gonadal mosaicism reported
      iv. Advanced paternal age recognized as a risk factor
   b. SED tarda
      i. X-linked recessive inheritance
         a) Most common
         b) The gene mapped to Xp22.12-p22.31
      ii. Autosomal recessive inheritance
      iii. Autosomal dominant inheritance
2. Molecular basis of SED (Cole et al. 1993)
   a. SED congenita
      i. Caused by mutations in *COL2A1* gene, which encodes the α1(II) chain of type II collagen. The gene was mapped on chromosome 12.
      ii. The mutations result in abnormal type II collagen, which is the major collagen of nucleus pulposus of the spine, hyaline cartilages, fibrocartilages, and vitreous humor of the eyes.
      iii. Other skeletal dysplasias affected by collagen II abnormalities
         a) Autosomal forms of SED tarda
         b) Achondrogenesis type II
         c) Hypochondrogenesis
         d) Kniest dysplasia
         e) Stickler dysplasia
         f) Spondylometaepiphyseal (Strudwick) dysplasia
   b. SED tarda, X-linked form (Christie et al. 2001; Savarirayan et al. 2003)
      i. Caused by mutations in *SEDL* (SED late) gene (designated "sedlin"), mapped on Xp22.12-p22.31
      ii. *SEDL* gene encodes a protein of 140 amino acids with a role in vesicular transport.
      iii. Over 30 novel mutations affecting the *SEDL* gene recognized: the most common type of *SEDL*-gene disruption being deletion, representing 50% of identified mutations

Clinical Features

1. SED congenita
   a. Clinical features present at birth
   b. Short newborn with disproportionately shortened trunk
   c. Delayed motor development
   d. Short neck

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e. Cervical myelopathy resulting from atlantoaxial instability, odontoid hypoplasia, and spinal cord compression, often presenting at age 5–10 years
   i. Delayed motor development
   ii. Decreased endurance
   iii. Progressive motor weakness
   iv. Hypotonia
   v. Sleep apnea
   vi. Alterations in respiration
   vii. Pyramidal tract signs (spasticity, hyperreflexia, Babinski sign, and clonus)
f. Respiratory insufficiency may develop secondary to thoracic dysplasia.
g. Barrel-shaped chest with pectus carinatum deformity
h. Protuberant abdomen
i. Spine abnormalities
   i. Lumbar lordosis
   ii. Thoracic kyphoscoliosis evident in adolescence
j. Hip abnormalities
   i. Hip flexion contractures
   ii. Coxa vara
      a) An almost universal finding
      b) Varying severity
      c) Progressive
      d) Associated progressive hip dislocation if ligamentous laxity present
   iii. The delayed ossification of the capital femoral epiphysis predisposing the hip to deformation with flattening, lateral extrusion, hinge abduction, and premature osteoarthritis
k. Knee abnormalities
   i. Valgus alignment of the knees often associated with overgrowth of the medial femoral condyle
   ii. Rare genu varum
l. Other clinical features
   i. Gait problems often attributed to hip and knee deformities
   ii. Clubfeet (talipes equinovarus) present in some patients
   iii. Ocular anomalies
      a) Myopia and retinal detachment (>50%): important clinical findings in many patients
      b) Cataracts
      c) Buphthalmos secondary glaucoma and strabismus
      d) Clear corneas
   iv. Deafness
   v. Cleft palate
   vi. Abdominal or inguinal hernias

2. SED tarda
   a. X-linked recessive form
      i. Normal appearance at birth
      ii. Variable age of onset
         a) Hip and trunk features appearing around 4 years of age
         b) Diagnosis not recognized until the adolescent years in some patients
      iii. Only males are affected.
      iv. Mild disproportionate trunk shortening
      v. Barrel-shaped chest
      vi. Atlantoaxial instability secondary to odontoid hypoplasia
      vii. Progressive joint and back pain with osteoarthritis commonly involving hip, knee, elbows, and shoulder joints
      viii. Hip involvement
         a) Hip pain or stiffness presenting around the first or second decade of life
         b) Changes mimic bilateral Legg-Calve-Perthes disease
         c) Varying degrees of coxa magna, flattening, extrusion, and subluxation
         d) Osteoarthritis of the hip, a common sequelae
      ix. Kyphoscoliosis
      x. Lumbar lordosis
      xi. Epiphyseal involvement
         a) Primarily in the shoulders, hips, and knees
         b) Symmetrical and bilateral
      xii. Rare association with nephrotic syndrome
      xiii. Craniofacial appearance, vision, and hearing not affected in X-linked SED tarda
      xiv. Normal intelligence
      xv. Normal life span
   b. Autosomal recessive form
      i. Onset between the age of 4 and 10 years
      ii. Short stature
      iii. Waddling gait
      iv. Disproportionately short trunk
      v. Accentuated spinal curvatures
      vi. Restricted mobility of the hip joints
      vii. Hip pain becomes worse with increasing age.

c. Autosomal dominant form
   i. Clinical features identical to those in the recessive form of SED tarda
   ii. Hip pain and waddling gait noted after the fourth year of life
   iii. Mild shortness of the trunk
   iv. Progressive hip changes causing considerable discomfort

Diagnostic Investigations

1. Radiography
   a. SED congenita
      i. A generalized delay in the development of ossification centers
         a) Absent epiphyseal centers of the distal femur and proximal tibia, os pubis, calcaneus, and talus, which are usually present at birth
         b) Femoral heads usually not visible on radiographs until patients are aged 5 years
         c) Femoral capital epiphyses: flattened and irregular in shape when they appear on radiographs
      ii. Vertebral abnormalities
         a) Varying degrees of platyspondyly
         b) Oval, trapezoid, or pear-shaped vertebrae resulting from posterior wedging of vertebral bodies
         c) Incompletely fused ossification centers of the vertebral bodies
         d) End plate irregularities and intervertebral disk spaces narrowing become obvious with an increased anteroposterior diameter of the vertebral bodies in adolescents and young adults.
         e) Exaggerated lumbar lordosis
         f) Progressive kyphoscoliosis developing in late childhood
         g) Odontoid hypoplasia or os odontoideum leading to atlantoaxial instability: common
      iii. Pelvic abnormalities
         a) Short and small iliac crests with horizontal acetabular roofs and delayed ossification of the pubis
         b) Small iliac bones with lack of normal flaring of the iliac wings
         c) Deep acetabular fossae appearing empty due to the severely retarded ossification of femoral heads
         d) Varying severity of coxa vara
         e) Delayed ossification of the femoral head predisposing hip to deformation with flattening, lateral extrusion, hinge abduction, and premature osteoarthritis
      iv. Tubular bone abnormalities
         a) Delayed ossification centers of the distal femur and proximal tibia leading to flattening and irregularity
         b) Genu valgum usually present with overgrowth of the medial femoral condyle
         c) Relatively short and broad long tubular bones
         d) Presence of some metaphyseal flaring especially in the region of the distal femur and proximal and distal humerus
         e) Delayed or disorganized ossification of carpal and tarsal centers with occasional extra epiphyses
   b. SED tarda, X-linked recessive form
      i. Radiographic changes usually apparent in children older than 4–6 years (not evident at birth)
      ii. Changes suggestive of atlantoaxial instability, platyspondyly, kyphoscoliosis, and epiphyseal involvement similar to those seen in patients with SED congenita
      iii. Predominantly affecting the spinal vertebral bodies and epiphyses during skeletal growth
      iv. A mound of bone ("donkey hump") typically present in the central and posterior portions of the superior and inferior end plates on lateral radiographs in patients with X-linked recessive type of SED tarda (not features of the autosomal dominant or recessive types of SED tarda). However, absence of ossification at the upper and lower anterior margins of the vertebral bodies is considered to be the distinctive radiographic feature.
      v. Symmetric epiphyseal involvement primarily in the shoulders, hips, and knees
      vi. Delayed ossification predisposing the weight bearing joints of the lower extremities to deformation and premature osteoarthritis

vii. Changes in the hip (dysplastic changes of femoral heads and neck), mimic bilateral Legg-Calve-Perthes disease
viii. Presence of varying degrees of coxa magna, flattening, extrusion, and subluxation
ix. Minor skeletal changes in carrier women with X-linked recessive SED tarda in a 6-generation kindred from Arkansas
a) Subtle abnormal shape of the pelvis and knees
b) Premature occurrence of degenerative changes in the spine leading to frequent complaint of arthralgia in the middle age

c. SED tarda, autosomal recessive form
i. Irregular upper and lower plates of the vertebral bodies
ii. Anteriosuperior ossification defects of some vertebras
iii. Less frequent findings
a) Additional ossification defects of the anterioinferior edges of the vertebral bodies
b) Anterior protrusion f central portions of the vertebral bodies
iv. Femoral heads
a) Well-developed capital femoral epiphyses in the younger child
b) Progressive flattening and destruction of the femoral heads with advancing age
c) Milder abnormalities in the knee joints
d) Small and irregular carpal bones
e) Slightly short and irregular metacarpals and phalanges in some patients

d. SED tarda, autosomal dominant form
i. Accentuated dorsal flattening of the vertebral bodies in the younger patient
ii. Platyspondyly with a rectangular shape of the vertebral bodies in the older patient
iii. Mild and slowly progressive deformities of capital femoral epiphyses and knee epiphyses
iv. Slightly short phalanges and metacarpals with narrowing of the joint spaces

2. MRI
a. To delineate cord compression due to C1–C2 instability
b. To evaluate severe spinal deformities prior to surgical intervention
c. To evaluate the condition of the epiphyseal centers prior to reconstructive procedures

3. CT scan
a. To assess the configuration of bones and joints prior to surgical intervention
b. To reconstruct three-dimensional images for help in surgical planning of severe cases

4. Hip arthrography
a. To document congruity of the femoral head or hinged abduction
b. To evaluate severe varus deformity of the femoral neck

5. Laboratory features of SED congenita
a. Fine metachromatic inclusions in the peripheral lymphocytes
b. Normal urinary excretion of acid mucopolysaccharides including keratosulfate
c. Histopathology
i. Mildly disorganized physis (epiphyseal growth plate)
ii. Chondrocytes containing PAS-positive cytoplasmic inclusions
iii. Ultrastructurally, the inclusions correspond to the accumulations of finely granular material in dilated cisterns of rough endoplasmic reticulum.

6. Molecular genetic analysis
a. Mutations in *COL2A1* gene in SED congenita
b. Mutation in *SEDL* gene in X-linked recessive SED tarda (Tiller and Hannig 2011)
i. Sequence analysis clinically available
ii. Mutation types
a) Deletions
b) Splice mutations
c) Missense mutations
d) Nonsense mutations
iii. Detected in >80% of affected males with X-linked spondyloepiphyseal dysplasia tarda
iv. Molecular genetic testing in new patients relied largely on mutation screening by sequencing the entire coding region.
v. Carrier testing of at risk female relatives available once the mutation has been identified in the proband

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Spondyloepiphyseal dysplasia congenita (autosomal dominant): recurrence risk low unless presence of parental gonadal mosaicism
      ii. Spondyloepiphyseal dysplasia tarda, X-linked
         a) The risk to sibs depends on the carrier status of the mother.
         b) When the mother is a carrier: a 25% risk of having an affected brother; a 25% risk of having an unaffected brother; a 25% risk of having a carrier sister; a 25% risk of having a noncarrier sister
         c) When the mother is not a carrier: The risk to sibs is low (the risk of gonadal mosaicism in mothers not yet known).
      iii. Spondyloepiphyseal dysplasia tarda, autosomal recessive: 25%
      iv. Spondyloepiphyseal dysplasia tarda, autosomal dominant: low unless a parent is affected
   b. Patient's offspring
      i. Spondyloepiphyseal dysplasia congenita, autosomal dominant
         a) When the spouse is not affected: 50% of offspring will be affected.
         b) When the spouse is also affected with spondyloepiphyseal dysplasia congenita: 50% of offspring are heterozygous and affected; 25% are homozygous, which is ordinarily fatal in the first few months of life and 25% are unaffected.
      ii. Spondyloepiphyseal dysplasia tarda
         a) Autosomal recessive form: recurrence risk to offspring low unless the spouse is a carrier
         b) Autosomal dominant form: 50%
      iii. Spondyloepiphyseal dysplasia tarda, X-linked recessive
         a) None of the sons of an affected male will be affected.
         b) All daughters of an affected male are carriers.
2. Prenatal diagnosis
   a. Molecular genetic diagnosis on fetal DNA from amniocytes or CVS available in families at risk for SED congenita, provided the disease-causing mutation (*COL2A1*) is identified in the proband
   b. Molecular genetic diagnosis on fetal DNA from amniocytes or CVS possible in families at risk for X-linked SED tarda, provided the disease-causing mutation (*SEDL*) is identified in the proband
   c. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified in an affected family member.
3. Management
   a. SED congenita
      i. Supportive care including psychosocial support
      ii. Tracheostomy for severe respiratory difficulties to maintain adequate ventilation
      iii. Posterior atlantoaxial fusion for patients with signs and symptoms of atlantoaxial instability measuring 8 mm or more or myelopathy
      iv. Brace for scoliosis initially
      v. Posterior spinal fusion for severe scoliosis or for patients resistant to bracing
      vi. Surgical correction for hip and knee abnormalities
      vii. Surgical correction of equinovarus deformities unmanageable by physical therapy or serial casting
   b. SED tarda, X-linked type
      i. Supportive care
         a) Avoid activities and occupations that place undue stress on the spine and weight bearing joints to prevent premature arthritis.
         b) Chronic pain management
         c) Psychosocial support for the patient and family
      ii. Bracing for scoliosis
      iii. Posterior spinal fusion for severe scoliosis
      iv. Posterior stabilization for atlantoaxial instability
      v. Valgus or valgus-extension intertrochanteric osteotomy to improve hip congruity
      vi. Total joint arthroplasty for osteoarthritis in adulthood

vii. Management of hip dysplasia
   a) Acetabular augmentation if the acetabulum is insufficient to contain the enlarged femoral head (coxa magna)
   b) May require hip replacement

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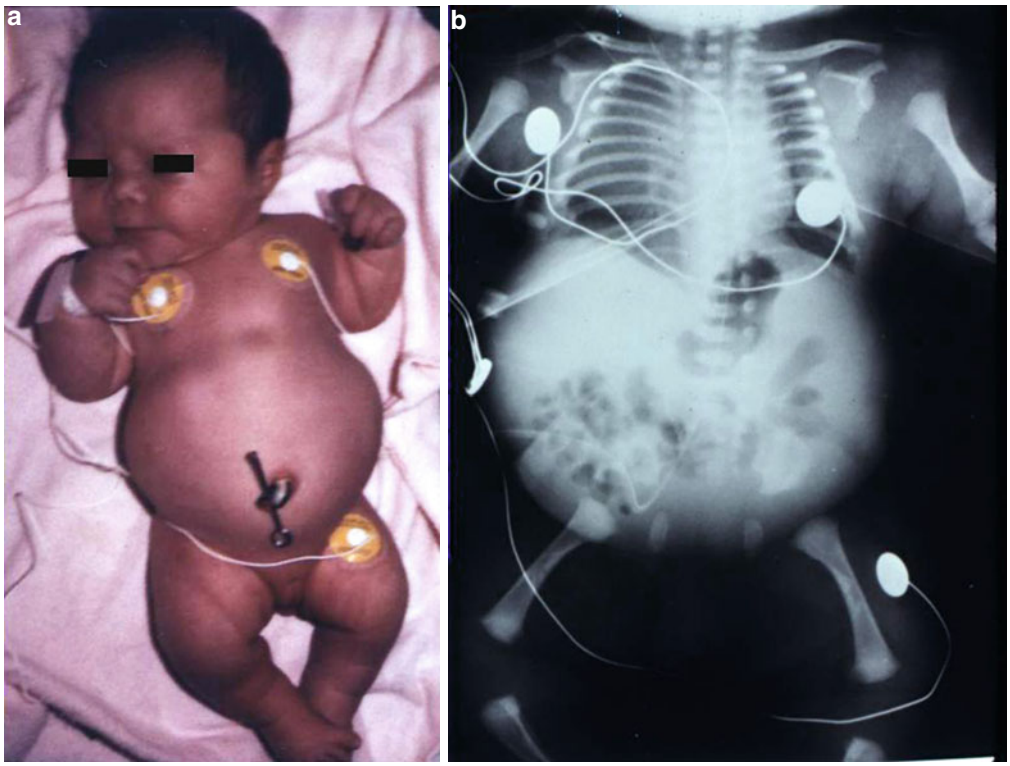

Fig. 1 (**a**, **b**) A neonate with SED congenita showing moderately shortened limbs, short trunk, and large head. Radiograph shows small oval vertebral bodies, reniform ilia, and moderately shortened limb bones

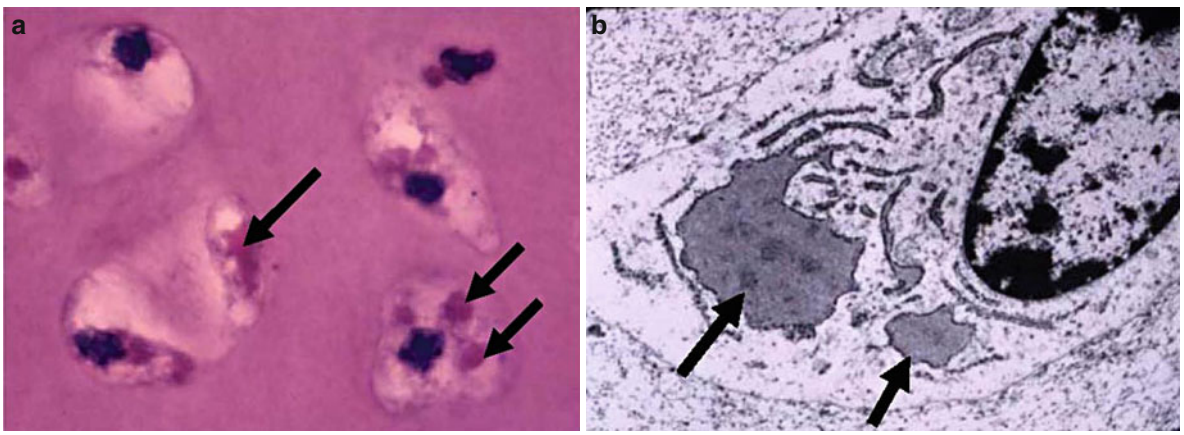

Fig. 2 (**a**, **b**) Photomicrograph of a neonate with SED congenita shows frequent presence of cytoplasmic inclusions in the chondrocytes of resting cartilage and the zone of proliferation. The cytoplasmic inclusion is a dilated rough endoplasmic reticulum containing finely granular material

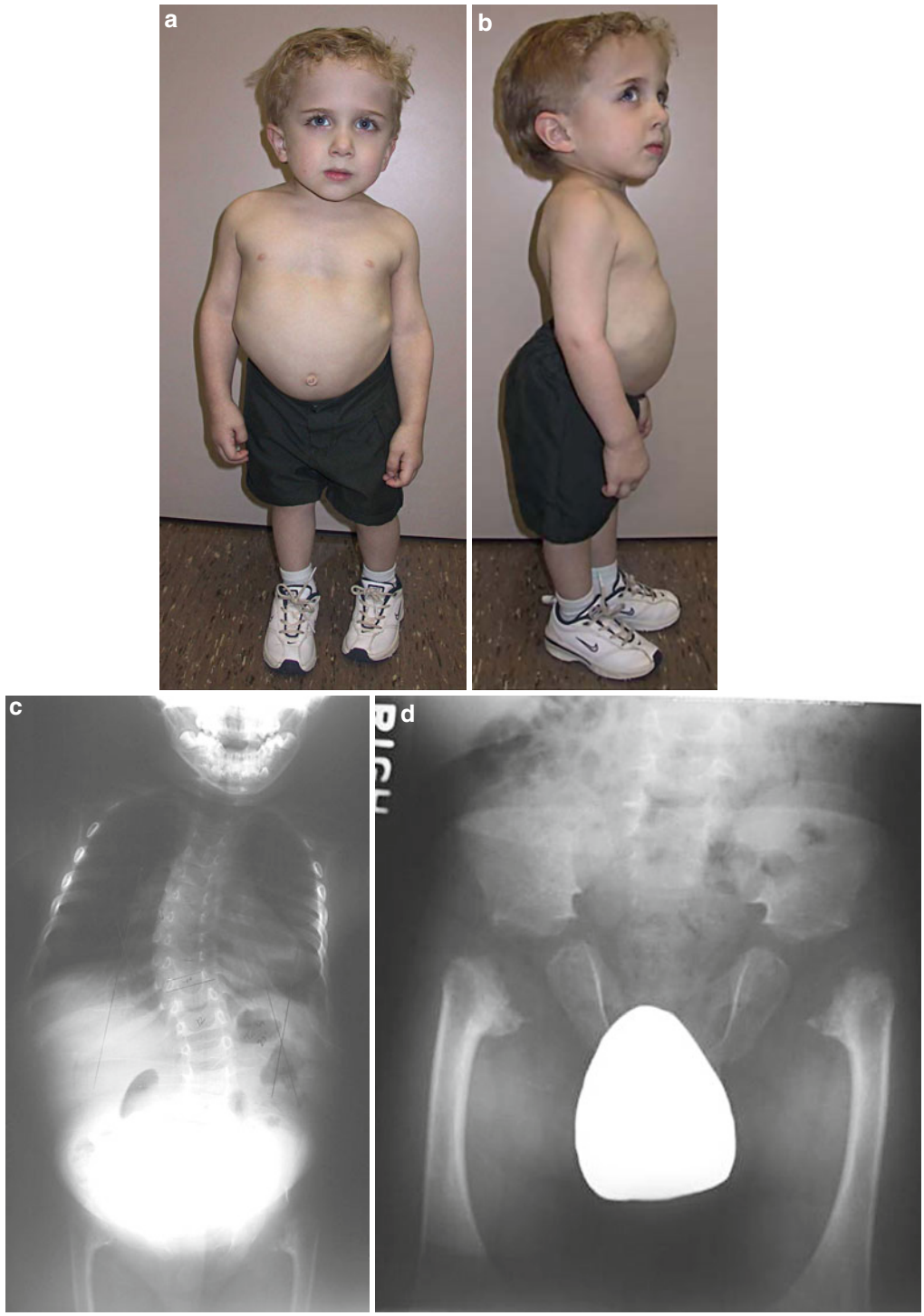

Fig. 3 (**a**–**d**) A boy with SED congenita showing short trunk, short, broad chest with pectus excavatum, globoid abdomen, and hyperlordosis. Radiographs showed lack of ossification of the femoral epiphysis, short femoral neck, generalized platyspondyly, and thoracolumbar scoliosis

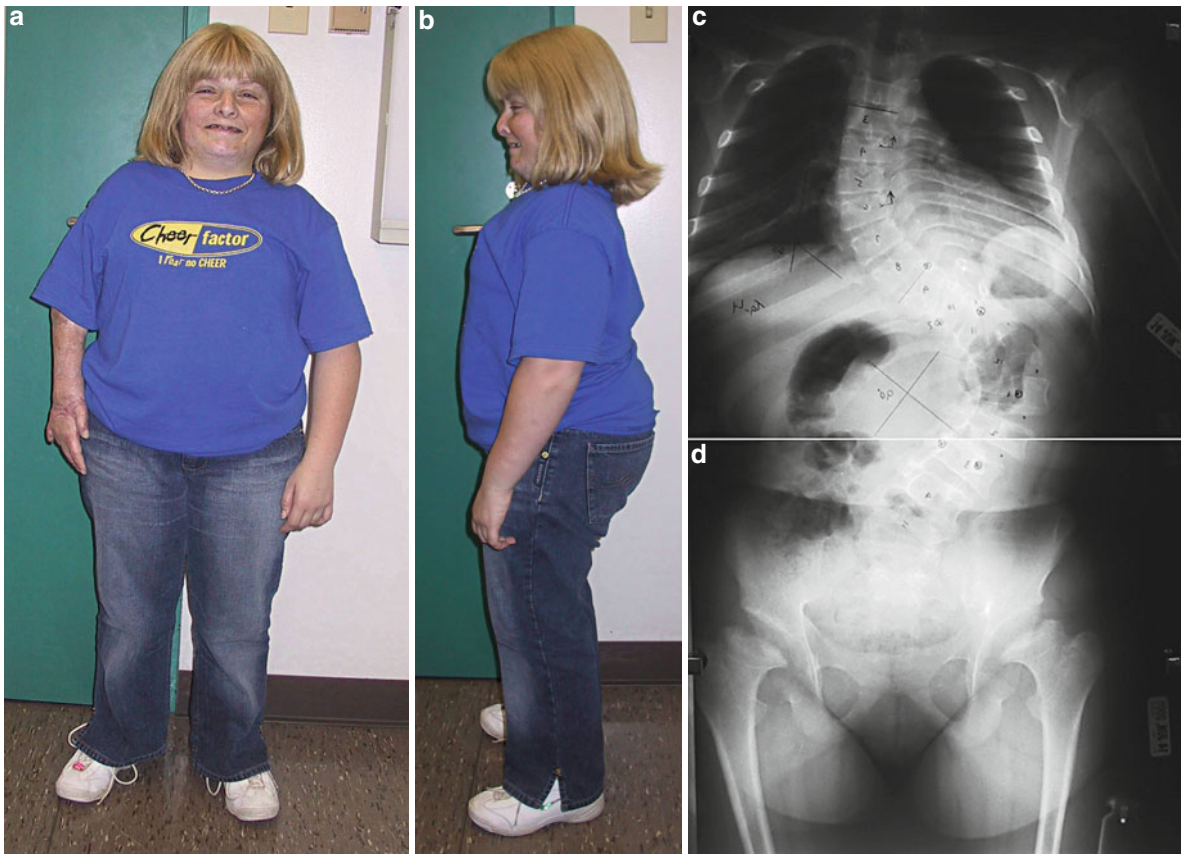

Fig. 4 (**a**–**d**) An adult with SED showing short-trunk dwarfism. Radiographs showed flat vertebral bodies, severe scoliosis, and retarded ossification of femoral head and neck

Fig. 5 (**a**–**d**) A 9-year-old boy with spondyloepiphyseal dysplasia tarda showing kyphosis. The spinal radiographs showed anterior body projection, widening of vertebral body spaces, and lumbar kyphosis. Femoral epiphysis was poorly developed (flat epiphyses) and acetabular sockets were not well formed

Stickler Syndrome

In 1965, Stickler et al. described a family with progressive myopia, retinal detachment and blindness, and premature degenerative changes in various joints. The disorder was subsequently termed "hereditary progressive arthroophthalmopathy." The incidence is estimated to be about 1 in 10,000 (Admiraal et al. 2002).

Synonyms and Related Disorders

Hereditary progressive arhroophthalmopathy

Genetics/Basic Defects

1. Inheritance: autosomal dominant with wide variation in expression
2. Association of the Stickler syndrome with following collagen gene mutations:
   a. *COL2A1* gene mutations (Hoornaert et al. 2010)
      i. Observed in membranous or type I vitreous phenotype (afibrillar phenotype)
      ii. The presence of vitreous anomalies, retinal tears or detachments, cleft palate and a positive family history was shown to be good indicator for a COL2A1 defect.
      iii. Stickler syndrome type 1 is predominantly caused by loss-of-function mutations in the COL2A1 gene as >90% of the mutations were predicted to result in nonsense-mediated decay.
   b. *COL11A1* gene mutations (Richards et al. 2010)
      i. Observed in beaded or type II vitreous phenotype
      ii. Stickler syndrome type II (Marshall syndrome)
         a) More severe facial features (short nose, midfacial flattening)
         b) High myopia
         c) Less risk of retinal detachment
         d) Moderate hearing impairment
      iii. Some mutations in *COL11A1* have been classified as Marshall syndrome, but as demonstrated by Annunen et al. (1999), the short nose, anteverted nares, midfacial hypoplasia, and flat nasal bridge that are common in cases of Marshall syndrome with *COL11A1* mutations, are also often present in young individuals with mutations in *COL2A1*, making differential diagnosis based on facial phenotypes difficult (Marjava et al. 2007).
   c. *COL11A2* gene mutations
      i. Cause nonocular Stickler syndrome type III
         a) Stickler-like facial features
         b) Mild to moderate deafness
         c) Normal eyes
      ii. Also found in patients with a recessively inherited variant denoted as otospondylomegaepiphyseal dysplasia (OSMED)
      iii. Also cause autosomal dominant nonsyndromic deafness (DFNA13)
   d. *COL9A1* mutations (autosomal recessive Stickler syndrome): vitreous syneresis with an optically empty vitreous due to progressive gel liquefaction (Van Camp et al. 2006)

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3. Genotype-phenotype correlations
   a. Type I Stickler syndrome: ocular Stickler syndrome with mutations in *COL2A1* (chromosome locus: 12q13.11-q13.2)
   b. Type II Stickler syndrome: ocular Stickler syndrome with mutations in *COL11A1* (chromosome locus: 1p21)
   c. Type III Stickler syndrome: nonocular Stickler syndrome with mutations in *COL11A2* (chromosome locus: 6p21.3)

Clinical Features

1. Considerable clinical variability within families and between families, explainable in part by locus and allelic heterogeneity
2. Ocular features
   a. Myopia
      i. Congenital
      ii. Nonprogressive
      iii. Of high degree
   b. Abnormalities of vitreous formation and gel architecture
      i. Pathognomonic of Stickler syndrome
      ii. A prerequisite for diagnosis
      iii. Vitreous anomalies
         a) Characteristic congenital "membranous" vitreous anomaly (type I phenotype) in type I Stickler syndromes
         b) Sparse and irregularly thickened bundles of fibers throughout the vitreous cavity (type II phenotype) in type II Stickler syndrome
   c. Retinal detachment: the most serious ophthalmologic complication
   d. Cataracts
   e. Strabismus
   f. Open-angle glaucoma
   g. No ocular abnormalities in Stickler syndrome type III
3. Hearing impairment (Admiraal et al. 2002)
   a. Considerable variability
   b. Conductive hearing impairment
      i. Resulting from recurrent otitis media
      ii. Secondary to cleft palate
   c. Sensorineural hearing impairment
      i. Type I Stickler syndrome with mutations in the *COL2A1* gene
         a) Occurring in 50–60%
         b) Typically mild to moderate degrees
         c) Predominantly affecting higher frequencies
         d) No tangible progression beyond presbycusis
      ii. Type II Stickler syndrome (Marshall syndrome) with the mutations in the *COL11A1* gene
         a) Occurring in 80–100%
         b) More severely affected
         c) Starting at a younger age or congenital in origin
         d) Showing progression
      iii. Type III Stickler syndrome with mutations in the *COL11A2* gene
         a) A typical feature
         b) Hundred percent penetrance
         c) Mild to moderate impairment
         d) Nonprogressive when accounted for presbycusis
         e) Showing different audiometric configurations
4. Associated anomalies
   a. Orofacial anomalies
      i. Facial bone hypoplasia
         a) Flat midface
         b) Depressed nasal bridge
         c) Maxillary hypoplasia
         d) Mandibular hypoplasia (Pierre-Robin anomaly)
      ii. High arched/cleft palate
      iii. Bifid uvula
      iv. Abnormal teeth
      v. Malocclusion
   b. Generalized musculoskeletal abnormalities
      i. Joint hyperextensibility
      ii. Enlarged joints
      iii. Premature osteoarthritis
      iv. Slender extremities
      v. Long fingers
      vi. Hypotonia
      vii. Relative muscle hypoplasia
      viii. Kyphosis

ix. Scoliosis
x. Pectus carinatum
xi. Accessory carpal ossicles
xii. Hip dislocation
xiii. Coxa valga
xiv. Genu valga
xv. Talipes equinovarus

c. Mitral valve prolapse
i. Fifty percent of patients in one series
ii. 0% in another series

5. Intelligence: normal
6. Clinical features seen in different types of Stickler syndrome (Li and Thorne 2010)
a. Type I
i. Ocular
a) Myopia
b) Vitreoretinal degeneration
c) Cataracts
d) Retinal detachment
ii. Musculoskeletal
a) Mild degenerative changes
b) Hypermobility
iii. Auditory: Normal to slight hearing impairment
iv. Craniofacial: cleft palate

b. Type II
i. Ocular
a) Congenital nonprogressive myopia
b) Cataracts
ii. Musculoskeletal
a) Mild degenerative changes
b) Hypermobility
iii. Auditory: early-onset sensorineural hearing loss
iv. Craniofacial: cleft palate

c. Type III
i. Ocular: none
ii. Musculoskeletal: early-onset osteoarthritis
iii. Auditory: high-tone sensorineural hearing loss
iv. Craniofacial: Pierre-Robin sequence

7. Differential diagnosis (Snead and Yates 1999; Bowling et al. 2000)
a. Wagner hereditary vitreoretinal degeneration
i. Consisting solely of ocular abnormalities
a) Myopia
b) Vitreous degeneration
c) Preretinal avascular membranes
d) Retinal degeneration and thinning
ii. No increased risk of retinal detachment or systemic abnormalities

b. Weissenbacher-Zweymüller syndrome and otospondylomegaepiphyseal dysplasia (OSMED)
i. Pierre-Robin sequence
ii. Snub nose
iii. Proximal limb shortening resolved by adulthood
iv. Dumbbell-shaped femora and humeri
v. Coronal vertebral clefts
vi. Sensorineural hearing loss
vii. No eye abnormalities
viii. *COL11A2* mutations
ix. Appears to represent the same entity as nonocular Stickler syndrome

c. Erosive vitreoretinopathy
i. Autosomal dominant eye disorder
ii. Phenotype resembling Wagner syndrome but lacking any systemic abnormalities
iii. Condition mapped to 5q13-q14 suggesting it may be an allelic variant of Wagner syndrome

d. Marshall syndrome
i. Autosomal dominant disorder
ii. Clinical phenotype
a) Cataracts
b) Myopia
c) Abnormal vitreous
d) Midfacial hypoplasia
e) Congenital deafness
iii. Associated with *COL11A1* mutation in a family affected with Marshall syndrome

e. Kniest dysplasia
i. Ocular abnormalities
a) Severe myopia
b) Vitreous veils
c) Perivascular lattice
d) Retinal detachment
e) Cataracts
ii. Systemic findings
a) Short trunk dwarfism
b) Kyphoscoliosis
c) Deafness
d) Depressed nasal bridge
e) Cleft palate

f. Spondyloepiphyseal dysplasia
g. Marfan syndrome

h. Goldmann-Farve syndrome
   i. A rare recessively inherited condition
   ii. Ocular abnormalities
      a) Night blindness
      b) Retinal detachment
      c) Pigmentary choroidoretinal degeneration
      d) Vascular sheathing in the fundus
i. Jansen syndrome
   i. Ocular abnormalities similar to Wagner syndrome
   ii. Absent systemic abnormalities
j. Congenital retinoschisis
   i. A sex-linked recessive trait
   ii. Usually occurring in emmetropic or hyperopic patients
   iii. Membrane-like structures in midvitreous

Diagnostic Investigations

1. Audiological testing for hearing loss
2. Radiographic features
   a. Generalized spondyloepiphyseal dysplasia
   b. Flattening of the epiphyses
   c. Narrowing of the diaphyses
   d. Flaring or widening of the metaphyses
   e. Wedging of the tubular bones
   f. Coxa valga
   g. Widening of femoral neck
   h. Acetabular protrusio
   i. Chondrolysis
   j. Avascular necrosis
   k. Premature arthritic changes
   l. Anterior maxillary and mandibular underdevelopment
3. Clinically available molecular genetic testing for mutations affecting four different genes (COL2A1, COL11A1, COL11A2, and COL9A1)
   a. Sequence analysis
   b. Deletion/duplication analysis

Genetic Counseling

1. Recurrence risk (Robin et al. 2010)
   a. Variable clinical expression of Stickler syndrome may complicate the genetic counseling (Faber et al. 2000).
      i. Exercise caution on assuming a de novo mutation: radiographic studies and clinical examination of the parents including formal testing of hearing and vision
      ii. Mutation search whenever possible
      iii. Uncertainty in predicting clinical consequences of inheriting a mutation
   b. Patient's sib
      i. Autosomal dominant inheritance (COL2A1, COL11A1, COL11A2-related Stickler syndrome)
         a) A 50% risk if a parent has Stickler syndrome
         b) A low recurrence risk if the parents are clinically affected and the disease-causing mutation not identified
      ii. Autosomal recessive inheritance (*COL9A1*): a 25% risk
   c. Patient's offspring
      i. Autosomal dominant: a 50% risk
      ii. Autosomal recessive: risk not increased unless the spouse is a carrier
2. Prenatal diagnosis
   a. Ultrasonographic demonstration of Pierre-Robin sequence as a part of Stickler syndrome
   b. Mutation analysis on amniocytes or CVS cells in at-risk families with known mutations
   c. Linkage analysis of the 3'VNTR polymorphism on the involved gene (*COL2A1*) using amniocytic DNA
   d. Preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutations in the family
3. Management (Bowling et al. 2000)
   a. Early evaluation of at-risk patients for the development of the following complications
      i. Retinal tears
      ii. Retinal detachment
      iii. Cataracts
      iv. Glaucoma
   b. Long-term monitoring
   c. Cleft palate repair with appropriate feeding techniques
   d. Corrective lenses for myopia
   e. Avoid contact sports which may lead to retinal detachment
   f. Laser photocoagulation of vitreoretinopathy as preventive treatment for retinal detachment

g. Surgical repair of retinal detachments and remove cataracts with possible lens implantation
h. Glaucoma management
i. Corrective treatment for strabismus
j. Hearing aids for hearing loss
k. Speech therapy
l. Symptomatic treatment for arthropathy
    i. Joint pain management
    ii. Appropriate splints for strengthening and stabilizing lax joints
    iii. Braces or aids to assist daily activities
    iv. Hydrotherapy or other physical therapy modalities to increase range of motion, endurance, and strength
m. Management for mitral valve prolapse
    i. Antibiotics prophylaxis
    ii. Beta-blocker for symptomatic patients

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Fig. 1 A 32-year-old female with Stickler syndrome having severe myopia, retinal detachment, cleft palate, sensorineural hearing loss, mitral valve prolapse, hyperextensible joints, and severe degenerative joint disease

Sturge-Webber Syndrome

Sturge-Weber syndrome comprises of vascular malformations of the central nervous system and the port-wine stain or nevus flammeus of the face in a trigeminal nerve distribution. The syndrome is also known as encephalotrigeminal angiomatosis. The incidence is estimated to be approximately 1 in 50,000 (Sturge 1879; Parkes Weber 1922; Thomas-Sohl et al. 2004).

Synonyms and Related Disorders

Encephalofacial or Encephalotrigeminal angiomatosis

Genetics/Basic Defects

1. Genetics
   a. A sporadic, nonfamilial disease
   b. Uncertain inheritance: only a few familial clusters of the syndrome reported; most of these have not exhibited the clear-cut autosomal dominant inheritance pattern
   c. Proposed to represent a genetically mosaic condition. Lesions in the Sturge-Weber syndrome result from somatic mutations in affected areas, such as the port-wine stain or leptomeningeal angioma, but not in blood or normal skin (Huq et al. 2002).
   d. A potential role of fibronectin in the pathogenesis of Sturge-Weber syndrome. The gene expression findings in fibroblast supported the hypothesis of a somatic mutation underlying the disorder.
   e. A novel synonymous mutation (c.1229G > A) (p.K420K) of RASA1 was identified in a Chinese patient with sporadic Sturge-Weber syndrome (Zhou et al. 2011): Further study is needed.
2. Basic defect: caused by residual embryonal blood vessels and their secondary effects on surrounding brain tissue
3. Pathophysiology: Neurologic dysfunction of the syndrome results from secondary effects of residual embryonal blood vessels on surrounding brain tissue.
   a. Hypoxia
   b. Ischemia
   c. Venous occlusion
   d. Thrombosis
   e. Infarction
   f. Vasomotor phenomenon
   g. Seizures

Clinical Features

1. Variable natural history of the disease (Mirowski et al. 1999)
2. Three cardinal features (Comi 2003)
   a. Capillary malformation (port-wine stain, cutaneous angioma) in the upper trigeminal neural distribution
      i. Involves the ophthalmic branch of the trigeminal nerve, in particular, the upper eyelid and supraorbital region
      ii. May extend into the maxillary and mandibular regions

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iii. May be associated with soft tissue and bony overgrowth
iv. May be hidden in scalp or mouth
v. May be absent in the forme fruste of Sturge-Weber syndrome

b. Ocular abnormalities
i. Ipsilateral to the port-wine stain
ii. Can be seen with V1 or V2 involvement
iii. Glaucoma (60%)
iv. Buphthalmos
v. Vascular malformations of the conjunctiva, episclera, choroids, and retina

c. Leptomeningeal vascular malformation (angioma)
i. May be unilateral (more common) or bilateral
ii. Usually ipsilateral to port-wine stain
iii. Capillary and venous anomalies of leptomeninges
iv. No correlation between the size of facial and CNS malformations

3. CNS manifestations
a. Seizures (75–90% of cases)
b. Mental retardation present in approximately 50% of cases
c. Contralateral hemiplegia or hemisensory deficits
d. Contralateral homonymous hemianopsia (impaired vision in half of the visual field)
e. Headaches
f. Developmental delay
g. Learning disorders
h. Attention deficit hyperactivity disorder

4. Soft tissue and skeletal overgrowth (60–83%) (Greene et al. 2009)
a. Often exhibit localized cutaneous growths, either pyogenic granuloma or fibrovascular nodules
b. Do not combine venous, lymphatic, or arterial anomalies in an extremity, although simple diffuse venous varicosities have been seen
c. Often erroneously diagnosed as having either Klippel-Trenaunay syndrome (extremity capillary-lymphatico- venous malformation with overgrowth) or Parkes Weber syndrome (extremity capillary-arteriovenous malformation with overgrowth)

5. Long-term outcome (Arzimanoglou et al. 2000)
a. Distribution of port-wine stain
i. Cranial: 98%
ii. Extracranial: 52%
b. Glaucoma (60%)
c. Seizures (83%)
d. Developmental delay usually associated with seizures
i. With seizures: 43%
ii. Without seizures: 0%
e. Presence of behavior and emotional problems
i. With seizures: 85%
ii. Without seizures: 58%
f. Require special education
i. With seizures: 71%
ii. Without seizures: 0%
g. Employability
i. With seizures: 46%
ii. Without seizures: 78%
h. Normal fertility
i. Indications of progressive nature
i. Increasing duration of seizures and postictal deficits
ii. Increase in atrophy or of calcified lesions or both

Diagnostic Investigations

1. Radiography
a. Asymmetric skull
b. Double contour "gyriform" patterns of intracranial calcifications
i. Classic "tram-line," "tram-track", or "trolley-track" intracranial calcifications
a) Considered pathognomonic prior to modern neuroimaging
b) Often a late finding
c) May not be present initially
ii. Distribution
a) In the subcortical region, primarily in the parietal and occipital regions
b) Unilateral (80%) or bilateral (20%)

2. EEG to evaluate seizure activities
3. Angiographic findings
a. Lack of superficial cortical veins
b. Nonfilling dural sinuses
c. Abnormal, tortuous vessels

4. CT scan findings (Di Rocco and Tamburrini 2006)
a. Intracranial dense gyriform or "tram-truck" calcifications which more commonly affect the parieto-occipital cortical area and/or the choroid plexus and are usually absent in early infancy

   b. Diffuse high attenuation of the superficial and deep white matter, presumably due to microcalcifications
   c. Gyriform enhancement after iodinated contrast enhancement, expression of the pial angiomatosis
   d. Brain atrophy, consequence of vascular steal phenomena of the pial angioma on the surrounding cortical structures
   e. Thickening of the calvarium, more frequently observed in patients with early onset symptoms as an indirect feature of loss of the brain substance
   f. Abnormal draining veins
   g. Enlarged ipsilateral choroid plexus
   h. Blood-brain barrier breakdown during seizures
5. MRI findings: the gold standard imaging modality for the identification of structural brain abnormalities (Di Rocco and Tamburrini 2006)
   a. Leptomeningeal enhancement with Gd-diethyltriaminepentaacetic acid on T1-weighted images is considered one of the most important signs that help define the extent of the vascular malformation; however, its absence does not exclude the diagnosis (Elster and Chen 1990).
   b. Enlarged choroid plexus
   c. Sinovenous occlusion
   d. Cortical atrophy
   e. Accelerated myelination
6. Single-photon emission computed tomography to measure cerebral blood flow (Pinton 1997)
   a. Hyperperfusion early (before 1 year)
   b. Hypoperfusion late (after 1 year)
7. Positron emission tomography (PET) for hypometabolism
8. Histology
   a. Thickened and discolored leptomeninges
   b. Abnormal venous structures
   c. Calcifications
      i. Cerebral vessel walls
      ii. Perivascular tissue
      iii. Rarely within neurons

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: low
   b. Patient's offspring: low
2. Prenatal diagnosis: not been reported
3. Management (Thomas-Sohl 2004)
   a. Medical care
      i. Medications for recurrent headaches/migraine
         a) Ibuprofen: first choice
         b) Abortive therapy with sumatriptan
         c) Preventive therapy with propranolol or nortriptyline
      ii. Management of glaucoma to control the intraocular pressure and prevent progressive visual loss and blindness
         a) Beta blocker drops: first choice
         b) Adrenergic drops or carbonic anhydrase inhibitor drops: second choice
      iii. Anticonvulsants for seizure (partial epilepsy most prevalent in children) control
         a) Carbamazepine: first choice
         b) Valproate, topiramate, phenobarbital, phenytoin
      iv. Strokelike episodes: aspirin
      v. Neurobehavioral problems
         a) Methylphenidate: first choice
         b) Clonidine: second choice
         c) Dextroamphetamine or risperidone
      vi. Dermatologic laser therapy for port-wine stain
   b. Surgical care
      i. Surgery (trabeculectomy) for glaucoma if medications fail to lower intraocular pressure
      ii. Option of early surgery for patients with Sturge-Weber syndrome with drug-resistant epilepsy
         a) Focal cortical resection
         b) Hemispherectomy
         c) Corpus callosotomy
         d) Vagal nerve stimulation
      iii. Lesionectomy provided that the pial angioma is unilateral and the resection can be complete

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Fig. 1 An infant with Sturge-Weber syndrome showing port-wine stain primarily affecting *right* side of the face

Fig. 2 A girl with typical Sturge-Weber syndrome showing port-wine stain affecting *left* side of the face

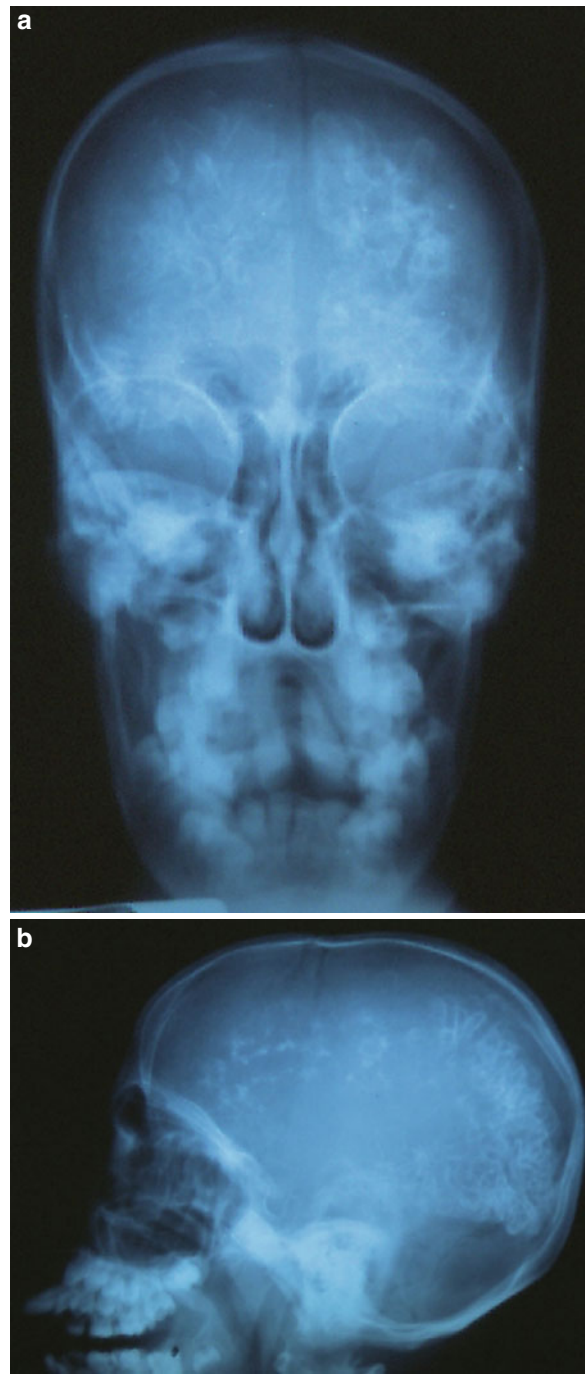

Fig. 3 (**a**, **b**) Radiographs of the skull in another patient demonstrate the typical gyriform pattern of cortical calcification

Tay-Sachs Disease

Tay-Sachs disease is a hereditary neurodegenerative disorder resulting from excess storage of GM2 ganglioside within the lysosomes of cells, caused by deficiency of hexosaminidase A. The incidence of the disease is estimated to be 1 in 3,600 in Ashkenazi Jews with carrier frequency of 1 in 30 and 1 in 360,000 in other population with carrier frequency of 1 in 300. Tay-Sachs disease is the most frequently occurring sphingolipidoses.

Synonyms and Related Disorders

GM2-gangliosidosis type 1; Hexosaminidase A deficiency

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Biochemical defect: deficiency of the isoenzyme β-hexosaminidase A (Hex A)
3. Genetic basis
   a. Mutations in the *HEXA* gene (on chromosome 15q23-q24) that codes for the subunit of the β-hexosaminidases result in the deficiency of Hex A (αβ) that results in Tay-Sachs disease.
   b. Over 100 different mutations have been identified in the *HEXA* gene to date.
   c. Presence of a small number of common mutations in populations where the carrier frequency is high (Sutton 2002)
      i. Ashkenazi Jews (Bach 2001)
         a) Two common mutations associated with Tay-Sachs disease [a four base-pair insertion into exon 11 of the *HEXA* gene (1278insTATC) accounting for 75–80% of all mutations in this population; a splice site mutation in intron 12 (1421+1G → C) accounting for 15% of mutations]
         b) One mutation associated with a late-onset form of the disease (G269S in 3% of carriers)
         c) Pseudodeficiency polymorphism (R247W in 2% of carriers)
      ii. Pennsylvania Dutch
         a) An intron 9 splice site mutation (1,073 +1G → A)
         b) Pseudodeficiency allele (R247W)
      iii. Cajuns in Southern Louisiana
         a) An intron 9 splice site mutations (1,073 +1G → A)
         b) Four base-pair insertion in exon 11 (1278insTATC)
      iv. French Canadians in Eastern Quebec
         a) A large (7.6 kb) deletion at the 5′ end of the gene
         b) A splice site mutation in intron 7 (805 +1G → A)
         c) Common 4 base-pair insertion in exon 11 seen in Ashkenazi Jews (1278insTATC)

Clinical Features

1. Classic infantile acute-onset Tay-Sachs disease
   a. Natural history (Sutton 2002)
      i. Appears normal at birth
      ii. Normal motor development in the first few months of life

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iii. Progressive weakness and loss of motor skills beginning around 2–6 months of life
iv. Followed by decreased social interaction, increased sensitivity to noise (hyperacusis), and an increased startle response to noise
v. Progressive neurodegeneration
vi. Uniformly fatal: death from pneumonia usually occurring between 2 and 5 years of age

b. Clinical features
i. Delayed development
ii. Poor feeding
iii. Lethargy
iv. Hypotonia
v. Hyperreflexia
vi. Opisthotonos
vii. Hyperacusis
viii. A cherry red spot on the fovea centralis of the macula, representing loss of ganglion cells in the foveal area with the remaining ones filled with the ganglioside
ix. Progressive neurodegeneration
a) Developmental regression
b) Macrocephaly secondary to accumulation of storage material within the brain after about 15 months of age. There is no evidence of hepatosplenomegaly or other peripheral evidence of storage disease.
c) Myoclonic seizures, most during the first year of life
d) Progressive macular degeneration leading to blindness, usually by 1 year of age
e) Deafness
f) Spasticity
g) Complete disability

2. Subacute (juvenile) Tay-Sachs disease (2–18 years of age) (Maegawa et al. 2006): characterized by progressive neurologic deterioration that mainly affects motor and spinocerebellar function leading to:
a. Progressive spasticity with seizures and dementia
b. A vegetative state by late childhood or mid-teens
3. Late-onset (adult) Tay-Sachs disease (Shapiro et al. 2008)
a. A chronic, progressive, lysosomal storage disorder caused by a partial deficiency of beta hexosaminidase A (HEXA) activity
b. Deficient levels of HEXA result in the intracellular accumulation of GM_2-ganglioside, resulting in toxicity to nerve cells
c. Clinical manifestations primarily involve the central nervous system (CNS) and lower motor neurons, including:
i. Ataxia
ii. Weakness
iii. Spasticity
iv. Dysarthria
v. Dysphagia
vi. Dystonia
vii. Seizures
viii. Psychosis
ix. Mania
x. Depression
xi. Cognitive decline
d. The prevalence of peripheral nervous system: a predominantly axon loss polyneuropathy affecting distal nerve segments in the lower and upper extremities (27% of cases)

Diagnostic Investigations

1. Diagnosis and carrier testing
a. Indications for carrier testing
i. Fully or partially Jewish
ii. Pennsylvania Dutch
iii. Cajuns of Southern Louisiana
iv. French Canadians of Eastern Quebec
b. Preconceptional counseling for at-risk couples
c. Enzyme assay
i. Using fluorimetric study measuring activity of both Hex A and Hex B in either serum or leukocytes
ii. Decreased activity of Hex A with normal or increased activity of Hex B in carriers
iii. Limitations of serum assay
a) Overlapping of the values between carriers and noncarriers
b) Unreliable in pregnant women and in women taking oral contraceptives
c) Inability to distinguish carriers of pseudodeficiency alleles from carriers of disease-causing mutations
iv. Clarification of abnormal or inconclusive results of enzyme assay by:
a) Enzyme assay on leukocytes

b) DNA mutation analysis for common mutations and pseudodeficiency alleles

d. Molecular genetic testing (Kaback and Desnick 2011)
   i. Targeted mutation analysis: using a panel of common *HEXA* mutations when assay of HEX A enzymatic activity is abnormal:
      a) In a symptomatic individual in order to identify the disease-causing mutations
      b) In an asymptomatic individual to evaluate for the presence of a pseudodeficiency allele
   ii. Sequence analysis/mutation scanning: to identify *HEXA* mutations in an individual who:
      a) Is affected but had only one or neither mutation identified using a panel of standard mutations, or
      b) Has carrier-level enzymatic results but did not have a mutation identified using a panel of standard mutations

2. CT scan of the brain: areas of low density in the basal ganglia and cerebral white matter
3. MRI of the brain: an increased signal in the basal ganglia and cerebral white matter on T_2-weighted images
4. MR spectroscopy (Aydin et al. 2005)
   a. Demonstrates an increase in myoinositol/creatine and choline/creatine ratios with a decrease in the N-acetyl aspartate/creatine ratio
   b. The spectroscopy findings support demyelination, gliosis, and neuronal loss in the neuropathological process of Tay-Sachs disease.
5. Characteristic neuropathological findings (Kaback et al. 1993)
   a. Pathologic changes are restricted to the nervous system.
   b. Ballooning of neurons with massive intralysosomal accumulation of lipophilic membranous bodies
   c. Nature and structure of the stored intraneuronal material : GM2 ganglioside
   d. Abnormal cytoplasmic inclusion bodies identified in fetal spinal cord at 12 weeks and retina and spinal ganglia during 19th–22nd week of gestation (Adachi et al. 1974)
   e. Cisternae of the endoplasmic reticulum: the primary site of lipid accumulation in neurons during the fetal stage of Tay-Sachs disease (Adachi et al. 1974)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring
      i. Acute infantile form: not surviving to reproductive age
      ii. Late-onset form may reproduce: risk not increased unless the spouse is a carrier
2. Prenatal diagnosis (Kaback and Desnick 2011) is available when HEX A enzyme assay has shown both parents to be heterozygous, and molecular genetic testing has ruled out the presence of a pseudodeficiency allele in either parent:
   a. Enzyme analysis (absence of hexosaminidase A) on cultured amniocytes or chorionic villus cells
   b. DNA analysis when one of the common mutations had been identified in the family
      i. Preferred method of prenatal diagnosis
      ii. Less prone to error
   c. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified in an affected family member.
3. Management
   a. No effective treatment to alter the natural history
   b. Primarily supportive
      i. Provide adequate nutrition and hydration
      ii. Manage infections
      iii. Protect airway
      iv. Control seizures
      v. Bowel management
   c. Enzyme replacement therapy and bone marrow transplantation: not yet successful
   d. Options to modify 25% risk of having an affected child with each pregnancy if both partners are found to be carriers (Sutton 2002)
      i. Prenatal diagnosis by amniocentesis or chorionic villus sampling
      ii. Egg or sperm donation
      iii. Preimplantation genetic diagnosis
      iv. Adoption

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Fig. 1 A cherry red spot on the fovea centralis of the macula from the fundus of an infant with Tay-Sachs disease

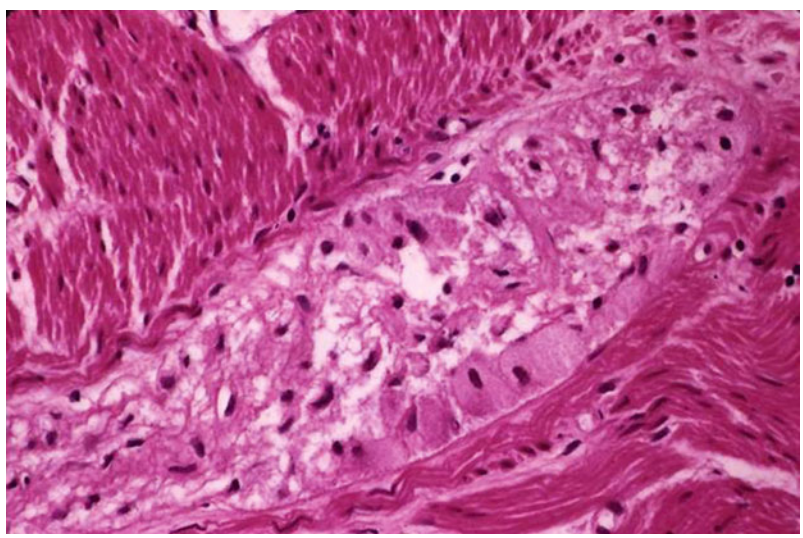

Fig. 2 Myenteric plexus of the rectum (H & E, ×400) showing many enlarged ganglion cells with abundant foamy cytoplasm due to ganglioside storage. Rectal biopsy can be a good source of neurons in confirming neuronal storage disease. In this patient, Tay-Sachs disease was confirmed by electron microscopic examination of ganglion cells

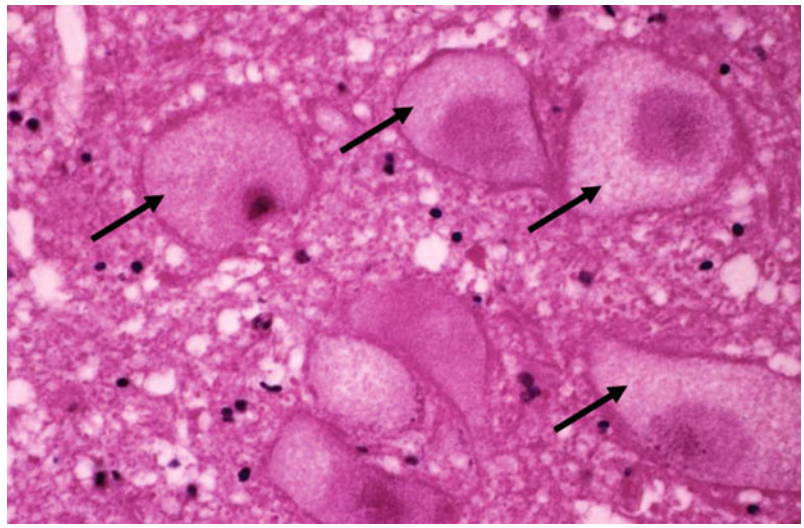

Fig. 3 A section of medulla showing a group of neurons with markedly distended foamy cytoplasm (*arrows*) due to accumulation of GM_2 ganglioside (H & E, ×1,000)

Tetrasomy 9p Syndrome

Tetrasomy 9p syndrome, a clinically diagnosable condition, is a rare cytogenetic disorder characterized by tetrasomy 9p associated with a distinctive patterns of multiple congenital anomalies. In 1973, Ghymers et al. first described the syndrome.

Synonyms and Related Disorders

Supernumerary isochromosome 9p syndrome

Genetics/Basic Defects

1. Caused by de novo supernumerary isochromosome 9p (presence of four copies of the short arm of the chromosome 9)
   a. Pure tetrasomy 9p
   b. Tetrasomy involving the varying segment of the short arm of chromosome 9
2. Cytogenetic types of tetrasomy 9p
   a. Presence of an extra dicentric chromosome 9 consisting entirely of 9p
   b. Presence of an extra dicentric chromosome 9 consisting of 9p and the proximal part of 9q
   c. Mosaicism involving tetrasomy 9p: mosaic of i(9p) cells
3. Hypotheses proposed to explain tetrasomy 9p
   a. A meiosis I disturbance with nondisjunction and rearrangement in two of the four chromatids of a bivalent 9, resulting in the formation of an isochromosome 9p
   b. Meiosis II nondisjunction followed by rearrangements (isochromosome formation) with duplication of the short arm and loss of the acentric long arm at the subsequent mitosis
   c. Dicentric vs monocentric (de Azevedo Moreira et al. 2003)
      i. Using conventional cytogenetics and banding techniques revealed an additional dicentric 9p chromosome in most cases.
      ii. Using molecular studies using a chromosome 9 classic satellite probe shows an error in the division of centromere 9 by a double-break event, resulting in the formation of a monocentric isochromosome 9p.

Clinical Features

1. Craniofacial abnormalities
   a. Delayed closure of the anterior fontanel
   b. Ocular hypertelorism
   c. Telecanthus
   d. Strabismus
   e. Enophthalmos/microphthalmia
   f. Epicanthal folds
   g. Prominent beaked or bulbous nose
   h. Down-turned corners of the mouth
   i. Microretrognathia
   j. Low-set, malformed ears
   k. Cleft lip/palate
   l. High-arched palate
2. Cardiac anomalies
   a. Ventricular septal defect
   b. Atrial septal defect
   c. Patent ductus arteriosus
   d. Persistent left superior vena cava

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   e. Double outlet of the right ventricle
   f. Hypoplastic right ventricle
   g. Hypoplastic left heart ventricle
3. Lung anomalies
   a. Lung hypoplasia
   b. Abnormal lobulation of the lung
4. Renal anomalies
   a. Renal hypoplasia
   b. Multicystic dysplasia
   c. Hydroureter
   d. Hydronephrosis
5. Genital anomalies
   a. Cryptorchidism
   b. Genital hypoplasia
   c. Micropenis
   d. Hypoplastic shawl-like scrotum
   e. Ambiguous genitalia
6. Gastrointestinal anomalies
   a. Intestinal malrotation
   b. Hirschsprung disease
7. CNS anomalies
   a. Psychomotor retardation
   b. Hypotonia
   c. Microcephaly
   d. Brachycephaly
   e. Hydrocephalus
   f. Cerebral hypoplasia
   g. Dandy-Walker cyst
   h. Absence of olfactory bulbs
   i. Hypoplastic cerebellum
8. Skeletal anomalies
   a. Growth retardation
   b. Short stature
   c. Short neck
   d. Dysplastic fingernails
   e. Limb anomalies
   f. Clinodactyly of the fifth fingers
   g. Club feet
   h. Articular dislocations
   i. Shortened hands and feet
9. Other features
   a. Single umbilical artery
   b. Failure to thrive
   c. Redundant skin
   d. Widely spaced nipples
   e. Single palmar crease
   f. Sacral dimple
10. The severity of the phenotype correlates with size of the tetrasomic region and the degree of tissue mosaicism for the tetrasomy 9p.

Diagnostic Investigations

1. Cytogenetic studies to identify supernumerary marker chromosomes (Tan et al. 2007)
   a. Conventional and high-resolution analyses
   b. A whole-chromosome paint probe for chromosome 9 to identify the supernumerary chromosome, using the fluorescence in situ hybridization (FISH) technique (Callen et al. 1992; Crolla et al. 1998)
   c. Microdissection and reverse FISH (micro-FISH) (Mahjoubi et al. 2005; de Pater et al. 2006)
   d. Multiplex-FISH (M-FISH) technique (Uhrig et al. 1999)
   e. Centromere-specific multicolor-FISH assays (Nietzel et al. 2001)
   f. AcroM-FISH technique (Langer et al. 2001)
2. Echocardiography for cardiovascular malformations
3. Radiography
   a. Microcephaly
   b. Hypertelorism
   c. Hypoplastic first and 12th ribs
   d. Kyphoscoliosis
   e. Clinodactyly and brachymesophalangy of the fifth fingers
   f. Delayed ossification of pubic bones and ischiopubic synchondrosis
   g. Delayed ossification of femoral heads
   h. Spina bifida occulta
   i. Generalized osteoporosis
4. Ultrasonography of renal abnormalities

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: patient not surviving to reproductive age

2. Prenatal diagnosis
   a. Ultrasonography (Tan et al. 2007)
      i. Intrauterine growth retardation
      ii. Genitourinary/renal anomalies
      iii. Cleft lip/palate
      iv. CNS anomalies
         a) Dandy-Walker malformation
         b) Ventriculomegaly
         c) Hypoplastic/absent vermis
         d) Agenesis of corpus callosum
      v. Limb malformations
      vi. Vertebral anomalies
      vii. Cardiac anomalies
      viii. Genitourinary anomalies
      ix. Polyhydramnios/oligohydramnios
   b. Chromosome analysis of amniocytes, CVS, or fetal blood: Microdissection and pre-G-banded FISH is important in determining the origin of supernumerary marker chromosome in prenatal diagnosis.
3. Management
   a. Early intervention programs for mild developmental delay with minor anomalies
   b. Supporting care for severe cases with early death

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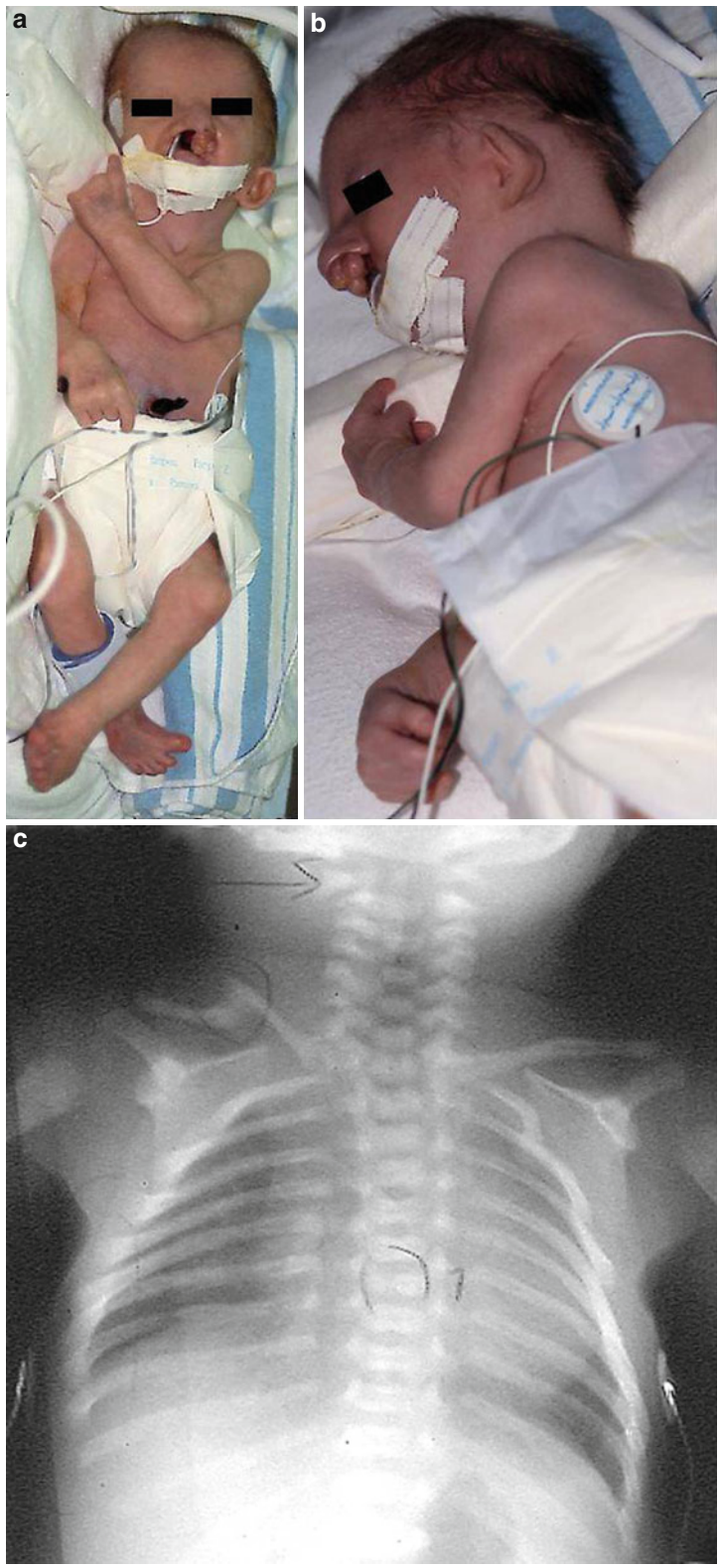

Fig. 1 (**a**–**c**) An infant with tetrasomy 9p syndrome presenting with widened anterior fontanel, microbrachycephaly, a broad nasal root, telecanthus, bilateral cleft lip and palate, retromicrognathia, small eyes, low-set lop ears, and a skin tag on the antihelix of the right ears. In addition, the infant had short neck with excess nuchal fold, bilateral webbing of the anterior axillary folds, pectus excavatum, congenital heart defects, right hydronephrosis, diastasis recti with an umbilical hernia, a right inguinal hernia, sacral dimple with a tag, micropenis, bilateral metatarsus adductus, bilateral transverse palmar creases, clinodactyly of the fifth fingers, short thumbs, and hypoplastic nails. Chest X-ray showed hemivertebrae in the thoracic spine and fractured right clavicle with callus formation. A rectal biopsy confirmed the diagnosis of Hirschsprung disease

Thalassemia

The term thalassemia was first applied to the anemias encountered frequently in people of the Italian and Greek coasts and nearby islands. The term now refers to a group of inherited disorders of globin chain synthesis. Thalassemia comprises of a group of hemoglobinopathies, which are classified according to the specific globin chain (α or β) whose synthesis is impaired. Thus, α- and β-thalassemia are depression of synthesis of the respective chain.

Synonyms and Related Disorders

Alpha-thalassemia (Hb H disease or alpha-thalassemia intermedia, Hb Bart's hydrops fetalis or alpha thalassemia major); Beta-thalassemia (beta-thalassemia major or Cooley anemia or homozygous beta-thalassemia, beta-thalassemia intermedia or compound heterozygote, beta-thalassemia minor or beta-thalassemia trait)

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. α-thalassemia (Vichinsky 2010)
   a. Normal fetal hemoglobin synthesis
      i. Early in gestation, embryonic hemoglobins (Gower1, Gower2, and Portland), which do not contain α-globin chains, are the predominant hemoglobins.
      ii. They are rapidly replaced by fetal and then adult hemoglobin, which contain α-globin chains.
      iii. Therefore, α-thalassemia mutations become phenotypically evident by 12 weeks of gestation.
   b. Synthesis of α-chains is directed by four α-genes, two on each chromosome 16.
   c. α-thalassemia represents a group of conditions with reduced or absent synthesis of one to all four of α-globin genes.
      i. α-thalassemia-2 (α-/αα): resulting from deletion of one of the two α-globin genes
      ii. α-thalassemia-1 (−−/αα): resulting from deletion of both α-globin genes
      iii. Hb H disease (−−/−α): resulting from deletion of three α-globin genes
      iv. Hb Bart's hydrops fetalis (−−/−−): resulting from deletion of all four α-globin genes: Physiologically nonfunctional homotetramers γ_4 and β_4 make up most of the hemoglobin in the erythrocytes in infants with the Bart's hydrops fetalis syndrome.
   d. When both α-genes on a single chromosome are inactive, the designation α^o-thalassemia is used. When there is some production of α-globin chains, α^+-thalassemia is designated.
3. β-thalassemia
   a. Synthesis of β-chains: directed by a single β-gene on each chromosome 11
   b. Caused by the reduced (β^+) or absent (β^o) synthesis of the β-globin chains of the hemoglobin tetramer which is made up of two α-globin and two β-globin chains ($\alpha_2\beta_2$).
   c. Mutations in β-thalassemia

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i. In contrast to the α-thalassemias, most of the common β-thalassemia mutants are caused by point mutations rather than by gene deletion.
ii. Single base–pair mutations in the DNA alter processing of messenger RNA: most common
iii. Chain terminator defects
iv. Frameshift mutations
v. Polyadenylation mutations
vi. Promoter mutations

d. β^{o}-thalassemia
i. The mutations prevent β-globin chain synthesis entirely.
ii. Absent β-globin synthesis in β^{o}-thalassemia homozygotes
iii. Accounts for about one-third of thalassemia patients

e. β^{+}-thalassemia
i. The mutations prevent β-chain synthesis partially.
ii. β-globin synthesis reduces to 5–30% of normal levels in β^{+}-thalassemia homozygotes.

f. β^{+}/β^{o}-thalassemia compound heterozygotes

4. Pathogenesis (Yaish 2010)
a. Basic defect in all types of thalassemia: imbalanced globin chain synthesis
b. A decrease in the rate of production of a certain globin chain (α, β, γ, δ) impedes hemoglobin (Hb) synthesis and creates an imbalance with the other globin chain that normally produce globin chains.
c. Consequences of impaired production of globin chains
i. Result in less Hb deposit in each RBC, leading to hypochromasia
ii. Deficiency in Hb causes RBCs to be smaller, leading to the classic hypochromic microcytic features of thalassemia.

5. Phenotype-genotype correlation (Cao and Galanello 2010)
a. Homozygosity or compound heterozygosity for β-thalassemia most commonly results in the clinical phenotype of transfusion-dependent thalassemia major.
b. However, a consistent proportion of homozygotes develop milder forms, called thalassemia intermedia, which range in severity from thalassemia major to the β-thalassemia carrier state.
c. Ascertained molecular mechanisms leading to thalassemia intermedia
i. β-thalassemia mutations
a) Mild mutation
b) Silent mutation
c) Mild/silent mutation
ii. Coinherited α-thalassemia
a) Single α-globin gene deletion (−α/αα)
b) Deletion of two α-globin gene (−α/−α or – /αα)
c) Point mutations of the major α-2-globin gene
iii. Genetic determinant of high Hb F production
a) Due to the β-thalassemia mutation per se (δβ-thalassemia, β-promoter deletion)
b) Coinherited Agamma or Ggamma promoter mutation (−158 Ggamma (A → T); −196 Agamma (C → T))
c) Heterocellular HPFH, BCL11A on chromosome 2, and HBS1L-MYB region on chromosome 6

Clinical Features

1. α-thalassemia (Harteveld and Higgs 2010)
a. The most common genetic disorder of hemoglobin synthesis, affects up to 5% of the world's population (Vichinsky 2010)
b. Found in people of African descent, Indochina, Malaysia, and China
c. Severity of resulting anemia quite variable ranging from asymptomatic carriers to a fatal in utero disease: depends on the number of functioning α-genes
i. α-thalassemia-2 or silent carrier α-thalassemia (α-/αα) (deficiency of only one globin gene)
a) Twenty-five percent of African Americans
b) 3.4% of Greek Americans
c) Slight microcytic red blood cells
d) Borderline or minimal anemia
ii. α-thalassemia-1 or α-thalassemia trait (– /αα) (deficiency of two globin genes)
a) Fifteen to twenty percent of Thai
b) Mildly anemic

c) Microcytic red blood cells
d) Slight variation in red blood cell size
e) Mild splenomegaly
f) Work capacity not impaired
g) Same phenotypic effect in the individual homozygous for α-thalassemia-2 (α−/α−): This form is much more common in black populations.

iii. Hb H disease or α-thalassemia intermedia (–/−α) (deficiency of three globin genes)
a) One percent of Thai
b) Significant hypochromic anemia in the neonatal period
c) Microcytic anemia
d) Reticulocytosis
e) Jaundice
f) Splenomegaly (may be severe and occasionally complicated by hypersplenism)
g) Growth retardation may be seen in children.
h) Hemolysis precipitated by infections or oxidant drugs (e.g., iron, sulfonamides)
i) Leg ulcers
j) Gallstones
k) Folic acid deficiency
l) Needs occasional transfusions, splenectomy, or avoidance of precipitating drugs
m) Severity of clinical features: related to the molecular basis of the disease: Patients with nondeletional types of Hb H disease are more severely affected than those with the common deletional types of Hb H disease

iv. Hb Bart's hydrops fetalis or α-thalassemia major (–/–) (deficiency of all four globin genes)
a) Most severe form of α-thalassemia
b) Incompatible with life unless intrauterine blood transfusion is given because not enough functional hemoglobin is produced to sustain tissue oxygenation
c) Profound oxygen deprivation in utero with resulting heart failure (hydrops fetalis)
d) Stillborn or die soon after birth
e) Pale edematous infant with signs of cardiac failure (edema and ascites) and prolonged intrauterine anemia
f) Massive hepatosplenomegaly
g) Severe erythroblastic anemia
h) Retardation in brain growth
i) Skeletal and cardiovascular anomalies
j) Enlargement of the placenta

2. β-thalassemia (Cao and Galanello 2010)
a. Found largely in people of African and Mediterranean descent, Far East, Middle East, and the Asian subcontinent
i. Highest incidence
a) Cyprus (14%)
b) Sardinia (12%)
c) Southeast Asia
ii. The high gene frequency of beta-thalassemia in these regions
a) Most likely related to the selective pressure from *Plasmodium falciparum* malaria, as it is indicated by its distribution quite similar to that of present or past malaria endemics. Carriers of beta-thalassemia are indeed relatively protected against the invasion of *Plasmodium falciparum*.
b) However, because of population migration and, to a limited extent, slave trade, beta-thalassemia is, at present, also common in Northern Europe, North and South America, Caribbean, and Australia.

b. Clinical features dependent on reduced (β^+) or absent (β^o) synthesis of β-globin
i. β-thalassemia major (also known as Cooley's anemia or homozygous β-thalassemia)
a) Due to inheritance of two β-thalassemia alleles, one on each copy of chromosome 11
b) Generally recognized to be a homozygous state for whichever thalassemia gene is involved
c) Clinically a severe disorder
d) Infants born free of significant anemia, protected by prenatal Hb F production
e) Onset: 6–12 months
f) Diagnosis: evident by 2 years of age
g) Manifestations in early childhood: anemia, pallor, growth retardation, tiredness, abdominal swelling due to hepatosplenomegaly, infection, and jaundice

h) Manifestations in childhood and adult: severe anemia, infection, tiredness, growth retardation, distinctive facies, hepatosplenomegaly, cardiomegaly, abdominal pain, leg ulcers, osteoporosis, and iron overload
i) At significant risk for developing overwhelming, often fatal infection after splenectomy (postsplenectomy syndrome)
j) Severe anemia usually necessitating chronic blood transfusions
k) Prognosis: average survival of children with untreated thalassemia major (<4 years)

ii. β-thalassemia intermedia (compound heterozygotes)
a) Due to inheritance of two β-thalassemia mutations (one mild and one severe or two mild mutations) or occasionally due to inheritance of complex combinations such as α-β-thalassemia
b) Affected individuals: either compound heterozygotes for two different thalassemia genes or heterozygotes for a structural variant plus a thalassemia gene. Homozygotes for the milder β^+-thalassemia also have thalassemia intermedia.
c) Less severe clinical phenotype: cardiomegaly, osteoporosis, fractures, arthritis, and splenomegaly in some patients
d) Significant anemia but usually do not require chronic blood transfusions

iii. β-thalassemia minor (also known as β-thalassemia trait or heterozygous β-thalassemia)
a) Due to presence of a single β-thalassemia mutation and a normal β-globin gene on the other chromosome
b) Clinically asymptomatic but may have mild or minimal anemia

iv. Silent carrier β-thalassemia
a) No symptoms except for possible low RBC indices
b) Mutation causing thalassemia is very mild and represents β+-thalassemia.

Diagnostic Investigations

1. Screening tests for thalassemias
   a. Low MCV
      i. Increased Hb A_2 and/or Hb F: indicate β-thalassemia syndrome
      ii. Normal Hb A_2 and Hb F, and ferritin >20 ng/mL: suggest possible α-thalassemia syndrome
   b. Normal MCV, normal electrophoresis: thalassemia syndrome unlikely
2. α-thalassemia: More difficult to diagnose because characteristic elevations in Hb A_2 ($\alpha_2\delta_2$) or Hb F ($\alpha_2\gamma_2$), seen in β-thalassemia, do not occur.
   a. α-thalassemia-2
      i. Laboratory notation: FA + Bart's
      ii. Small amount of Hb Bart's (1–2%) in affected infants at birth
      iii. Remainder of the hemoglobin: Hb F and Hb A ($\alpha_2\beta_2$)
      iv. Hb F and Hb Bart's: disappear after a few months of age
      v. Minimal microcytosis: remains
   b. α-thalassemia-1
      i. Laboratory notation: FA + Bart's (impossible to differentiate the two forms of α-thalassemia from the electrophoretic pattern)
      ii. Slightly larger amount of Hb Bart's in cord blood (3–5%)
      iii. Hb F and Hb Bart's: disappear after birth
      iv. Unequivocal microcytosis: Mean red cell volume of 65–70 fl/cell remains.
      v. Abnormally low Hb A_2 proportion
   c. Hb H disease
      i. Reduction in α-chain does not affect the production of β-chain which is produced in excess and tends to form tetramers (β^4 or Hb H).
      ii. Hb A + Hb H (β^4) + Hb Bart's (γ^4)
      iii. Presence of Heinz bodies: inclusions representing β-chain tetramers (Hb H), which are unstable and precipitate in the RBC, giving the appearance of a golf ball
   d. Hb Bart's hydrops fetalis
      i. Hypochromic macrocytes with nucleated red blood cells

ii. γ^4 (Bart's hemoglobin): nonfunctional as an oxygen transporter

3. β-thalassemia
   a. β-thalassemia major
      i. Small, thin, and distorted red blood cells containing markedly reduced amounts of hemoglobin
      ii. Peripheral blood smear
         a) Severe microcytic hypochromic anemia (no anemia at birth)
         b) Anisocytosis
         c) Poikilocytosis (speculated teardrop and elongated cells)
         d) Abundant nucleated red cells (i.e., erythroblasts)
         e) Occasional immature leukocytes
      iii. Hemolytic anemia
      iv. Hemoglobin profile: predominant Hb F
      v. In patient with homozygous β^o-thalassemia: absent Hb A with normal amounts of Hb A_2
      vi. In newborn with β^+-thalassemia: Hb F (about 90%) decreases with advancing age but always considerably higher than normal (10–90%).
   b. β-thalassemia intermedia
      i. Intermediate Hb concentration (8–10 gm/dL)
      ii. Microcytic hypochromic anemia
      iii. Hb F (5–99%)
   c. β-thalassemia minor
      i. Mild hypochromic microcytosis
      ii. Target cells
      iii. Mild to minimal anemia (hemoglobin concentration average 1–2 gm/dL below normal)
      iv. Elevation of Hb A_2 and Hb F (70–99%) during early years of life
      v. Anemia worsen during pregnancy
4. Imaging studies
   a. Chest X-ray to evaluate cardiac size and shape
   b. Skeletal survey
      i. Skeletal response to marrow proliferation
         a) Expanding marrow space
         b) Thinning of cortical bone
         c) Resorption of cancellous bone
         d) Resulting in generalized loss of bone density
         e) Frequent small lucencies resulting from focal proliferation of marrow
         f) "Periosteal response" caused by perforation of the cortex by hypertrophic and hyperplastic marrow subperiosteally
      ii. Classic facies observed in thalassemia major
         a) Classic "hair-on-end" appearance of the skull
         b) Maxilla overgrowth resulting in maxillary overbite
         c) Prominent upper incisors
         d) Separation of the orbits
      iii. Various bone deformities seen in ribs, long bones, and flat bones
      iv. Premature fusion of the epiphyses
   c. MRI/CT scans to evaluate the amount of iron in the liver in patients on chelation therapy
5. Carrier screening
   a. α-thalassemia (Vichinsky 2010)
      i. Commonly, microcytosis using an MCV <82 fL and/or hypochromia (MCH <27 pg) is often used as a population screening technique.
         a) Anemia is unreliable and is often not present in adults with two α-globin gene deletions.
         b) Once iron deficiency is ruled out or corrected, microcytosis should be further evaluated in the individual and his or her partner in order to determine their risk for hydrops.
      ii. Molecular diagnosis for α-globin mutations: essential for at-risk couples
   b. β-thalassemia
      i. Ongoing in several at-risk populations in the Mediterranean (Cao et al. 2002)
      ii. Carrier testing relies on hematological analysis: When the hematological analysis indicates a beta-thalassemia carrier state, molecular genetic testing of *HBB* can be performed to identify a disease-causing mutation.
6. Molecular genetic testing for α- and β-thalassemias
   a. α-thalassemia (Galanello and Cao 2008)
      i. *HBA1*, the gene encoding α_1-globin, and *HBA2*, the gene encoding α_2-globin, are the two genes most commonly associated with α-thalassemia.

ii. Molecular genetic testing of *HBA1* and *HBA2* detects deletions in about 90% and point mutations in about 10% of affected individuals.

b. β-thalassemia (Cao and Galanello 2010)
   i. Molecular genetic testing of the gene encoding the hemoglobin subunit beta (HBB): available clinically
      a) Targeted mutation analysis
      b) Sequence analysis

Genetic Counseling

1. Recurrence risk
   a. α-thalassemia
      i. Patterns of inheritance of the α-thalassemia when both parents are α-thalassemia-1 (−−/αα)
         a) 25% normal
         b) Fifty percent α-thalassemia-1
         c) Twenty five percent Hb Bart's (hydrops fetalis)
      ii. Patterns of inheritance of the α-thalassemia syndrome when one parent is α-thalassemia-1 (−−/αα) and the other parent is α-thalassemia-2 (α-/αα)
         a) Twenty-five percent normal
         b) Twenty-five percent α-thalassemia-1
         c) Twenty-five percent α-thalassemia-2
         d) Twenty-five percent Hb H disease
      iii. If the carrier of α^{+}-thalassemia is a homozygote, clearly, the risk of Hb H disease is 1:2 (50%) (Harteveld and Higgs 2010)
      iv. Patient's offspring: not increased unless the spouse is a carrier
      v. Twenty-five percent of African Americans have heterozygous α-thalassemia-2 (α-/αα). Thus, 1.5% are homozygotes for α-thalassemia-2 (α-/α-). But since the more severe α-thalassemia-1 is not present, subsequent children are not at risk of having Hb H or Bart's hydrops fetalis.
   b. β-thalassemia
      i. Patient's sib: 25%
      ii. Patient's offspring: not increased unless the spouse is a carrier

2. Prenatal diagnosis: available to all families at risk of either severe α-thalassemia or β-thalassemia
   a. α-thalassemia
      i. Ultrasonography (Tongson et al. 1998)
         a) Hepatosplenomegaly (>90%)
         b) Cardiomegaly (>90%)
         c) Edematous placenta (>90%)
         d) Ascites (>90%)
         e) Oligohydramnios (82%)
         f) Subcutaneous edema (75%)
         g) Decreased fetal movement (74%)
         h) Cord edema (63%)
         i) Enlarged umbilical vessel (62%)
         j) Pericardial or pleural effusion (15%)
      ii. Molecular hybridization technique to detect complete absence of α-genes in fetal amniocytes in a pregnancy at risk for homozygous α-thalassemia-1 and the hydrops fetalis syndrome
      iii. Quantitative polymerase chain reaction for the rapid prenatal diagnosis of homozygous α-thalassemia (Hb Bart's hydrops fetalis)
   b. β-thalassemia
      i. Available to couples who are carriers of β-thalassemia and their hemoglobin gene mutations have been identified by DNA analysis
      ii. Direct DNA analysis by molecular hybridization methods for the presence of the thalassemia mutation from fetal cells obtained by amniocentesis and chorionic villus biopsy
      iii. DNA analysis of fetal nucleated RBCs from maternal peripheral blood
      iv. Approach to prenatal diagnosis complicated by presence of the heterogeneity of thalassemia mutations
      v. Preimplantation genetic diagnosis available for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.

3. Management
   a. α-thalassemia (Segel et al. 2002)
      i. No therapy necessary for patients with α-thalassemia trait
      ii. Avoid exposure to oxidant medications (e.g., iron, sulfonamides) which accelerate precipitation of Hb H and exacerbate hemolysis

iii. Prompt treatment of infection especially in postsplenectomy
iv. Hb H disease
  a) Folate supplementation
  b) Chronic transfusion therapy (consider iron chelation therapy to avoid iron overloading)
  c) Splenectomy in rare instances of hypersplenism
  d) Allogeneic bone marrow transplantation limited to the most severely affected patients
v. Bart's hemoglobinopathy
  a) Usually results in neonatal death
  b) Patients rarely salvaged by intrauterine transfusions and subsequent stem cell transplantation
  c) The diagnosis, management, and prognosis of homozygous α-thalassemia/hydrops fetalis is changing; advances in antenatal diagnosis, intrauterine intervention, and postnatal therapy have resulted in long-term survival of children previously felt to have an invariably fatal disease(Singer et al. 2000; Weisz et al. 2009; Vichinsky 2010).

b. β-thalassemia
  i. No specific therapy required for β-thalassemia trait
  ii. Regular blood transfusions in thalassemia major
    a) Correct the anemia
    b) Suppress erythropoiesis
    c) Inhibit increased gastrointestinal absorption of iron
  iii. Treatment of individuals with thalassemia intermedia
    a) Symptomatic treatment
    b) Splenectomy
    c) Folic acid supplementation
    d) Treatment of extramedullary erythropoietic masses (radiotherapy, transfusions, or hydroxyurea in selected cases)
  iv. Iron chelation with desferrioxamine to eliminate the iron overload secondary to multiple blood cell transfusions and to increase iron absorption
  v. Bone marrow transplantation
    a) From an HLA-identical sib
    b) Outcome dependent on pretransplantation clinical conditions, specifically the presence of hepatomegaly, extent of liver fibrosis, and magnitude of iron accumulation
    c) Risk of chronic graft-versus-host disease of variable severity: 5–8%
  vi. Cord blood transplantation (Kelly et al. 1997)
    a) Human umbilical cord blood contains hematopoietic stem cells capable of reconstituting bone marrow.
    b) Possibility of using cord blood obtained from unrelated donors with a decrease in the incidence of graft-versus-host disease
  vii. Attempts to increase Hb F production by following agents: variable without substantial effects
    a) 5-azacytidine
    b) Erythropoietin
    c) Butyrate compounds
    d) Hydroxyurea
  viii. Hematopoietic stem cells to correct the molecular defect by transfer of a normal gene via a suitable vector or by homologous recombination: currently under investigation

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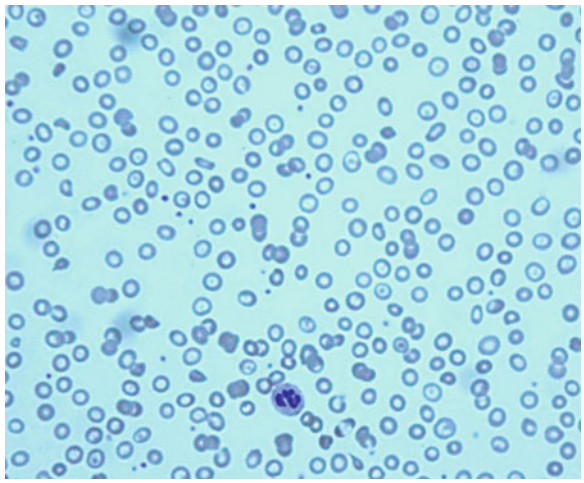

Fig. 1 Peripheral blood smear from a 58-year-old woman with microcytic anemia and frequent target cells (codocytes). Hemoglobin electrophoresis showed an AA pattern with an increased hemoglobin A_2 (5.8% by HPLC) consistent with beta$^+$- thalassemia trait

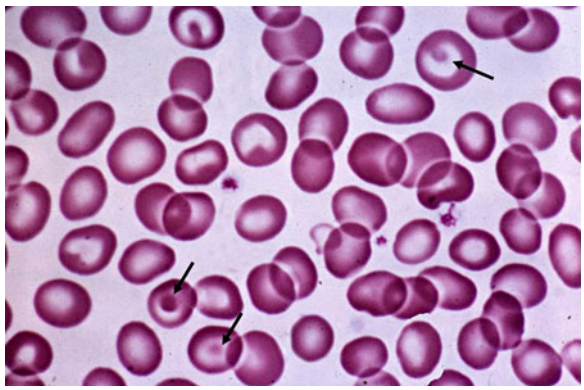

Fig. 2 Peripheral blood smear from a patient with alpha-thalassemia minor shows hypochromia, target cells (*arrows*), and anisopoikilocytosis (Wright-Giemsa stain, ×1,000)

Thanatophoric Dysplasia

Thanatophoric dysplasia was originally described by Maroteaux et al. in 1967. The term "thanatophoric" was coined to mean "death bearing" in Greek. Thanatophoric dysplasia is probably the most common lethal neonatal dwarfism with an estimated incidence of 0.2–0.5 per 10,000 births.

Synonyms and Related Disorders

Thanatophoric dysplasia type I (thanatophoric dwarfism, lethal short-limbed platyspondylic dwarfism, San diego type, platyspondylic lethal skeletal dysplasia, San Diego type); Thanatophoric dysplasia type II (cloverleaf skull with thanatophoric dwarfism, thanatophoric dysplasia with kleeblattschaedel, thanatophoric dysplasia with straight femur and cloverleaf skull)

Genetics/Basic Defects

1. Genetic heterogeneity
   a. Sporadic in most cases
   b. A new autosomal dominant mutation
   c. Caused by mutations in the transmembrane domains of the fibroblast growth factor receptor 3 (*FGFR3*)
2. Having the most extreme micromelia and the most extensive craniofacial involvement compared to two other short limb skeletal dysplasias (achondroplasia and hypochondroplasia) which are also caused by mutations of *FGFR3*
3. Pathogenesis for the phenotypic features of thanatophoric dysplasia
   a. Normal function of *FGFR3*: to regulate endochondral ossification by "putting the brakes on growth"
   b. "Gain-of-function" type of known mutations on *FGFR3*
      i. Primarily affects the cranial base and nasal capsule (endochondral bones)
      ii. With secondary effect on membrane bones which articulates with endochondral bones
4. Two major forms (TD1, TD2) of thanatophoric dysplasia, postulated based on subtle differences in skeletal radiographs and the underlying genetic mutation
   a. TD1
      i. Curved femora
      ii. Very flat vertebral bodies
      iii. Very few TD1 patients with cloverleaf skull
      iv. Molecular defect consisting of a stop codon mutation or missense mutation in the extracellular domain of the FGFR3 protein, resulting in a newly created cysteine residue (Arg248Cys, most common)
   b. TD2
      i. Straight femora
      ii. Taller vertebral bodies
      iii. Most TD2 patients with cloverleaf skull (severe craniosynostosis)
      iv. Molecular defect consisting of a single nucleotide substitution resulting in replacement of lysine with glutamine at position 650 (Lys650Glu) in the tyrosine kinase 2 domain of the receptor
5. Activating mutations in the *FGFR3* gene can cause following conditions:
   a. Achondroplasia

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b. Thanatophoric dysplasia type I and type II
c. Hypochondroplasia
d. Severe achondroplasia with developmental delay and acanthosis nigricans

Clinical Features

1. Unique and homogeneous clinical features observed in patients with TD1
2. General features
   a. Virtually lethal neonatally
   b. A few reports with survival up to 4–5 years of age with aggressive neonatal intervention
      i. Markedly limited growth potential
      ii. Markedly delayed cognitive development
      iii. Respiratory insufficiency
      iv. Neurologic abnormalities
      v. Long-term medical care and chronic ventilator dependence
3. Craniofacial features
   a. Head
      i. Disproportionally large (macrocephaly)
      ii. Frontal bossing
      iii. With or without cloverleaf (Kleeblattschdel) anomaly of the skull resulting from premature closure of cranial sutures
   b. Facial features
      i. Bulging eyes
      ii. Hypertelorism
      iii. Severely depressed or indented nasal bridge
4. Short neck
5. Chest
   a. Extremely narrow
   b. Constricted thoracic cage
   c. Reduced size of the thoracic cavity
   d. Short ribs
   e. Hypoplastic lungs
6. Protuberant abdomen
7. Limbs
   a. Extremely short
   b. Thickened skin
   c. Excessive skin folds
   d. Usually outstretched arms
   e. Externally rotated legs with abducted thighs
   f. Syndactyly
8. Early death in most children secondary to:
   a. Chest constriction and consequent respiratory insufficiency
   b. Foramen magnum stenosis resulting in failure of respiratory control
9. A few children with longer survival (up to 9–10 years)
   a. Respiratory insufficiency
      i. Reduced chest circumference
      ii. Upper cervical cord compression resulting from a diminutive foramen magnum
   b. Markedly limited growth potential
   c. Markedly delayed cognitive development
   d. Seizures
   e. Hearing loss
   f. Additional CNS anomalies (Baker et al. 1997)
      i. Hydrocephalus
      ii. Polymicrogyria
      iii. Neuronal heterotopia
      iv. Megalencephaly
      v. Cerebral gyral disorganization
      vi. Hippocampal malformation
      vii. Temporal lobe malformations
      viii. Nuclear dysplasia
      ix. Abnormal axonal bundles
      x. Cerebellar hypoplasia in the small posterior fossa
      xi. Partial agenesis of the corpus callosum
      xii. Spinal stenosis
      xiii. Hyperreflexia
      xiv. Clonus
   g. Acanthosis nigricans, an associated rare skin disorder
10. Differential diagnosis (Schild et al. 1996)
   a. Achondroplasia
      i. Autosomal dominant disorder
      ii. Rhizomelic shortening of the bones, less prominent than thanatophoric dysplasia
      iii. Macrocrania
      iv. Heterozygous achondroplasia
         a) Compatible with normal life span
         b) Normal intelligence
      v. Homozygous achondroplasia with two affected parents
   b. Campomelic dysplasia
      i. Autosomal recessive disorder
      ii. Typical anterior bowing of the lower limbs
      iii. Hypoplastic fibula
      iv. Hypoplastic scapulae
      v. A sex reversal phenomenon (phenotypical female with male karyotype)
   c. Osteogenesis imperfecta type II and type III

i. Varying degree of bone demineralization
ii. Shortened long bones with multiple fractures
iii. Blue sclerae
iv. Polyhydramnios frequently associated with type II

d. Hypophosphatasia
i. Demineralization of bone tissue
ii. Lack of calcification of the fetal skull
iii. Mild to moderate shortening of limb bones
iv. Difficult to differentiate from osteogenesis imperfecta if fractures are present

e. Achondrogenesis
i. Severe micromelia
ii. Poor ossification of the vertebral bodies, cranium, pelvis, and sacrum
iii. Narrow and shortened thorax
iv. Frequent complications with fetal hydrops and hydramnios

f. Short rib-polydactyly and other rare skeletal dysplasia syndromes

Diagnostic Investigations

1. Radiographic features
a. Skull
i. Relatively large calvarium
ii. A small foramen magnum
iii. Trilobed skull with a towering calvarium and bitemporal bulging in the cloverleaf skull type (type II)

b. Ribs
i. Very short ribs with cupped anterior ends
ii. Short ribs (type II)

c. Vertebrae
i. Flat vertebral bodies (platyspondyly)
ii. Increasing intervertebral disc space
iii. "Inverted U–shaped or H-shaped" vertebral bodies
iv. Narrow interpedunculate distance at the lumbar level
v. Taller vertebral bodies (type II)

d. Pelvis
i. Short
ii. Small sacrosciatic notches

e. Tubular bones
i. Extremely shortened long bones of the limbs
ii. Rhizomelic shortening of the limbs
iii. Flared metaphyses
iv. "Telephone receiver"–like curved femora in the noncloverleaf type
v. Relatively straight femora (type II)

2. Histologic features
a. Generalized disruption of endochondral ossification
i. Hallmark of the histologic findings
ii. Physeal growth zone shows minimal proliferation and hypertrophy of chondrocytes with absence of column formation.
iii. Lateral overgrowth of metaphyseal bone around the physis
iv. Mesenchymal cells extending inward from the perichondrium as a narrow band at the periphery of the physeal zone (the so-called fibrous band)
v. Increased vascularity of the resting cartilage

b. Brain
i. Neuronal migration abnormalities of the temporal lobe
ii. Hydrocephalus
iii. Partial agenesis of the corpus callosum
iv. Upper cord compression
v. Spinal stenosis

3. DNA mutation analysis of *FGFR3*
a. TD1
i. 742C → T (Arg248Cys): most common
ii. Tyr373Cys
iii. Ser249Cys
iv. Other missense mutations
v. Stop codon mutations

b. TD2: missense mutation of 1948A → G (Lys650Glu) in TD2

c. Clinical testing
i. Targeted mutation analysis
ii. Sequence analysis of select regions of FGFR3 or of the entire *FGFR3* coding region

Genetic Counseling

1. Recurrence risk
a. Patient's sib: about 2%
b. Patient's offspring: not surviving to reproduction age

2. Prenatal diagnosis
a. Ultrasonography
i. Hydramnios in most cases

ii. Megacephaly with or without cloverleaf-shaped skull
iii. Progressive hydrocephaly
iv. Hypoplastic thorax disproportionately small in relation to the abdomen
v. Small chest and lung measurement to predict severe pulmonary hypoplasia
vi. Short ribs
vii. Short limbs with curved "telephone handle–shaped" or straight femurs
viii. Excessive skin giving fetus a "boxer's face" appearance
ix. Flattened vertebrae with increased intervertebral spaces, giving the vertebral bodies the form of an "H"

b. Prenatal radiography for documenting characteristic skeletal anomalies
c. DNA mutation analysis of *FGFR3* in fetal cells from amniocentesis or CVS
d. Prenatal and preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified

3. Management
a. Limited intervention
i. Appropriate because of the inevitable lethal outcome
ii. Aggressive neonatal management, at times, not even resulting in short-term survival
b. Debatable issues about the level of intensity of medical care for unanticipated long-term survival
i. Long-term medical care
ii. Chronic ventilator support
iii. Requiring extensive health maintenance measures
iv. Anticipate frequent medical exacerbations requiring recurrent hospitalizations
v. Possibility of lethal complication, an ever present concern
vi. Special education programs for the longer survivals

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Fig. 1 (**a**–**c**) Front views of three infants showing frontal bossing, flat facies, short neck, micromelia, and small chest

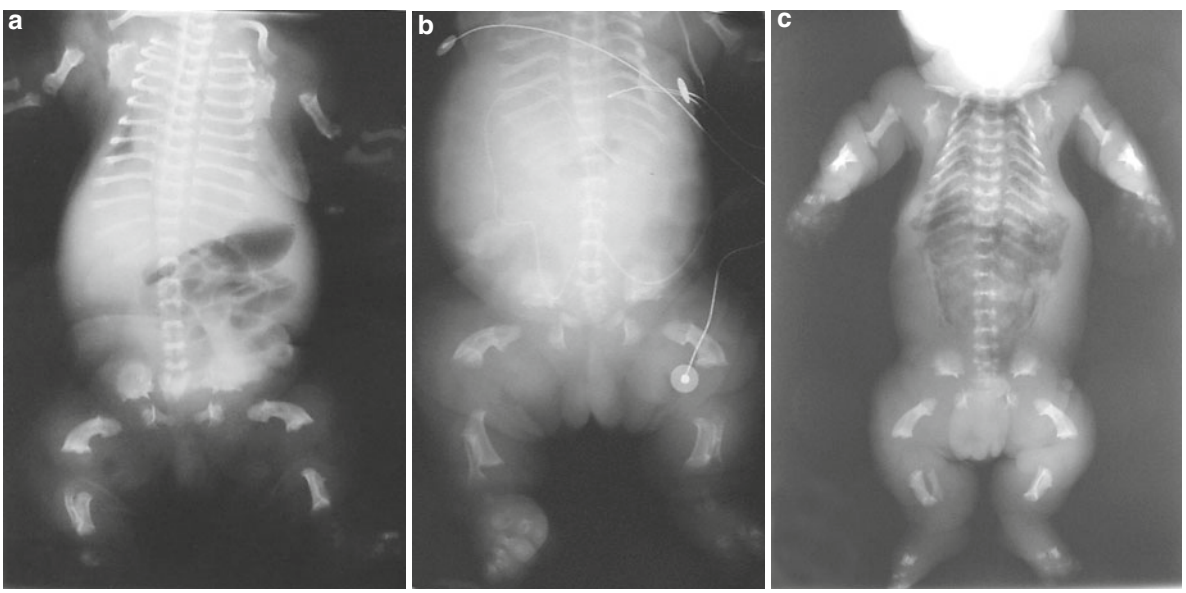

Fig. 2 (**a**–**c**) AP radiographic views of three infants with typical findings of TD1 showing profound platyspondyly, decreased thoracic volume, characteristic pelvic configuration, micromelia, and so-called "telephone receiver" femoral bowing

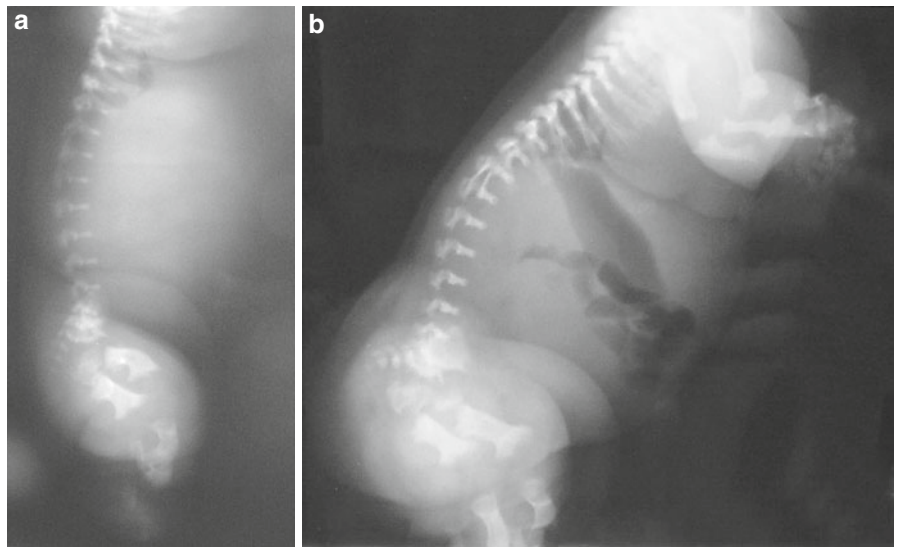

Fig. 3 (**a**, **b**) Lateral radiographic views of the spines of two infants with typical TD1 showing extreme platyspondyly and short ribs

Fig. 4 Gross appearance of a femur resembling a "telephone receiver"

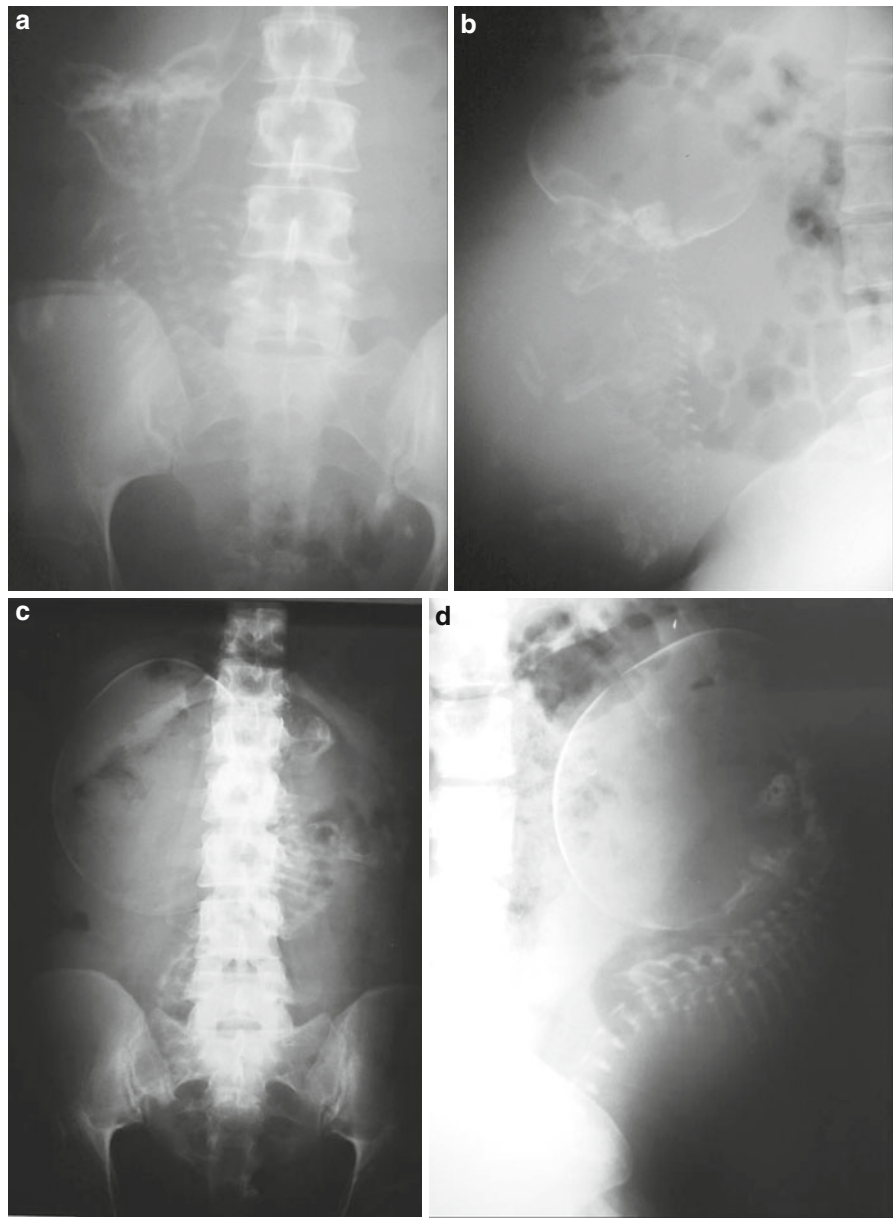

Fig. 5 (**a**–**d**) Prenatal radiographs of two fetuses affected with thanatophoric dysplasia showing platyspondyly, short ribs, and micromelia

Fig. 6 Thanatophoric dysplasia in identical twin fetuses. The pregnancy was terminated following ultrasonographic diagnosis at 22 weeks' gestation. The placenta was diamniotic monochorionic, consistent with monozygotic pregnancy

Fig. 7 Thanatophoric dysplasia with cloverleaf skull in a neonate. The head is large and trilobed. The narrow chest and rhizomelic shortening of limbs are similar to those of classic thanatophoric dysplasia. Radiograph revealed platyspondyly and small ilium that are similar to those of classic thanatophoric dysplasia (not shown). However, the femur is straight and not as curved as seen in the classic type

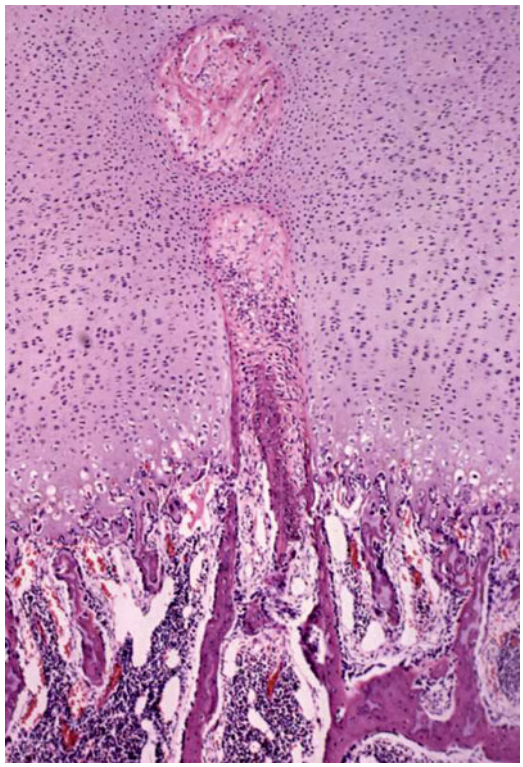

Fig. 8 Photomicrograph of the cartilage-bone junction, cloverleaf skull type of thanatophoric dysplasia. The physeal growth zone is markedly retarded and disorganized. Similar changes are seen in the classic type thanatophoric dysplasia. A partially ossified cartilage canal is present at the center of physis. It is more prominent in size and number in cloverleaf type than in classic type

Fig. 9 A neonate with short limb dwarfism, characterized by flat face, short neck, short chest, and micromelia. A single sequence mutation (Nt742C > T) was identified in the *FGFR3* gene. This causes the substitution of arginine for cysteine at codon 248 (C248R). This mutation has been previously reported in thanatophoric dysplasia type I

Thrombocytopenia-Absent Radius Syndrome

Thrombocytopenia-absent radius (TAR) syndrome is a congenital malformation syndrome characterized by bilateral absence of the radii and congenital thrombocytopenia.

Synonyms and Related Disorders

TAR syndrome

Genetics/Basic Defects

1. Genetic inheritance: unknown but autosomal recessive inheritance was suspected based on the following observations
   a. Families with at least two affected children born to unaffected parents
   b. Rare instances of association with consanguinity
2. Associated with an interstitial microdeletion of 200 kb on chromosome 1q21.1 in all 30 investigated patients with TAR syndrome, detected by microarray-based comparative genomic hybridization (Klopocki et al. 2007)
   a. Analysis of the parents revealed that this deletion occurred de novo in 25% of affected individuals.
   b. The phenotype develops only in the presence of an additional as-yet-unknown modifier.
3. Etiology of thrombocytopenia: unknown but is considered to be the result of a decreased production of platelets from the bone marrow

Clinical Features

1. Thrombocytopenia (100%)
   a. May be transient
   b. Symptomatic in over 90% of cases within the first 4 months of life
      i. Purpura
      ii. Petechiae
      iii. Epistaxis
      iv. Gastrointestinal bleeding
         a) Hematemesis
         b) Melena
      v. Hemoptysis
      vi. Hematuria
      vii. Intracerebral bleeding
   c. More severe thrombocytopenia can be precipitated by stress, infection, gastrointestinal disturbances, or surgery (Fayen and Harris 1980).
   d. Platelet count tends to rise as the child gets older and may approach normal levels in adulthood (spontaneous improvement of platelet counts after 1 year).
2. Upper extremity anomalies (100%) (Hall 1987)
   a. Bilateral absence of the radius (100%): the most striking skeletal manifestation
   b. Hand anomalies
      i. Presence of the thumbs (100%)
         a) An important clinical feature distinguishing TAR syndrome from other disorders featuring radial aplasia, which are usually associated with absent thumbs
         b) Relatively functional thumbs

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c) Thumbs often adducted
d) Thumbs often hypoplastic
ii. Radially deviated
iii. Limited extension of the fingers
iv. Hypoplasia of the carpal and phalangeal bones
c. Associated ulnar anomalies
i. Usually short
ii. Usually malformed
iii. Absent ulna
a) Absent bilaterally in about 20% of cases
b) Absent unilaterally in about 10% of cases
d. Associated humeral anomalies
i. Often abnormal in about 50% of cases
ii. Absent humeri in about 5–10% of cases (rare phocomelia)
e. Associated shoulder and arm anomalies
i. One arm shorter than the other in about 15% of cases
ii. Hypoplasia of muscles and soft tissue in the arm and shoulder
iii. Abnormal shoulder joint secondary to abnormal humeral head
3. Lower limb anomalies (47%)
a. Correlation exists between the severity of skeletal changes in the lower limbs and the severity of abnormalities of the upper limbs.
b. Variable involvement but usually milder than the upper limbs
i. Dislocation of the patella and/or of the hips
ii. Knee involvement
a) Dysplasia: rare severe knee dysplasia due to agenesis of cruciate ligaments and menisci
b) Ankylosis
c) Subluxation
iii. Hip dislocation
iv. Coxa valga
v. Absent tibiofibular joint
vi. Femoral or tibial torsion
vii. Lower limb phocomelia
viii. Valgus and varus foot deformities
ix. Abnormal toe placement
x. Severe cases with lower limb phocomelia
4. Cow's milk intolerance (62%)
a. Presentation symptoms
i. Persistent diarrhea
ii. Failure to thrive
b. Thrombocytopenia episodes
i. Precipitated by introduction of cow's milk
ii. Relieved by its exclusion from the diet
5. Urogenital anomalies (23%)
a. Horseshoe kidney
b. Absent uterus
6. Cardiac anomalies (22–33%)
a. Tetralogy of Fallot
b. Atrial septal defect
c. Ventricular septal defect
7. Other associated congenital anomalies
a. Facial capillary hemangiomata in the glabella region
b. Micrognathia
c. Cleft palate
d. Intracranial vascular malformation
e. Sensorineural hearing loss
f. Epilepsy
g. Other skeletal anomalies
i. Scoliosis
ii. Cervical rib
iii. Fused cervical spine
iv. Short stature
h. Neural tube defect
8. Prognosis
a. Variable clinical course among patients
b. Survival related to the severity and duration of thrombocytopenia
c. Good prognosis after surviving the first year of life
d. Early diagnosis and treatment with platelet therapy minimize mortality risks.
e. Mental retardation secondary to intracranial bleed (7%)
f. Good hand and upper extremity functions, especially if bilateral radial aplasia is the only skeletal abnormality
9. Differential diagnosis (Hedburg and Lipton 1988 Greenhalgh et al. 2002)
a. Holt-Oram syndrome
i. An autosomal dominant condition caused by mutations in the *TBX5* gene
ii. Often with a family history of heart and limb defects
iii. Absence of the thumb associated with radial aplasia
iv. Absence of thrombocytopenia
b. Roberts syndrome
i. An autosomal recessive trait
ii. Pre- and postnatal growth retardation

iii. Facial clefting
iv. Genitourinary abnormalities
v. Limb defects involving upper or lower limbs or both
vi. Characteristic chromosome abnormality in the majority (79%) of cases
  a) Premature centromeric separation (PCS)
  b) "Puffing" of the chromosomes caused by repulsion of the heterochromatic regions near the centromeres of chromosomes 1, 9, and 16 with splaying of the short arms of the acrocentric chromosomes and of distal Yp.33
  c) Evidence of abnormal mitosis
vii. Postulated that TAR syndrome and Roberts syndrome might be part of the same condition, with TAR syndrome being the milder and Roberts the severer variant

c. Fanconi anemia
  i. An autosomal recessive disorder
  ii. Bone marrow failure
  iii. Skeletal defects
  iv. Cutaneous pigmentation
  v. Microcephaly
  vi. Short stature
  vii. May present with thrombocytopenia
  viii. Upper limb abnormalities also involve the radial ray.
  ix. Hypoplastic thumbs may be accompanied by radial hypoplasia but absence of the radius is associated with absence of the thumbs.
  x. Spontaneous chromosome breakage, a consistent feature of Fanconi anemia and is a reliable diagnostic test

d. Aase syndrome
  i. Radial hypoplasia
  ii. Triphalangeal thumbs
  iii. Hypoplastic anemia, similar to Blackfan-Diamond syndrome
  iv. Thrombocytopenia not a feature

e. Thalidomide embryopathy
  i. May present with radial anomalies of the upper limb
  ii. Malformations of the lower limbs showing a less consistent pattern
  iii. Diagnosed based on:
    a) Phenotype
    b) History of exposure to thalidomide during pregnancy
    c) Increasing use of thalidomide as a therapeutic agent for the treatment of conditions such as Beçhet disease, graft versus host disease, multiple myeloma, and Kaposi sarcoma

f. Rapadilino syndrome
  i. Absent thumbs and radial aplasia/hypoplasia
  ii. Patellar aplasia/hypoplasia
  iii. Cleft palate

g. Other syndromes with limb reduction abnormalities predominantly involving the upper extremities (Donnenfeld et al. 1990)
  i. Adams-Oliver syndrome
    a) Transverse limb defects
    b) Aplasia cutis congenita
    c) Growth deficiency
  ii. Aglossia-adactylia
    a) Absence/hypoplasia of digits
    b) Absence/hypoplasia of the tongue
  iii. Amniotic band sequence
    a) Limb constriction or amputation
    b) Asymmetric facial clefts
    c) Cranial defects
    d) Compression deformities
  iv. CHILD syndrome
    a) Unilateral hypomelia
    b) Ichthyosiform erythroderma
    c) Cardiac septal defect
  v. Cornelia de Lange syndrome
    a) Micromelia
    b) Growth deficiency
    c) Facial dysmorphism
  vi. Femur-fibula-ulnar syndrome
    a) Femoral/fibular defects associated with malformations of the arms
    b) Amelia
    c) Peromelia at the lower end of the humerus
    d) Humeroradial synostosis
    e) Defects of the ulna and ulnar rays
  vii. Poland anomaly
    a) Unilateral defect of pectoralis major muscle
    b) Ipsilateral limb abnormalities
  viii. VATER association (vertebral, anal, tracheoesophageal, renal, and radial anomalies)
  ix. Weyers ulnar ray/oligodactyly syndrome
    a) Deficient ulnar and fibular rays
    b) Oligodactyly
    c) Hydronephrosis

h. Megakaryocytic aplasia
   i. Amegakaryocytic thrombocytopenia
   ii. Congenital hypoplastic thrombocytopenia with microcephaly
   iii. Thrombocytopenia associated with trisomy 13 and trisomy 18

Diagnostic Investigations

1. Hematological studies
   a. Blood platelet counts: thrombocytopenia
   b. Anemia secondary to bleeding
   c. Eosinophilia
   d. Leukemoid reaction (Hall 1987)
      i. Reported in about 60–70% of patients during the first year of life
      ii. White blood counts >35,000 per mm^3 with a shift to the left, particularly with the stress and infections
      iii. Usually associated with worse thrombocytopenia and often with hepatosplenomegaly
   e. Bone marrow aspirates
      i. Normal or hypercellular bone marrow
      ii. Hypomegakaryocytic thrombocytopenia (<100,000 platelets per mm^3) (Hall 1987)
         a) Absence of megakaryocytes in two thirds of cases
         b) Decreased in number of megakaryocytes, which are small, immature, basophilic, and vacuolated, in the rest of cases
2. Chromosome analysis: normal to differentiate from chromosome abnormality syndrome
3. Array comparative genomic hybridization (aCGH) (Toriello 2009)
   a. Individuals with TAR syndrome have a minimally deleted 200-kb region at chromosome band 1q21.1, which is distinct from the region involved in the 1q21.1 deletion/duplication syndrome.
   b. Deletion of this segment is necessary but not sufficient to cause the phenotype.
   c. Identification of the 200-kb minimally deleted region is sufficient to verify the diagnosis of TAR syndrome in individuals with bilateral absence of the radius and presence of thumbs.
4. Radiography
   a. Upper extremities
      i. Bilateral radial aplasia
      ii. Radial club hand
      iii. Hypoplastic carpals and phalanges
      iv. Thumb and fingers always present
      v. Hypoplastic ulnae, humeri, and shoulder girdles
      vi. Syndactyly and clinodactyly of fingers and toes
   b. Lower extremities
      i. Hip dislocation
      ii. Femoral torsion
      iii. Tibial torsion
      iv. Knee dysplasia
      v. Absent patella
      vi. Valgus and varus foot deformities
      vii. Abnormal toe placement
      viii. Overriding toes

Genetic Counseling

1. Recurrence risk (Toriello 2009)
   a. The mode of inheritance of TAR syndrome is unknown.
   b. Presence of the minimally deleted 200-kb region at chromosome band 1q21.1 is necessary but not sufficient to cause the phenotype.
   c. Approximately 75% of probands have inherited the 200-kb minimally deleted region from one of his/her unaffected parents; the deletion occurs de novo in about 25% of probands.
   d. Sibs of a proband are at increased risk of also having TAR syndrome, although the recurrence risk appears to be less than 25%.
   e. Although reports of parent-to-child transmission have been published, no empiric risk figures are available.
   f. Patient's offspring
      i. Offspring of a proband are at increased risk of also having TAR syndrome.
      ii. Although reports of parent-to-child transmission have been published, no empiric risk figures are available.
      iii. The risk to each child of an individual with TAR syndrome of inheriting the 200-kb minimally deleted region at 1q21.1 is 50%. However, the presence of the deletion alone is not sufficient to cause TAR syndrome.
2. Prenatal diagnosis: reported mostly in pregnancies with a prior affected sibling (Donnenfeld et al. 1990; Toriello 2009)

a. Ultrasonography
   i. Bilateral radial aplasia
   ii. Club hands with normal thumbs and metacarpals
b. Cordocentesis to evaluate fetal platelet count (thrombocytopenia) and anemia
c. Identification of the interstitial microdeletion 1q21.1 in an unaffected parent and detection of the same microdeletion in a terminated fetus with upper limb deformities (Uhrig et al. 2007). Physical examination of the fetus revealed malformed upper extremities and absence of both radii, with opposable thumbs in an adducted position.
d. Prenatal diagnosis for pregnancies at increased risk for TAR syndrome is possible using molecular genetic testing to detect the 200-kb minimally deleted region and ultrasound examination to evaluate the limbs.

3. Management (McLaurin et al. 1999; Wu et al. 2003)
   a. Platelet infusions
      i. Remains the only real option for treatment of thrombocytopenia
      ii. To prevent the intracerebral hemorrhage, which was previously the main cause of mortality
      iii. Potential risks of platelet transfusion
         a) Infection (hepatitis viruses, HIV)
         b) Anaphylaxis
         c) Hemolytic reaction
   b. Injury prevention strategies
      i. Avoid contact sports
      ii. Use appropriate protective gear (helmet, padding)
   c. Splenectomy usually effective for the treatment of thrombocytopenia in adults
   d. Bone marrow transplantation as an option for patients who continue to remain thrombocytopenic with bleeding despite platelet transfusions
   e. Physical and occupational therapies to improve function and quality of life
   f. Management of the upper extremity
      i. Postpone surgery till later as thrombocytopenic-related bleeding problems are less frequent in older individuals.
      ii. Prosthetic fitting is generally rejected by patients as most patients are able to perform tasks by approximating themselves closely enough to an object to use their own hands.
      iii. Adaptive devices for feeding, dressing, and toileting are generally well tolerated.
   g. Management of the lower extremity
      i. Rejection of any lower extremity intervention by most patients
      ii. Use of power wheelchair or motorized cart for ambulation

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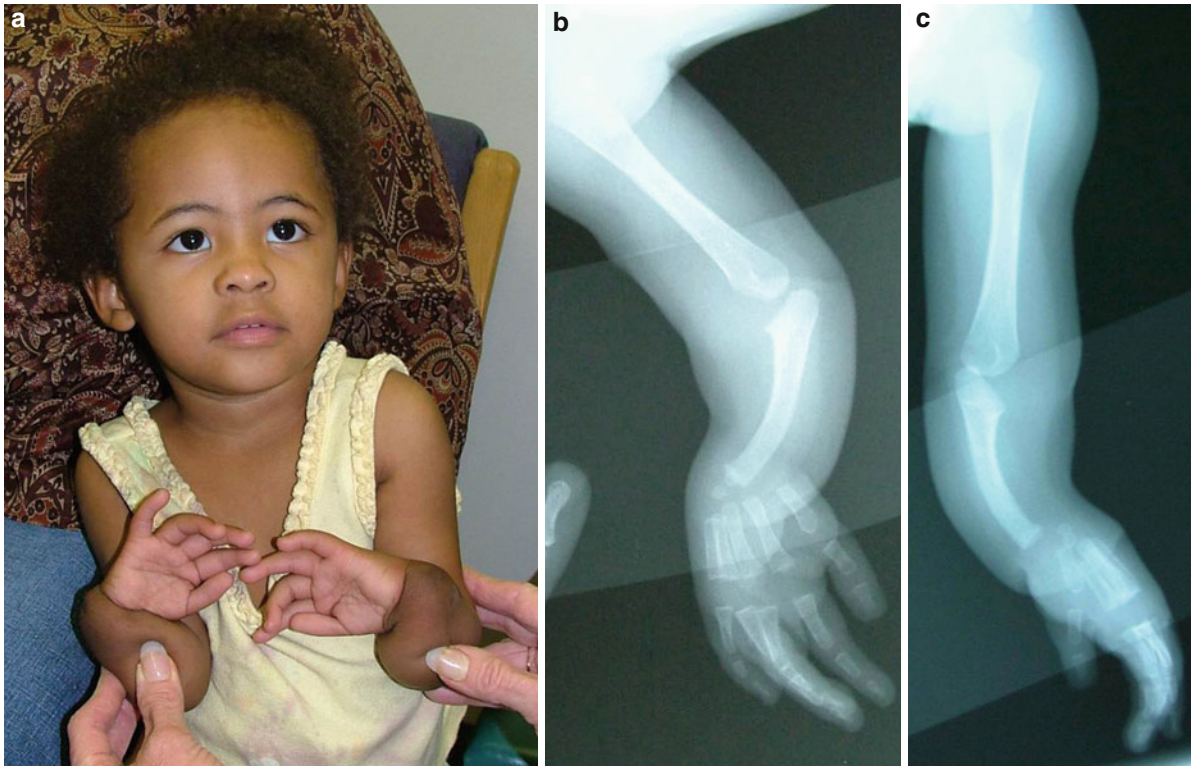

Fig. 1 (**a**–**c**) A 2 1/2-year-old girl with TAR syndrome showing club hands with fingerlike thumbs and radial aplasia, illustrated by radiographs. The patient had thrombocytopenia early in life

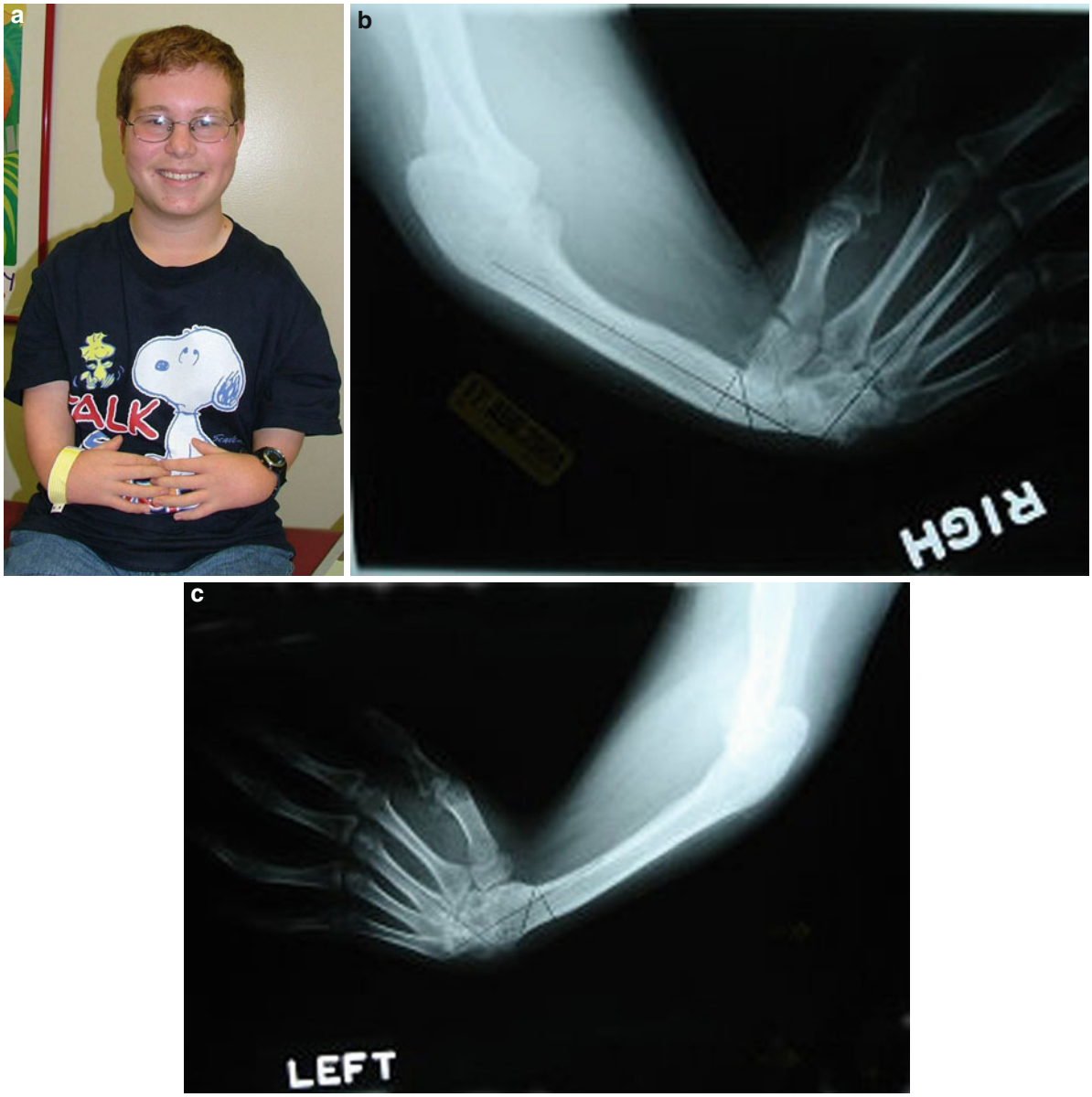

Fig. 2 (**a**–**c**) A 14-year-old boy with TAR syndrome showing similar clinical and radiographic features

Fig. 3 (**a**–**c**) An 8-month-old boy was noted to have club hands with radial aplasia. Platelet count was 28,000 at birth. He was diagnosed to have thrombocytopenia necessitating repeat platelet infusions

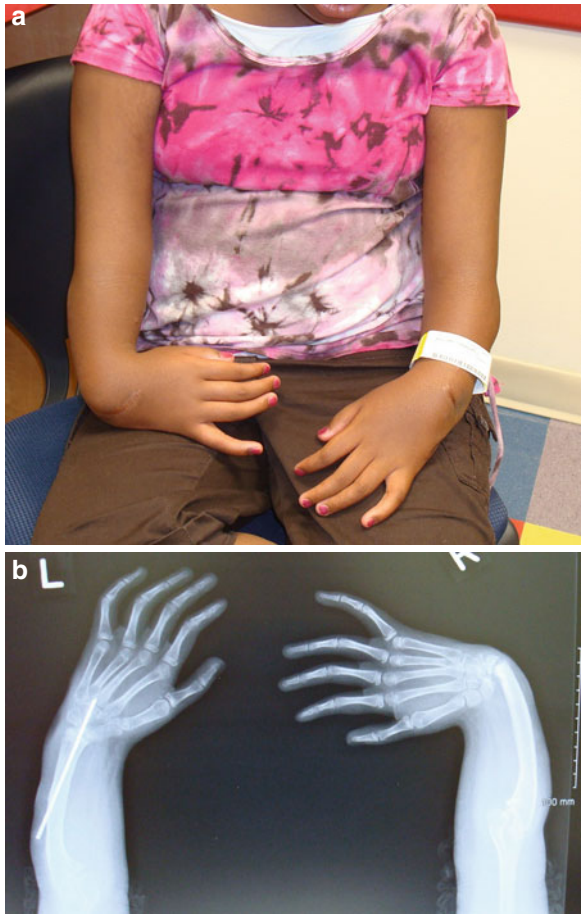

Fig. 4 (**a**, **b**) An 8-year-old girl with TAR syndrome showing similar clinical and radiographic features

Treacher-Collins Syndrome

Treacher-Collins syndrome (TCS), also called Treacher Collins-Franceschetti syndrome or mandibulofacial dysostosis, is an autosomal dominant disorder affecting the development of structures derived from the first and second branchial arches during early embryonic development (Poswillo 1975). The incidence is estimated to be 1 in 50,000 live births.

Synonyms and Related Disorders

Mandibulofacial dysostosis; Treacher Collins-Franceschetti syndrome

Genetics/Basic Defects

1. Inheritance
   a. An autosomal dominant disorder
      i. Rare incomplete penetrance
      ii. Wide variability
   b. Forty percentage of cases have a previous family history.
   c. Sixty percentage of cases possibly arise from de novo mutations of *TCOF1*.
2. The *Treacher Collins-Franceschetti syndrome 1* (*TCOF1*) gene
   a. The only gene currently known to be associated with TCS
   b. Mapped to chromosome 5q32-q33.1
   c. Encoding a serine/alanine–rich protein, called "treacle" (Jones et al. 1999)
   d. A complete coding sequence of the Treacher Collins-Franceschetti syndrome 1 gene (*TCOF1*) has been identified.
   e. Mutations in the *TCOF1* gene (Marszalek et al. 2002)
      i. Type of mutations
         a) Deletions
         b) Insertions
         c) Missense mutations
      ii. Two mutations affecting splicing of the primary transcript are located in:
         a) Introns 3 (304+5 G → C)
         b) Introns 22 (3550+1G → A)
      iii. Most mutations result in a premature termination codon, producing a truncated protein devoid of the nuclear localization signals (NLSs).
3. Pathogenesis (Trainor et al. 2009)
   a. General cranioskeletal hypoplasia occurs due to generation of insufficient neural crest cells.
   b. Insufficient neural crest cell number is a consequence of neuroepithelial progenitor cell death.
   c. Tcof1/Treacle is an important spatiotemporal regulator of ribosome biogenesis.
   d. Haploinsufficiency of Tcof1/Treacle results in deficient ribosome biogenesis, which is incapable of meeting the proliferative needs of the neuroepithelium.
   e. Deficient ribosome biogenesis leads to nucleolar stress activation and stabilization of p53, which causes the high degree of neuroepithelial apoptosis and consequent loss of neural crest cells.
   f. In an experimental animal-based strategy, genetic and/or chemical inhibition of p53-dependent apoptosis can restore the normal complement of neural crest cells and prevent the development of TCS craniofacial anomalies.

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Clinical Features

1. Interfamilial and intrafamilial variability
2. Eyes
   a. Antimongoloid slant of the palpebral fissures
   b. Colobomata and hypoplasia of the lower lids and lateral canthi
   c. Partial absence of eyelid cilia
   d. Hypertelorism
3. Ears (Posnick and Ruiz 2000)
   a. External ear anomalies
      i. Symmetric
      ii. Normal
      iii. Absent
      iv. Malformed
      v. Malposed
   b. External auditory canal abnormalities
      i. Symmetric (88%)
      ii. Atretic (54%)
      iii. Stenotic (31%)
      iv. Normal (15%)
   c. Middle ear cavity ossicular deformities
      i. Symmetric (96%)
      ii. Hypoplastic (85%)
   d. Conductive hearing loss results from variable degrees of hypoplasia of the external auditory canals and ossicles of the middle ears.
4. Nose/mouth
   a. Respiratory compromise in severely affected patients as a result of the following two factors (Posnick and Ruiz 2000):
      i. Presence of maxillary hypoplasia, which tends to constrict the nasal passages and results in a degree of choanal stenosis or atresia
      ii. Presence of mandibular micrognathia and a retropositioned tongue obstructing the oropharyngeal and hypopharyngeal spaces
   b. Nasal deformity
   c. Macrostomia
   d. Cleft palate with or without cleft lip
   e. High-arched palate
   f. Malocclusion
   g. Open bite
5. Facial bone malformations: the most characteristic findings
   a. Hypoplasia of the malar bones
      i. Often with clefting through the arches
      ii. Limited formation of the residual zygomatic complex
   b. Orbits
      i. Hypoplastic lateral aspects of the orbits
      ii. Dysplastic inferior-lateral orbits
   c. Maxilla and mandible
      i. Characteristically hypoplastic (malar hypoplasia)
      ii. Variable effects on the temporomandibular joints and the muscles of mastication
      iii. Anterior open bite malocclusion
      iv. A steep (clockwise-rotated) occlusal plane
6. Sleep apnea and sudden infant death syndrome
7. Differential diagnosis (Dixon 1995)
   a. Nager acrofacial dysostosis
      i. Features similar to those of TCS
         a) Zygomatic hypoplasia
         b) Downward slanting of the palpebral fissures
         c) Micrognathia
         d) Anomalies of the external ears
         e) Cleft palate
      ii. Limb defects (not observed in TCS)
         a) Often asymmetrical
         b) Preaxial limb defects
         c) Hypoplastic or absent thumbs
         d) Radial hypoplasia or aplasia
         e) Radioulnar synostosis
   b. Miller acrofacial dysostosis
      i. Facial features similar to TCS and Nager syndrome
      ii. Limb defects
         a) Postaxial limb defects
         b) Most commonly with absence or incomplete development of the fifth digital ray of all four limbs
   c. Oculoauriculovertebral (OAV) spectrum
      i. OAV spectrum
         a) Sporadic occurrence in vast majority of cases
         b) One to two percentage of cases with a previous family history
         c) Includes hemifacial microsomia and Goldenhar syndrome

ii. Hemifacial microsomia
  a) Primarily affecting development of the ear, mouth, and mandible
  b) Wide variable expression
  c) Affecting primarily only one side of the face
iii. Goldenhar syndrome
  a) Facial involvement
  b) Vertebral anomalies
  c) Epibulbar dermoids

Diagnostic Investigations

1. Radiography and CT for evaluation of craniofacial abnormalities
   a. Mandibular hypoplasia
   b. Bilateral condylar hypoplasia
   c. Coronoid process absence/hypoplasia
   d. Maxillary bone hypoplasia
   e. Malar bone hypoplasia
   f. Narrowed frontal bone
   g. Maxillary sinus walls hypertrophy
   h. Auricular canals atresia
   i. C1-C2 fusion
   j. Temporal muscle hypotrophy
   k. Masseter muscle hypotrophy
   l. Lateral pterygoid hypotrophy
   m. Decreased oropharyngeal space
   n. Conchae hypertrophy
2. Audiological evaluation for hearing impairment
3. DNA diagnosis: Direct sequencing of the coding and flanking intronic regions of *TCOF1* detects mutations in about 90–95% of patients (Katsanis and Cutting 2006).

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: low unless a parent is affected in which case the risk to the sibs is 50% or has germline mosaicism
   b. Patient's offspring: 50%
2. Prenatal diagnosis available for pregnancies at increased risk for TCS
   a. Two-dimensional and preferably three-dimensional sonography (Hsu et al. 2002)
      i. Polyhydramnios
      ii. Demonstration of characteristic facies of TCS
         a) Downward slanting palpebral fissures
         b) Micrognathia
         c) Abnormal appearance of the nose with narrow nostrils
         d) Cleft lip/palate
         e) Low-set dysplastic ears
         f) Abnormal fetal swallowing
   b. Amniocentesis or CVS
      i. To detect *TCOF1* mutation
      ii. The disease-causing allele of an affected individual must be identified before prenatal testing can be performed.
      iii. The presence of a *TCOF1* mutation detected by prenatal diagnosis does not predict the specific malformations or severity of the disease.
   c. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified in an affected family member.
3. Management
   a. Multidisciplinary team (Thompson et al. 2009)
      i. Geneticist
      ii. Neonatologist
      iii. Pulmonologist
      iv. Ophthalmologist
      v. Otolaryngologist
      vi. Audiologist
      vii. Speech pathologist
      viii. Dentist/orthodontist
      ix. Radiologist
      x. Psychologist/social worker
      xi. Craniofacial surgeons
   b. Severe case
      i. Secure airway by tracheostomy if necessary
      ii. A gastrostomy for feeding
   c. To promote normal language development
      i. Cleft palate repair
      ii. Evaluation by an otolaryngologist, audiologist, and speech pathologist
   d. Orthodontic alignment of the teeth
   e. Craniofacial reconstruction
      i. Zygomatic and orbital reconstruction
      ii. Maxillomandibular reconstruction

iii. Nasal reconstruction
iv. Soft tissue reconstruction
v. External ear reconstruction
vi. External auditory canal and middle ear reconstruction

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Fig. 1 (**a**, **b**) A child and the father with Treacher-Collins syndrome. The faces are characterized by an antimongoloid slant of the palpebral fissure, colobomata and hypoplasia of the lower lids, and small and receding chins

Fig. 2 An infant and his mother with Treacher-Collins syndrome showing similar features. The infant is mildly affected

Fig. 3 (**a**–**d**) A newborn and a child with Treacher-Collins syndrome showing antimongoloid slant of the palpebral fissures, coloboma and hypoplasia of the lower lids, and microtia

Fig. 4 (**a**–**c**) Another infant with typical Treacher-Collins syndrome

Trimethylaminuria

Trimethylaminuria, also called fish odor syndrome, is a metabolic disorder characterized by a distinctive decaying fish odor of sweat, urine, breath, and other body secretions due to presence of abnormal amounts of the dietary-derived tertiary amine, trimethylamine (TMA).

Synonyms and Related Disorders

Fish-odor syndrome

Genetics/Basic Defects

1. Inheritance (Rehman 1999)
   a. Autosomal recessive
   b. The incidence of heterozygous carriers of the allele for impaired N-oxidation is estimated to be of the order of 1%.
2. Basic defect
   a. Caused by deficiency of the flavin-containing mono-oxygenase isoform 3 (FMO3). A defect in hepatic N-oxidation of dietary-derived TMA causes excess excretion of TMA, leading to affected individuals to have a body odor resembling rotten fish (Basarab 1999).
   b. Caused by loss-of-function mutations in the *FMO3* gene (mapped on 1q24.3) encoding an isoform of flavin-containing mono-oxygenase have been shown to underlie trimethylaminuria/fish odor syndrome (Lunden 2002).
   c. Common variants in the FMO3 gene lead to greatly reduced enzyme activity in vivo, shown to cause mild to transient trimethylaminuria
   d. Also can be caused by liver, kidney, and/or gastrointestinal dysfunction, including dietary carnitine overloading secondary to the gut-generated substrate overwhelming the hepatic enzymes' oxidizing capacity
   e. Trimethylaminuria reflects how genetic constitution can adversely influence interactions with one's diet (Mitchell 2001).
3. TMA (Lunden 2002)
   a. Derived from the intestinal bacterial degradation of foods rich in choline and carnitine, such as egg yolk, liver, kidney, soybeans, peas, and saltwater fish
   b. Readily absorbed from the gut and is normally oxidized by the liver FMO3 to odorless trimethylamine N-oxide which is then excreted in the urine
   c. Impaired oxidation of TMA, thought to be the cause of the fish odor syndrome, is responsible for the smell of rotting fish.
4. FMO3
   a. One of the major enzyme systems protecting humans from the potentially toxic properties of drugs and chemicals
   b. Converts nucleophilic heteroatom-containing chemicals and endogenous materials to polar metabolites, which facilitate their elimination
   c. N-oxygenates trimethylamine to trimethylamine N-oxide which is excreted in a detoxication and deoderation process
   d. Prevalent polymorphisms of the human FMO3 may contribute to low penetrance and predispositions to diseases associated with adverse environmental exposures to heteroatom-containing

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chemicals, drugs (e.g., tricyclic antidepressants, ranitidine, amphetamine, methamphetamine, clozapine, chlorpromazine, methimazole), and endogenous amines

5. Classification of the disorder (Mitchell 2001)
   a. Primary genetic form
      i. The best understood of the various forms of the disorder
      ii. Accounts for a large proportion of the known cases
      iii. Human FMO3
         a) Highly polymorphic
         b) Some mutations, either alone or in combination, are associated with dysfunctional enzyme activity and the metabolic disorder.
         c) Two relatively common polymorphisms (P153L and E305X) appear to account for the majority of severe cases of trimethylaminuria.
         d) Some other mutations are associated with inactivation of FMO3.
         e) Combinations of intragenic polymorphisms within FMO3 appear to determine a modified and less severe form of the condition.
         f) Some mutations appear to be benign.
   b. Acquired form
      i. Several cases of clinical and biochemically diagnosed trimethylaminuria have been reported to emerge in adult life.
      ii. No previous history in childhood
      iii. No familial background
      iv. Possible mechanism: Viral hepatitis may have been responsible for precipitation of the condition possibly by insertion of viral DNA into the genome thereby affecting normal expression of the human *FMO3* gene.
   c. Transient childhood forms
      i. A transient or mild form of trimethylaminuria may occur during early childhood.
      ii. Compound heterozygosity for several mutations has been detected by molecular analysis in some cases.
   d. Transient form associated with menstruation
      i. Fish odor intensifies with onset of menstruation.
      ii. Trimethylaminuric condition deepens just prior to the onset of menstruation.
   e. Precursor overload
      i. Overload of precursors, such as choline, lecithin, and carnitine, saturates the existing levels of flavin monooxygenase.
      ii. Exposure to unusually high levels of such precursors may hasten a fish odor syndrome, especially if the individual is a haplotype for certain mutations.
   f. Disease states that impair trimethylamine metabolism
      i. Advanced liver disease
      ii. Advanced renal disease
      iii. Association with temporal lobe epilepsy and behavioral disturbances
      iv. Bacterial vaginosis with fish odor in vaginal secretions
   g. Exacerbating factors
      i. Pyrexic states
      ii. Stress
      iii. Puberty
      iv. Sweating
      v. Exercise
      vi. Emotional upsets
      vii. Menstruation
      viii. Oral contraceptives
      ix. Foods rich in choline

Clinical Features

1. Present from birth but manifests itself with the introduction of a diet, including foods that contain high amounts of choline or trimethylamine N-oxide (Chalmers et al. 2006)
2. Unmistakable, strong fishy body odor from excess unmetabolized trimethylamine in the urine, sweat, and other body secretions (breath, saliva, vaginal secretions)
3. Skin sores induced by choline-rich foods
4. Serious social/behavioral problems resulting from strong body odor (Mitchell 2001)
   a. Subject to ridicule, loss of confidence, and school disruption
   b. Destructive to personal, working, and career lives of the affected individuals
   c. Clinical depression
   d. Attempted suicide
5. Highly variable severity of the syndrome

Diagnostic Investigations

1. Demonstration of elevated TMA after a choline-rich diet by gas chromatography-mass spectrometry measurement. TMA challenge test (with a 600 mg TMA oral challenge dose and analysis of 0–8 h urine samples) is useful in confirming unequivocally the trimethylaminuric patients as well as indicating the status of the parents as carriers.
2. Mass spectroscopy and proton nuclear magnetic resonance (NMR) spectroscopy
   a. Have the advantage of being able to detect TMA and TMA *N*-oxide simultaneously with great sensitivity
   b. NMR has further advantage of requiring no prior extraction or separation of metabolites and thus measurement can be done directly on urine samples
3. Increase in urinary excretion of trimethylamine with decreased trimethylamine oxide
4. Sequence analysis of *FMO3* gene to detect mutations (>99%): clinically available
5. Combination of the proton nuclear magnetic resonance (NMR) spectroscopy to assess activity of the mutant enzyme with gene sequence and expression technology provides a powerful means of determining genotype-phenotype relationships in trimethylaminuria (Murphy 2000).

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is a carrier
2. Prenatal diagnosis: possible by demonstrating the previously characterized mutation in the fetal DNA obtained by amniocentesis or CVS
3. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified
4. Management (Rehman 1999; Mitchell 2001; Chalmers et al. 2006)
   a. Restriction of dietary sources of trimethylamine: the main therapeutic approach (Chen and Aiello 1993; Phillips and Shephard 2008)
      i. Restriction of trimethylamine (milk obtained from wheat-fed cows)
      ii. Restriction of its precursors including choline-rich food
         a) Egg yolk
         b) Liver
         c) Kidney
         d) Peas
         e) Beans
         f) Peanuts
         g) Soya products
         h) Brassicas (include cabbage, broccoli, and turnip)
         i) Legumes
         j) Fish
      iii. Trimethylamine N-oxide source
         a) Some saltwater fish (cod, skate)
         b) Cephalopods (include cuttlefish, squid, and octopus)
         c) Crustaceans (include crabs, lobsters, and shrimp)
      iv. Dietary restriction appears to be successful in the management of the majority of patients.
      v. Appears to be most effective in mild to moderate forms of fish odor syndrome arising from particular mutations or haplotypes
   b. Suitable diet include:
      i. Dark green leafy vegetables
      ii. Fortified bread and cereals
      iii. Orange juice
   c. Freshwater fish may be eaten freely.
   d. Avoid exacerbation factors such as pyrexia and stress.
   e. Vitamin supplementation with riboflavin, a precursor of the FAD cofactor for flavin monooxygenase function, in an attempt to maximize any residual activity
   f. Drug treatment: Occasionally a short course of metronidazole, neomycin, and lactulose may suppress production of TMA by reducing the activity of gut microflora in some patients (Fraser-Andrews 2003).
   g. Copper-chlorophyllin tablets to moderate gut flora activity and complex TMA
   h. Use of "malodor suppressants" in hygiene products and soaps and body lotions with a low pH (3.5–6.5) to disguise the offensive smell of trimethylamine
   i. Counseling of the social/behavioral problems
   j. Gene therapy and enzyme induction with drugs provide hope for the future.

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Fig. 1 (**a**–**d**) A 12-year-old girl with trimethylaminuria showing multiple sores on the hands and legs. At age 4, she developed unpleasant fish odor and constant scratching of her skin. Trimethylaminuria was diagnosed based on markedly increased urinary TMA by gas chromatography after loading with choline. The patient started with a baseline level of 0.28 mg TMA mg/mg creatine that is 4 times of control. After 8, 16, and 24 h of loading with choline, the values went up to 2.8 mg (41×), 3.99 mg (57×), and 9.93 mg (95×), respectively. In addition, the diagnosis of Prader–Willi syndrome was made at age 9 because of relative obesity, hypotonia, delayed psychomotor development, almond-shaped eyes, small hands and feet, and presence of chromosome abnormality of del(15)(q11q13)

Triploidy

Triploidy is defined as the presence of three sets of haploid (69) chromosomes. Triploid fetuses occur in about 1% of recognized pregnancies, 1 in 100,000 live borns, and constitute about 15% of all fetuses with chromosome abnormalities. There is a slight excess of males (M1.5:F1). Most triploid fetuses often result in spontaneous abortions between 7 and 17 weeks of gestation. However, rare instances of a live triploid infant have been reported (Allen and Pritchard 2000).

Synonyms and Related Disorders

Partial hydatidiform mole of the placenta; Triploid fetus (69,XXY, 69,XXX, diploid/triploid mosaicism)

Genetics/Basic Defects

1. Origin of triploidy (Allen and Pritchard 2000; Benn et al. 2001)
   a. Diandric origin of the triploid fetuses (type I)
      i. Mechanisms of paternal origin of the supernummary haploid set
         a) Dispermy: fertilization of a haploid egg by two haploid sperms (dispermy) accounting for 66% (most common mechanism leading to triploidy)
         b) Faulty meiotic division in the male: fertilization of a normal ovum by a diploid sperm (diandry) (about 24%)
      ii. Characteristics of diandric fetuses
         a) Relatively normal fetal growth
         b) Slight macrocephaly
         c) Marked syncytiotrophoblastic hyperplasia
         d) Hydatidiform changes of the placental villi (partial mole) (large cystic placenta)
   b. Digynic origin of triploid fetuses (type II)
      i. Mechanisms of maternal origin of the supernummary haploid set
         a) Mitotic errors in female germ cell precursors: fertilization of a diploid ovum by a normal sperm (digyny) (about 10%)
         b) Errors in maternal meiosis: an error at meiosis I or II or incorporation of the second polar body postulated
      ii. Characteristics of digynic fetuses
         a) Generally marked fetal (asymmetric) growth retardation
         b) Relative macrocephaly
         c) Small, non-cystic placenta
         d) Maternally derived triploidy was often found in those fetuses that survived until late pregnancy.
2. Diploidy/triploidy mosaicism
   a. Mechanisms (Phelan et al. 2001)
      i. Postzygotic maldivision of a triploid or diploid zygote
      ii. Incorporation of the second polar body into a daughter nucleus of the developing embryo
      iii. Fertilization of a diploid ovum with incorporation of the second diploid polar body
      iv. Fertilization of the first polar body and ovum by individual spermatozoa with suppression of one second polar body
      v. Dispermy or diploid sperm fertilization with incorporation of an independently fertilized second polar body

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vi. Chimera formation by union of diploid and triploid embryos
vii. Vanishing twin and chimerism
b. Characteristics of diploid/triploid fetuses: rarer and less severe phenotype than true triploidy

3. Triploidy and in vitro fertilization (IVF)/ intracytoplasmic sperm injection (ICSI) (Dayal et al. 2009)
a. Diandric triploidy is observed with spontaneous as well as conventional IVF and is assumed to be the most common form of triploidy (Jun et al. 2006).
b. Intracytoplasmic sperm injection, by its virtue of injecting a single sperm into a single oocyte, negates the potential for dispermic triploidy.
c. Digynic triploidy occurs secondary to failed meiosis II expulsion of the second polar body and subsequent fertilization of a diploid oocyte. Cytogenetic evidence of three pronuclei post-ICSI zygotes that result from failed extrusion of the second polar body (Tsuchiya et al. 2002).
d. Mechanistically, this may occur with a damaged metaphase plate or oocyte cytoskeleton (Kimura and Yanagimachi 1995), after abnormal spindle formation or increased female age (Spandorfer et al. 1998; Tsuchiya et al. 2002). The latter etiologies may represent an occult oocyte factor.

Clinical Features

1. Prenatal history
a. IUGR
i. Asymmetrical (digynic)
ii. Symmetrical (diandric)
b. Prematurity
c. Hydrops
d. Polyhydramnios
e. Oligohydramnios
f. Partial hydatidiform mole (placenta)
2. Craniofacial features
a. Dysplastic calvarium
b. Microcephaly
c. Large posterior fontanelle
d. Ocular hypertelorism or hypotelorism
e. Epicanthal folds
f. Exomphalos
g. Microphthalmia
h. Iris and choroid colobomas
i. Midfacial hypoplasia
j. Arhinia
k. Small upturned nose
l. Choanal atresia
m. Single nostril (in holoprosencephaly)
n. Micrognathia
o. Cleft lip/palate
p. Low-set ears
q. Short neck
r. Thick nuchal fold
s. Cystic hygroma
3. CNS
a. Hypotonia
b. Arnold-Chiari malformation
c. Posterior fossa cyst (Dandy-Walker malformation)
d. Holoprosencephaly
e. Hydranencephaly
f. Hydrocephalus (20%)
g. Absent corpus callosum (15%)
h. Absent gyri of the brain
i. Hypoplastic cerebellum
j. Absent first cranial nerve
k. Encephalocele
l. Lumbosacral meningomyelocele (20%)
4. Gastrointestinal malformations
a. Omphalocele
b. Ventral wall defects
c. Incomplete rotation of colon
d. Agenesis of gallbladder
e. Meckel diverticulum
f. Duodenal atresia
g. Malfixation of cecum
h. Inguinal hernia
5. Endocrine abnormalities
a. Adrenal hypoplasia
b. Thyroid hypoplasia
c. Lingual thyroid
d. Thymic hypoplasia
e. Leydig cell hyperplasia
f. Gonadal dysgenesis
6. Genitourinary abnormalities
a. 69,XXY triploid fetus
i. Varying degree of ambiguous genitalia (40%)
ii. Hypospadias (40%)
iii. Cryptorchidism (85%)
iv. Micropenis (75%)

v. Scrotal abnormalities (60%) including bifidity, scrotal hypoplasia, or agenesis
vi. Leydig cell hyperplasia (20%)
b. 69,XXX triploid fetus
i. Gonadal dysgenesis
ii. Renal abnormalities
a) Multicystic kidneys
b) Hydronephrosis
c) Glomerulosclerosis
7. Gastrointestinal abnormalities
a. Omphalocele
b. Diaphragmatic hernia
c. Gastroschisis
d. Malrotation
e. Gallbladder hypoplasia
f. Pancreas hypoplasia
8. Cardiovascular anomalies
a. VSD
b. ASD
c. PDA
d. PA
e. Tetralogy of Fallot
f. Truncus arteriosus
g. Aberrant right subclavian artery
h. Cardiomegaly
9. Respiratory tract abnormalities
a. Small chest
b. Pulmonary hypoplasia
c. Absent lung lobation
d. Congenital cystic adenomatoid malformation of the lung
10. Prognosis
a. Majority die early in gestation.
b. Very few surviving into the third trimester
c. The fetuses rarely survive to delivery.
i. Profoundly malformed
ii. Growth-restricted
iii. Survival measured in hours to days
d. Fetuses with extra maternal haploid set of chromosomes appear to survive longer in utero than those with extra paternal haploid set of chromosomes (Allen and Pritchard 2000).
e. Some cases of diploid/triploid mixoploidy survive after the neonatal period, which is exceptional.
11. Diploid/triploid mosaicism (Van De Laar et al. 2002)
a. A well-known malformation syndrome
b. Common features
i. Mental retardation
ii. Growth retardation
iii. Body and/or facial asymmetry
iv. Hypotonia
v. Truncal obesity
vi. Prominent forehead
vii. Depressed nasal bridge
viii. Micrognathia
ix. Malformed low-set ears
x. Syndactyly
xi. Clinodactyly
xii. Transverse palmar creases
xiii. A small phallus
xiv. Cryptorchidism
xv. Precocious puberty
c. Additional features
i. Sandal gap
ii. Short halluces
iii. Seizures
iv. Respiratory distress
v. Microstomia
vi. Irregular skin
vii. Feeding difficulties
viii. Muscular atrophy of the limbs
d. Rarer and less severe than true triploidy in which infants can survive beyond neonatal period till over 20 years
e. Presence of a normal diploid cell line and a second triploid cell line in varying degrees and with varying tissue distribution

Diagnostic Investigations

1. Karyotype of fetus and newborn
a. 69,XXX (one third of cases)
b. 69,XXY (Two thirds of cases)
c. Diploid/triploid mosaicism
i. Less severe phenotype
ii. More compatible with life
iii. Harder to diagnose clinically
iv. Peripheral lymphocyte cultures showing a normal karyotype only
v. Need fibroblast culture to show the cell line with triploid complement
d. Molecular determination of the origin of the extra haploid set of chromosomes
i. Fluorescent polymerase chain reaction (F-PCR) analysis of short tandem repeats (STRs) located on chromosomes such as 21, 18, and 13 (Bán et al. 2002)

ii. Assessment of numerous polymorphic DNA markers

2. Radiography
   a. Poor ossification of calvarium
   b. Craniolacunae
   c. Chondrodysplasia punctata-like calcification
   d. Vertebral fusions
   e. Harlequin orbits
   f. Gracile ribs
   g. Upswept clavicles
   h. Diaphyseal overtubulation of long bones
   i. Vertical ilia
   j. Proximal radioulnar synostosis
   k. Asymmetry of occipitoparietal calvaria (50%)
3. CT and MRI of the brain
   a. Cortical hypoplasia
   b. Agenesis of corpus callosum (15%)
   c. Hypoplasia of basal ganglia/occipital lobe
   d. Dandy-Walker anomaly
   e. Arnold-Chiari malformation
4. Histopathology of the placenta
   a. Partial hydatidiform mole change of villi on gross and microscopic examination
   b. The partial mole is caused by a triploidy (Devriendt 2005).
   c. The villi with molar change show hydropic swelling of the stroma, and trophoblastic proliferation (hyperplasia) is also present in scattered areas.
   d. Irregular cystic cavitation may be seen in larger hydropic villi.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: The true recurrence risk for cytogenetic abnormalities in subsequent offspring is uncertain but may be slightly increased and higher than expected (Graham et al. 1989).
   b. Patient's offspring: a lethal condition not surviving to reproduce
2. Prenatal diagnosis
   a. First-trimester markers screening (De Graaf et al. 1999)
      i. Low serum marker pregnancy-associated plasma protein A (PAPP-A)
      ii. Low serum marker free β-chain of chorionic gonadotrophin (free β-hCG)
   b. Second trimester maternal serum screening (Benn et al. 2001)
      i. High maternal serum hCG associated with triploidy
         a) Nearly always indicating placenta with partial mole (93%)
         b) A high frequency of open neural tube defects or ventral wall defects (29%)
         c) With either XXX or XXY karyotype
      ii. Low hCG associated with triploidy
         a) Infrequently associated with a molar placenta (9%)
         b) Not appear to be associated with open neural tube defects or ventral wall defects
         c) An excess of XXX over XXY karyotypes
      iii. Large placentas with molar changes (diandry) generally associated with increased maternal serum AFP (MSAFP) and high hCG levels
      iv. Those with digyny and small monocystic placentas generally associated with normal MSAFP and low hCG
   c. Isolation of nucleated red blood cells from the maternal peripheral circulation at the first trimester (12 weeks gestation): FISH analysis using X and Y and other chromosome-specific probes (De Graaf et al. 1999)
   d. Amniocentesis/CVS
      i. Triploidy
      ii. Diploidy/triploidy mosaicism
   e. Ultrasonography of structural anomalies compatible with triploidy
      i. Severe, early-onset asymmetrical growth restriction in the late first and early second trimester (the head size remains almost normal whereas the remainder of the fetal body and skeleton is severely growth-restricted)
      ii. Oligohydramnios, asymmetric growth restriction, and a small placenta when the third set of chromosomes is maternal
      iii. Large, hydropic-appearing placenta consistent with partial moles (60–80%) when the third set of chromosomes is paternal
      iv. Most common sonographic abnormalities
         a) Large thickened placenta containing multiple sonolucent areas
         b) Characteristic sharply defined, large and small cystic spaces within the placenta

c) Hydrops
d) Ventriculomegaly
e) Dandy-Walker malformation
f) Holoprosencephaly
g) Agenesis of the corpus callosum
h) Micrognathia
i) Echogenic bowel
j) Omphalocele
k) Renal malformations
l) Thickened nuchal folds
m) Neural tube defects
n) Club feet
o) Syndactyly of the third and fourth fingers

f. Preimplantation genetic diagnosis in conjunction with in vitro fertilization by a single sperm injection: a viable approach when there are clinical or genetic indications of repeated dispermy, unreduced (diploid) spermatozoa, or unreduced (diploid) oocytes (Pergament et al. 2000)

3. Management
   a. No treatment available for true triploidy, a lethal condition.
   b. Supportive therapy for diploid/triploid mosaicism who may survive beyond neonatal period.

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Fig. 1 (**a**–**e**) A newborn with triploidy (69,XXY) showing woolly hair, distinctive facial appearance (epicanthal folds, microphthalmia, beaked nose, small mouth, receding jaw, low-set and malformed ears), partial syndactyly between third-fourth fingers and toes, and ambiguous genitalia. The infant also had bilateral coloboma and cataracts, short neck, loud continuous heart murmur along the *left* sternal border, and bilateral transverse palmar creases. The infant died at 25 h

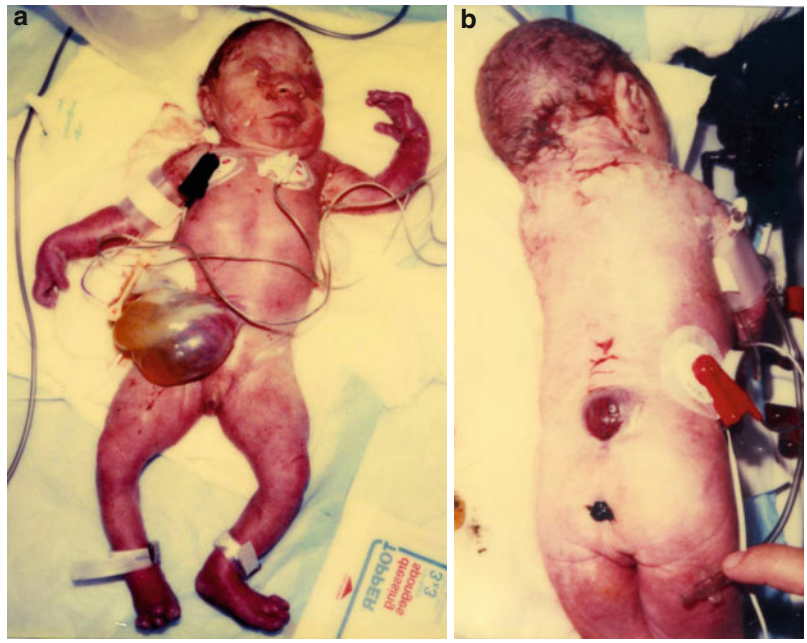

Fig. 2 (**a**, **b**) An infant with triploidy showing abnormal craniofacial features, omphalocele, thick nuchal fold, and lumbosacral meningomyelocele

Fig. 3 (**a**–**c**) An infant with triploidy (69,XXX) showing low-set/malformed ears, syndactyly of two-three-four fingers, spina bifida, and pulmonary hypoplasia at autopsy. The infant also had a large ventricular septal defect

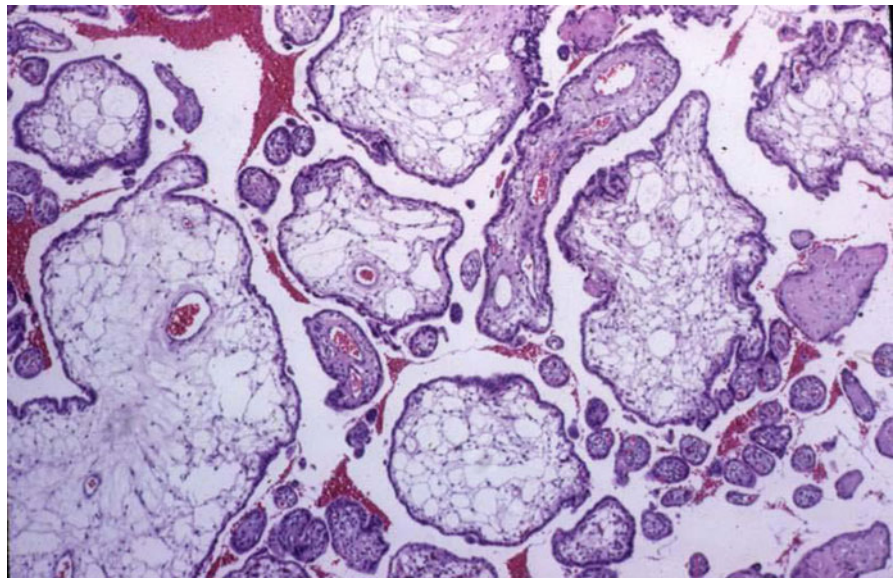

Fig. 4 Partial mole of triploidy placenta. Many villi are enlarged, hydropic, and hypovascular. Prominent infolding and nests of trophoblastic cells in the villous stroma are seen in other areas

Fig. 5 A G-banded karyotype showing 69,XXX

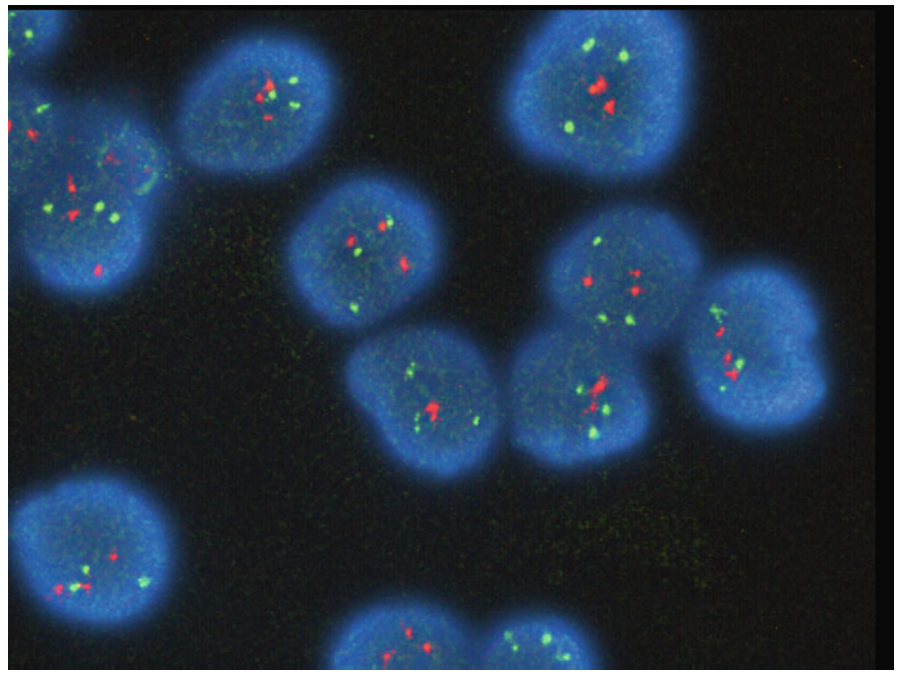

Fig. 6 Triploidy for all chromosomes shown by multicolor FISH on interphase cells. Three copies of chromosome 13 (*green*) and chromosome 21 (*orange*) are shown here

Trismus-Pseudocamptodactyly Syndrome

The trismus-pseudocamptodactyly syndrome, a relatively rare hereditary disorder, is characterized by inability to open the mouth fully, pseudocamptodactyly, mild foot deformities, and mild short stature. This malformation syndrome was first reported by Hecht and Beals and Wilson et al. in 1969 (Hecht and Beals 1969; Wilson et al. 1969). The term Dutch–Kentucky syndrome was coined for trismus pseudocamptodactyly by Mabry et al. because the earliest affected member was a young Dutch girl who emigrated to the southern United States soon after the American Revolution.

Syonyms and Related Disorders

Dutch–Kentucky syndrome; Hecht–Beals syndrome

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant
   b. High penetrance
   c. Variable expression
2. Caused by a single mutation, p.R674Q, in *MYH8* (myosin heavy chain 8) gene (Toydemir et al. 2006a)
3. Pathogenesis
   a. Possible mechanisms of trismus
      i. The shortened lengths of certain mastication muscles presumed to be responsible for the clinical manifestations.
         a) Temporalis muscle
         b) Internal pterygoid muscle
         c) Masseter muscle
      ii. Enlarged coronoid processes
         a) Resulted from tension exerted by short temporal muscle tendon units
         b) Impinging on the body of the zygomatic bone and inner margin of the arch, thereby limiting mandibular excursion
      iii. Secondary to an abnormal ligament between the maxilla and that of the mandible anterior to the masseter muscles
      iv. Fibrotic abnormality of the masseter muscle mass in the vicinity of the ascending ramus
   b. Pseudocamptodactyly of fingers
      i. More appropriate term than camptodactyly because of
         a) Not associated with progressive deformities
         b) Not associated with fixed joint contractures
      ii. Caused by a shortening of the flexor digitorum profundus muscle tendon units, involving all fingers
   c. Foot deformities explainable by a shortening of the various muscle tendon groups in the leg and foot
   d. Several individuals with this mutation also had a so-called variant of Carney complex (a high incidence of myxomas, skin pigmentation disorders, endocrine tumors, or overactivity in schwannomas that manifest with cardiac myxomas and spotty skin pigmentation) (Veugelers et al. 2004), suggesting that the pathogenesis of trismus-pseudocamptodactyly syndrome and Carney complex might be shared. However, none of the individuals with

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trismus-pseudocamptodactyly syndrome studied had features of Carney complex, and p.R674Q was not found in 49 independent cases of Carney complex that were screened. The findings show that distal arthrogryposis syndromes share a similar pathogenesis and are, in general, caused by disruption of the contractile complex of muscle (Toydemir et al. 2006a).

e. The trismus found in trismus-pseudocamptodactyly syndrome can also be present in Freeman–Sheldon syndrome (also known as distal arthrogryposis type 2A) and Sheldon–Hall syndrome (also known as distal arthrogryposis type 2B). Both of these conditions are caused by mutations in the *MYH3* gene (Toydemir et al. 2006b), confirming the hypothesis that the distal arthrogryposis syndromes are caused by aberrant function of the contractile complex of fast-twitch myofibers.

Clinical Features

1. Highly variable expression
2. Two main clinical features
   a. Limited excursion of the mandible
      i. Trismus (restricted opening of the mouth)
         a) Present at birth and persisting throughout life
         b) Greatly variable degree of restricted opening of the mouth
         c) The mouth opening is measured between the incisal edges of the central upper and lower incisors (in millimeter).
         d) Children: less than the value for normal children (36.6 ± 5.7 for age 7 years to 47.2 ± 6.4 for age 18 years)
         e) Adults: less than the value for normal adults (53.8 ± 6.5 for males, 50.4 ± 5.9 for females)
      ii. Mastication problems
      iii. Feeding problems with inadequate caloric intake
      iv. Swallowing difficulty (dysphagia)
      v. Difficulty with dental care
      vi. Delayed in speech development
      vii. Difficulty in endotracheal intubation for general anesthesia
   b. A flexion deformity of the fingers
      i. Clenched fists may be present at birth.
      ii. Typically crawling on the knuckles later in infancy
      iii. Occurring with wrist extension (pseudocamptodactyly) which is reversed by wrist flexion
      iv. Flexion of the fingers when the hand is dorsiflexed in minimally affected patients
      v. Pronounced flexion with ulnar deviation of the fingers in severely affected patients
3. Other clinical features
   a. Lower extremity and foot deformities (5% of cases)
      i. Mild calcaneovalgus
      ii. Equinovarus
      iii. Metatarsus varus
      iv. Camptodactyly
      v. Vertical talus
      vi. Hammertoe deformities
      vii. Shortening of both the gastrocnemiae and hamstring muscles
   b. Soft-tissue syndactyly occasionally present
   c. Mild short stature
4. Differential diagnosis of restricted mouth opening and/or (pseudo)camptodactyly
   a. Restricted mandibular opening caused by
      i. Intra-articular processes
         a) Trauma
         b) Infection
         c) Ankylosis
      ii. Extra-articular processes
         a) Soft tissue and bony obstructions
         b) Neurologic disorders such as tetanus
   b. Trismus in temporomandibular joint dysfunction
   c. Trismus caused by hypoplasia and fibrosis of the muscles around the mouth in Freeman–Sheldon syndrome
   d. Trismus and camptodactyly in patients with distal arthrogryposis who may have hyperextension of the metacarpophalangeal joints but also have contractures of the hips and feet, and short stature
   e. Trismus with a fixed facies secondary to hypoplasia or atrophy of small muscle fibers in Schwartz–Jampel syndrome
   f. A new arthrogryposis syndrome with facial and limb anomalies
      i. An autosomal dominant disorder

ii. Small mouth and jaw with limited jaw movement in infancy
iii. Associated with short stature and severe flexion contractures of the hands and feet

g. Digitotalar syndrome
i. An autosomal dominant disorder
ii. Flexion deformities
iii. Ulnar deviation and narrowing of the fingers
iv. Soft-tissue webbing causing abnormal positions of the thumbs
v. A vertical talus

Diagnostic Investigations

1. Radiography
   a. Enlargement of the coronoid processes
   b. Normal hands and forearms
2. Manometry for demonstrating abnormal swallowing
3. Histology of the affected muscles showing presence of fibrous tissue along with some muscle atrophy
4. Molecular genetic testing of *MYH8* mutations

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased unless a parent is affected (A mildly affected parent may be missed) or has germinal mosaicism (Bonapace et al. 2010)
   b. Patient's offspring: 50%
2. Prenatal diagnosis: not been reported but possible in family at risk by *MYH8* mutation analysis of fetal DNA obtained from amniocentesis of CVS, provided the mutation has been previously identified in the affected family member
3. Management
   a. Use a flattened nipple to assist feeding in infancy.
   b. Anesthetic implications
      i. Limited excursion of the mandible
      ii. Potentially difficult or impossible to apply artificial ventilation and endotracheal intubation
      iii. Inhalational anesthesia with spontaneous breathing recommended for minor surgery
      iv. Bullard laryngoscope, an excellent device for intubating patients with limited mouth opening
      v. Fiber-optic nasotracheal intubation
      vi. Needs for emergency tracheostomy and cricothyrotomy
   c. Surgical release in the severe cases of trismus
      i. Bilateral coronoidotomies with excision of accessory fibrous tissue
      ii. Bilateral excision of hypertrophic coronoid processes
      iii. Surgical release of the shortened muscle–tendon units
      iv. Ongoing physical therapy with postsurgical stretching of the jaw opening on a daily basis to avoid relapse
   d. Surgical flexor slide-through procedure on the flexion tendons of the forearms

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Fig. 1 Facial appearance of a child and his mother with trismus pseudocamptodactyly

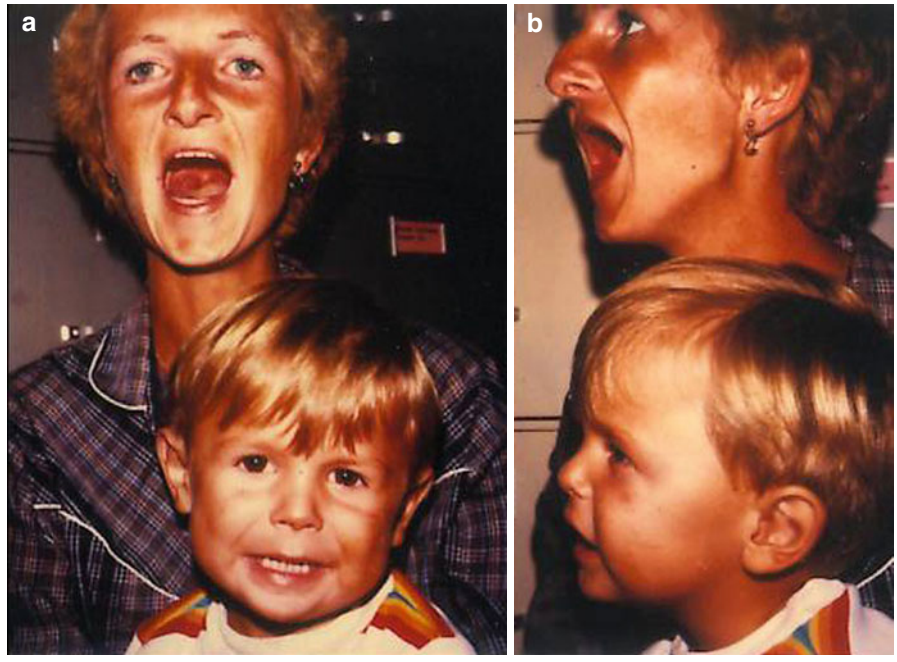

Fig. 2 (**a**, **b**) Front and lateral views of the child and his mother illustrating maximal abilities to open their mouth. The mother and the child both had *MYH8* mutations (p. R674Q)

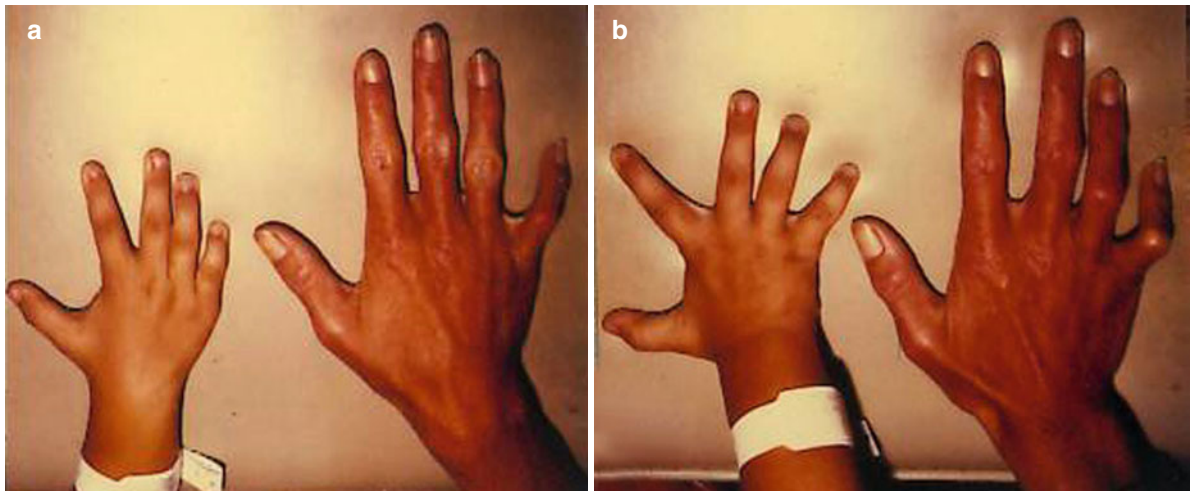

Fig. 3 (**a**, **b**) Hands of the child and his mother demonstrating no contractures of fingers on neutral positions but flexion contractures of fingers on dorsiflexion. Interphalangeal webbings are also seen

Fig. 4 (**a**, **b**) Marked flexion contractures of fingers on dorsiflexion in the mother and her brother

Fig. 5 Affected father and son in different family showing trismus and flexion contractures of fingers on dorsiflexion

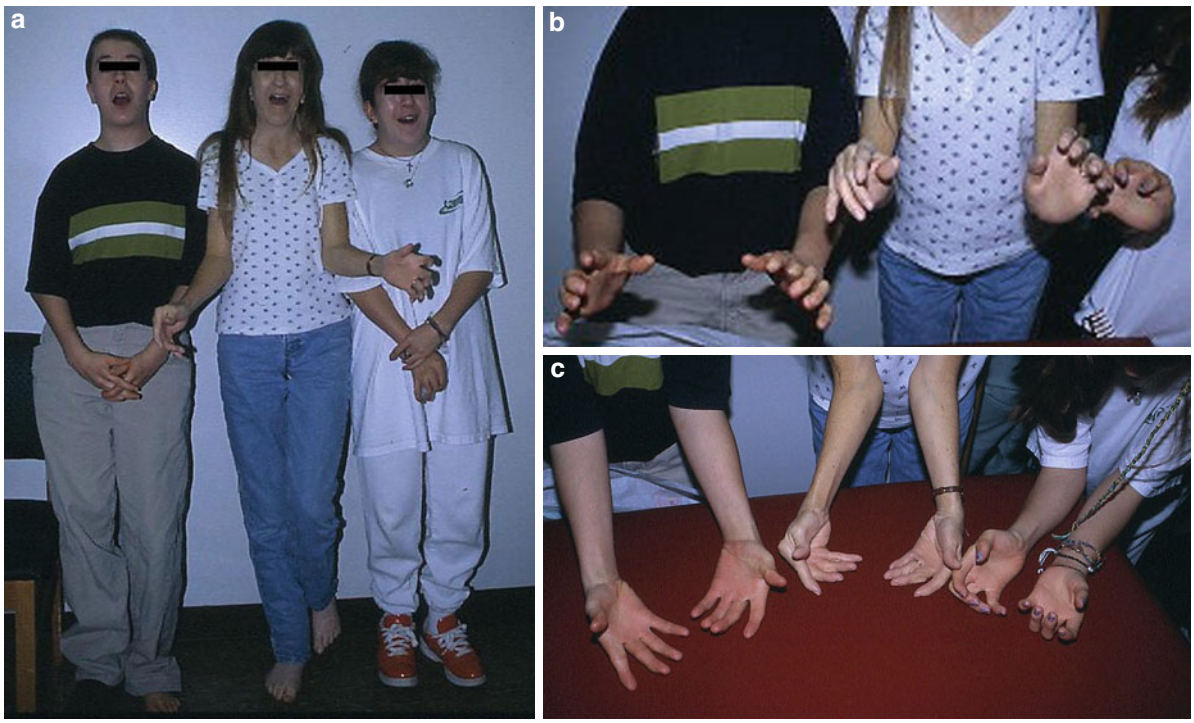

Fig. 6 (**a**–**c**) Affected three individuals in two generations in different family showing trismus and flexion contractures of fingers on dorsiflexion

Trisomy 8 Mosaicism Syndrome

In 1971, de Grouchy et al. first described trisomy 8 mosaicism which was further delineated by Fryns et al., Sanchez and Yunis, Schinzel, and Riccardi in 1977. This syndrome, also known as Warkany syndrome, is a well-recognized syndrome despite its phenotypic variability.

Synonyms and Related Disorders

Warkany syndrome

Genetics/Basic Defects

1. Trisomy 8 mosaicism: chromosome complement mosaic for chromosome 8 (presence of a chromosomally normal cell line in addition to the trisomic 8 cell line)
2. Origin of trisomy 8 mosaicism
   a. Different from the common autosomal trisomies that usually result from maternal meiotic errors
   b. Trisomy 8 in spontaneous abortions: meiotic origin in the majority of cases
   c. Postzygotic (mitotic) nondisjunction error in a diploid conceptus: the most likely origin of trisomy 8 in the live-born population
   d. Postzygotic (mitotic) nondisjunction error in a diploid conceptus, followed by nonrandom distribution of aneuploid cells between the different compartments
   e. Affected fetuses usually show a pattern of absence, or low levels of trisomy in cytotrophoblast cells (STC villi), high levels in extraembryonic mesoderm (LTC villi), and again low levels of trisomic cells in AF cells and/or fetal blood lymphocytes.
   f. LTC villi are more likely to reflect the true fetal chromosomal constitution than STC villi.

Clinical Features

1. Wide range of phenotypic variation
2. Central nervous system
   a. Intelligence: range from normal to mental retardation
   b. Agenesis of the corpus callosum
   c. Arrhinencephaly
3. Craniofacial features
   a. Skull
      i. Asymmetrical skull
      ii. Microcephaly
      iii. Hydrocephaly
      iv. Prominent forehead
      v. Flattened occiput
      vi. Low posterior hairline
   b. Eyes
      i. Ocular hypertelorism
      ii. Deep-set eyes
      iii. Strabismus
      iv. Corneal clouding
      v. Cataracts
      vi. Amblyopia
   c. Nose
      i. Plump nose with broad base
      ii. Prominent nares
   d. Mouth
      i. Micrognathia
      ii. Everted lower lip

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   iii. High palate
   iv. Cleft soft palate
4. Chest
   a. Pectus excavatum
   b. Widely spaced nipples
5. Heart: congenital heart disease
6. Gastrointestinal tract
   a. Meckel diverticulum
   b. Hirschsprung disease
   c. Anal anomalies
7. Genitourinary tract
   a. Cryptorchidism
   b. Unilateral renal agenesis
   c. Wilms tumor
   d. Ureteral anomalies
   e. Perineal anomalies
   f. Inguinal hernia
   g. Genital hypoplasia in males
8. Skeletal system
   a. Short stature
   b. Abnormal clavicle
   c. Absent or dysplastic patellae
   d. Joint contracture or limitation
   e. Vertebral anomalies
   f. Narrow pelvis
   g. Rib anomalies
   h. Scoliosis
   i. Camptodactyly of second through fifth fingers and toes
9. Skin
   a. Deep palmar skin furrows
   b. Deep plantar skin furrows: a hallmark of the syndrome
10. Fertility: an increased risk of infertility for males and females with trisomy 8
11. Life expectancy: usually normal

Diagnostic Investigations

1. Traditional cytogenetic diagnosis
   a. Detection of mosaic trisomy 8 from various tissue
   b. Abnormal cell line tends to disappear from lymphocytes with age.
   c. In older patients, aneuploidy can sometimes be demonstrated in fibroblast cultures only.
2. Interphase fluorescent in situ hybridization (FISH) using a chromosome 8 centromere-specific probe
3. Array comparative genomic hybridization (array-CGH)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: recurrence risk not increased
   b. Patient's offspring
      i. An increased risk of spontaneous abortion for trisomic conceptuses
      ii. Fetuses with complete trisomy 8: nonviable
      iii. Chromosomally normal pregnancies possible
2. Prenatal diagnosis
   a. Prenatal cytogenetic diagnosis of mosaicism
      i. Metaphase analysis of cultured cells from either amniotic fluid or chorionic villi: currently the standard technique (analysis of 30 colonies needed to exclude 10% mosaicism with a 95% confidence level)
      ii. Interphase fluorescent in situ hybridization (FISH) with a centromere-specific probe: to further define the level of mosaicism
      iii. Array comparative genomic hybridization (array-CGH): enables faster results than standard cell culture and metaphase analysis (capable of detecting mosaicism at levels as low as 7%)
   b. Problems in genetic counseling
      i. Prediction of phenotype difficult since clinical severity is not related to the level of mosaicism
      ii. Problems in detecting trisomy 8 mosaicism in chorionic villi
         a) Do not necessarily reflect a constitutional mosaicism of the fetus
         b) Most likely represent confined placental mosaicism (a chromosomally abnormal cell line limited to the trophoblast tissue and/or extraembryonic mesoderm, with a normal karyotype in the fetus proper)
         c) Possible false-negative cases of trisomy 8 mosaicism in short-term culture villi, as well as cultured amniotic fluid cells

   d) Follow-up investigations in fetal blood cells recommended when trisomy 8 mosaicism is encountered in chorionic villi
  iii. Problems in detecting trisomy 8 mosaicism in amniotic fluid
    a) Amniocentesis: not the best way to reveal trisomy 8 mosaicism
    b) Cases of missed trisomy 8 mosaicism reported
3. Management
  a. Mostly supportive
  b. Surgical management may be needed for those individuals with major malformations

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Fig. 1 (**a**–**d**) An infant boy with trisomy 8 mosaicism showing typical craniofacies (prominent forehead, ocular hypertelorism, plump nose with broad base, micrognathia) and characteristic deep plantar skin furrows. Chromosome analysis showed trisomy 8 mosaicism (only trisomy 8 karyotype is shown here)

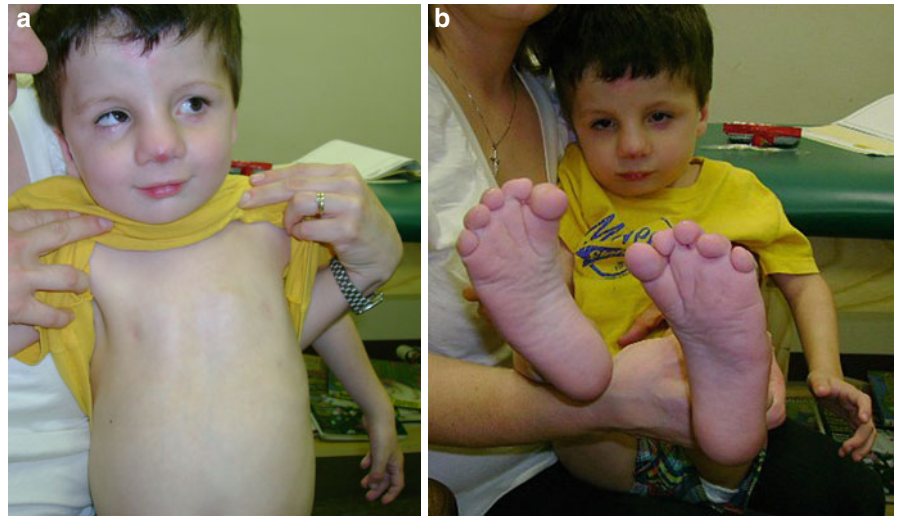

Fig. 2 (**a**, **b**) A 2-year-and-6-month-old boy with trisomy 8 mosaicism showing typical craniofacial features (prominent forehead, ocular hypertelorism, plump nose with broad base, micrognathia) and characteristic deep plantar furrows in both feet

Fig. 3 Another child with trisomy 8 mosaicism with typical phenotype

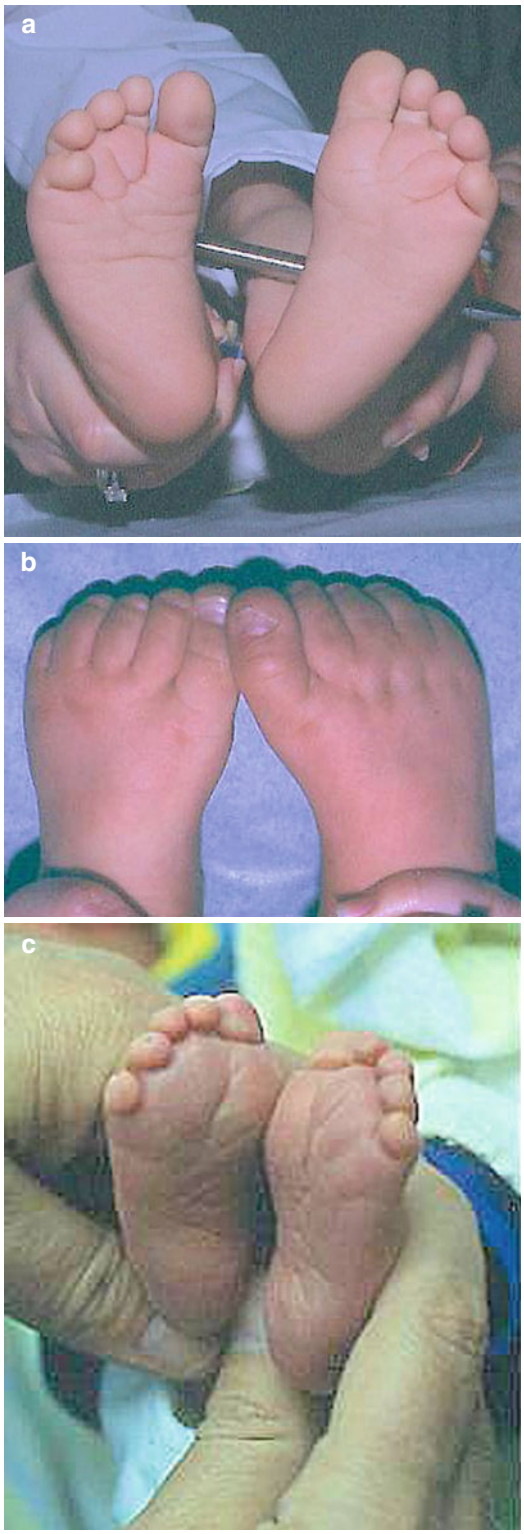

Fig. 4 (**a**–**c**) Two infants with trisomy 8 mosaicism showing characteristic deep plantar furrows in both feet

Trisomy 13 Syndrome

In 1960, Patau et al. first recognized the relation of trisomy 13 to a clinical syndrome. Incidence is estimated to be 1/4,000–1/10,000 live births.

Synonyms and Related Disorders

Patau syndrome

Genetics/Basic Defects

1. Trisomy 13
   a. Mechanism: due to meiotic nondisjunction
      i. Maternal origin of the extra chromosome (90%)
      ii. Stage of nondisjunction: mostly maternal meiosis I (vs. meiosis II in trisomy 18)
      iii. Paternal origin of the extra chromosome (10%): The majority is primarily postzygotic mitotic errors.
   b. Frequency: 75% of cases
2. Translocation trisomy 13
   a. Mechanism: de novo (75%) or familial transmission (25%)
   b. Frequency: 20% of cases
   c. Trisomy 13 due to t(13;13): The structural abnormalities are usually isochromosomes originating in mitosis.
3. Mosaic trisomy 13
   a. Mechanism: due to postzygotic (postfertilization) mitotic nondisjunction
   b. Frequency: 5% of cases
   c. Variable phenotype from full trisomy to near normal
   d. Variable mental retardation with longer survival
   e. Trisomy 13/triploidy mosaicism: a rare event
4. Partial trisomy 13
   a. Partial trisomy of proximal segment with nonspecific clinical features and little similarity to full trisomy 13
   b. Partial trisomy of distal segment with specific clinical features

Clinical Features

1. General
   a. Low birth weight
   b. Thrombocytopenia
2. CNS
   a. Severe mental retardation
   b. Holoprosencephaly
   c. Seizures
   d. Central apnea
3. Craniofacial abnormalities
   a. Microcephaly
   b. Wide sagittal sutures
   c. Wide fontanels
   d. Scalp defect (aplasia cutis congenita, 50%)
   e. Capillary hemangioma of the forehead
   f. Ocular abnormalities
      i. Microphthalmia/anophthalmia
      ii. Colobomas
      iii. Retinal dysplasia
   g. Cleft lip/palate
   h. Abnormal auricles
   i. Low-set ears
   j. Sensorineural and conductive deafness

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k. Recurrent otitis media
l. Abundant nuchal skin folds
4. Cardiovascular abnormalities
a. Ventricular septal defect
b. Atrial septal defect
c. Patent ductus
d. Coarctation of the aorta
e. Dextrocardia
5. Gastrointestinal abnormalities
a. Omphalocele
b. Malrotation
c. Umbilical hernia
d. Inguinal hernia
e. Accessory spleen
f. Heterotopic pancreatic tissue
g. Meckel's diverticulum
h. Diaphragmatic defects
i. Large gallbladder
6. Genitourinary abnormalities
a. Polycystic kidneys
b. Cryptorchidism
c. Hypospadias
d. Bicornuate uteri
e. Abnormal fallopian tubes
f. Hypoplastic ovaries
7. Skeletal abnormalities
a. Polydactyly
b. Posterior prominence of heel
c. Flexed fingers
d. Hypoplasia of pelvis
e. Shallow acetabulum
f. Thin posterior ribs
g. Flexion deformity of large joints
h. Limb deficiency (5.3%)
i. Radial aplasia
j. Hyperconvex narrow fingernails
8. Dermatoglyphics
a. Transverse palmar crease
b. t′
c. Hallucal arch fibular or loop tibial
9. Others
a. Thymic cyst
b. Persistence of fetal hemoglobin
10. Prognosis
a. Majority of trisomy 13 conceptuses
i. Abort during pregnancy
ii. Stillborn
b. Twenty-five percent die by 24 h of life
c. Forty-five percent die by 1 month of life
d. Sixty percent die by 6 months of life
e. Seventy-two die by 1 year of age
f. Usual mode of death: primary apnea
g. Survivals up to 11 and 19 years old reported
11. Mosaic trisomy 13
a. The phenotype ranges
i. Typical features of trisomy 13
ii. More mild mental retardation or even normal intellectual function (rare), milder physical features, and longer survival
b. The range in clinical severity is likely due to the varying proportion of trisomy 13 cells and their distribution within the body.
12. Partial trisomy 13 of the proximal segment
a. Severe mental retardation
b. Large nose
c. Short upper lip
d. Receding mandible
e. Clinodactyly of the fifth fingers
13. Partial trisomy 13 of the distal segment
a. Severe mental retardation
b. Bushy eyebrows (synophrys) with long incurved lashes
c. Frontal capillary hemangioma
d. Long philtrum
e. Prominent antihelix

Diagnostic Investigations

1. Cytogenetic studies
a. Conventional technique
b. FISH of interphase cells for rapid diagnosis
c. Parental karyotyping in case of translocation trisomy 13
d. Trisomy 13 mosaicism
2. Echocardiography for cardiovascular anomalies
3. EEG: hypsarrhythmia
4. CT/MRI for central nervous system anomalies
5. Radiography
a. Wide anterior fontanel
b. Presence of a cervical rib
c. Absence of the 12th rib
d. Anomalies of rib morphology
e. Low acetabular angle
f. Long distal phalanges
g. Cranial bone abnormalities in case of holoprosencephaly
h. Clefting of the vertebral bodies

i. Abnormal postsphenoid component of the sphenoid bone
j. Agenesis of the nasal bones

6. Placenta: Partial molar change of the placenta may rarely occur in trisomy 13 (Has et al. 2002).

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Trisomy 13: about 1 in 4,000
      ii. De novo translocation: about 1 in 4,000
      iii. Familial translocation: 5–15%
      iv. Mosaicism: 1 in 4,000
   b. Patient's offspring: not surviving to reproductive age
2. Prenatal diagnosis
   a. Prenatal ultrasonography: prevalence of ultrasound abnormalities (91%)
      i. General
         a) IUGR (48%)
         b) Single umbilical artery
         c) Polyhydramnios (15%)
         d) Oligohydramnios (12%)
      ii. Cranium and CNS abnormalities (58%)
         a) Holoprosencephaly (39%)
         b) Neural tube defects
         c) Lateral ventricular dilatation without holoprosencephaly (9%)
         d) Enlarged cisterna magna or Dandy-Walker variant (15%)
         e) Microcephaly (12%)
         f) Linear branching echogenicity of the thalamus or basal ganglia (representing vasculopathy)
         g) Choroid plexus cyst
      iii. Facial anomalies
         a) Cyclopia
         b) Proboscis
         c) Hypotelorism
         d) Hypoplastic midface
         e) Cleft lip/palate (36%)
         f) Micrognathia
      iv. Neck anomalies
         a) Nuchal thickening
         b) Cystic hygroma
         c) Hydrops
         d) Lymphangiectasia
      v. Chest/cardiac abnormalities
         a) Diaphragmatic hernia
         b) Ventricular septal defect
         c) Hypoplastic left heart
         d) Echogenic chorda tendineae (30%)
      vi. Renal abnormalities (33%)
         a) Echogenic kidneys
         b) Pyelectasis
         c) Enlarged kidneys
         d) Hydronephrosis
      vii. Abdominal abnormalities
         a) Omphalocele
         b) Echogenic bowel (6%)
         c) Bladder exstrophy
      viii. Limb abnormalities (33%)
         a) Clenched and overlapping digits
         b) Polydactyly
         c) Radial aplasia
         d) Short femur length
         e) Talipes equinovarus
         f) Rocker bottom feet
   b. Chromosome analyses
      i. Amniocentesis
      ii. CVS, followed by amniocentesis
      iii. Fetal cells isolated from maternal blood using either flow sorting or magnetic sorting
   c. Dilemma for genetic counseling with trisomy 13 mosaicism
      i. Infrequent occurrence
      ii. Single-cell pseudomosaicism (3.3%)
      iii. Multiple-cell pseudomosaicism (4%)
      iv. Often represents pseudomosaicism or confined placental mosaicism
      v. True fetal mosaicism (in the context of low-level single-digit percentage mosaicism): not necessarily associated with congenital defects and/or mental abnormalities
      vi. An optimistic approach in case of normal ultrasonography and absence of trisomy 13 cells in the fetal blood
      vii. Possibility of adverse phenotype and intellectual function in case of true low-level fetal mosaicism
3. Management
   a. Feedings
      i. Nasal tube feeding
      ii. Oral gastric tube feeding
      iii. Gastrostomy feeding

b. Nissan fundoplication for gastroesophageal reflux
c. Risk for anesthesia
d. Early intervention programs
e. Seizure control
f. Monitor apneic spells
g. Treat infections
h. Symptomatic treatment for heart failure
i. Cardiac operation rarely performed

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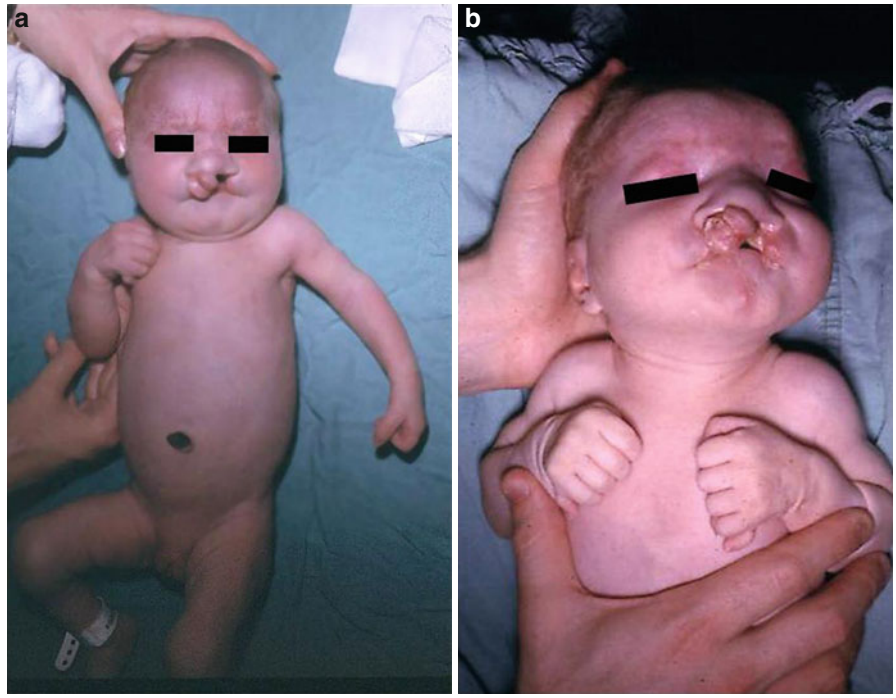


Fig. 1 (**a**, **b**) An infant with trisomy 13 showing microcephaly, microphthalmia, forehead hemangioma, cleft lip/palate, and postaxial polydactyly

Fig. 2 (**a**, **b**) An infant with trisomy 13 showing microcephaly, microphthalmia, cleft lip/palate, and omphalocele

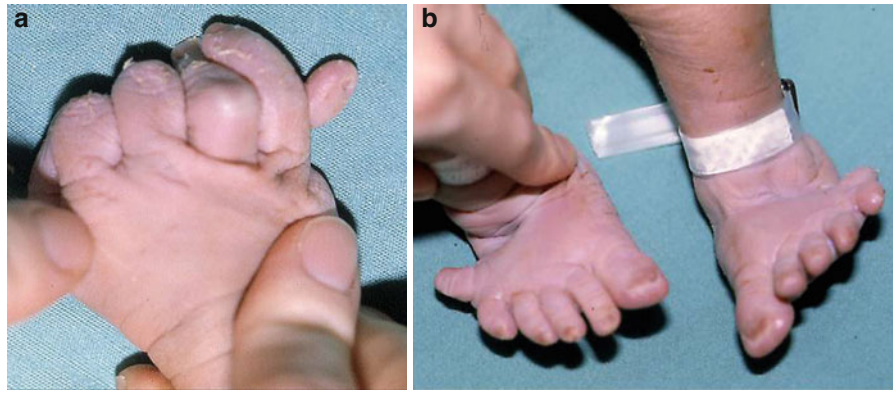


Fig. 3 (**a**, **b**) Postaxial polydactyly of the hand and the feet in an infant with trisomy 13

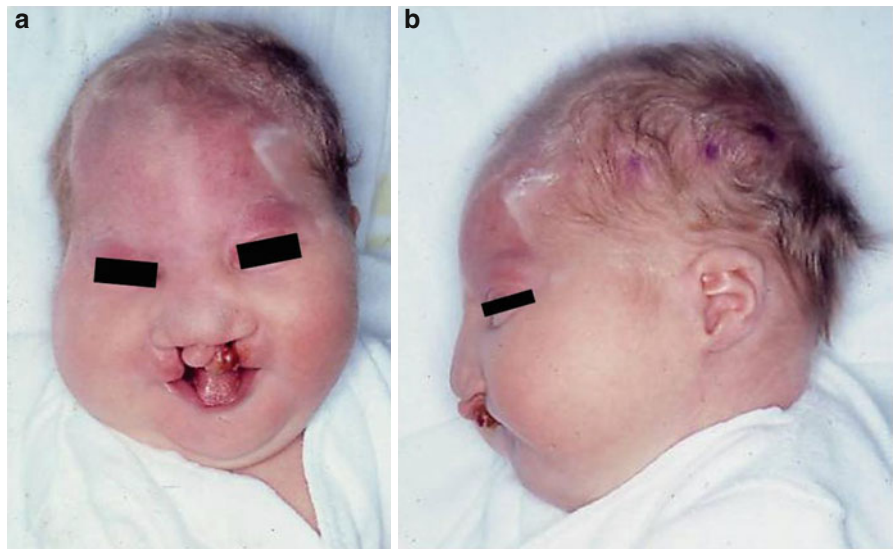


Fig. 4 (**a**, **b**) An infant with trisomy 13 showing microcephaly, forehead hemangioma, upslanted palpebral fissures, cleft lip/palate, and short neck

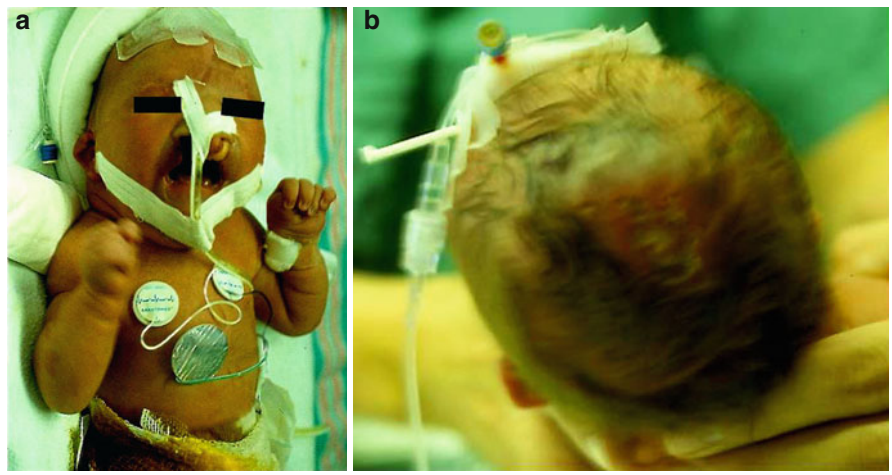


Fig. 5 (**a**, **b**) An infant with trisomy 13 showing scalp defect on the vertex

Fig. 6 Another infant with trisomy 13 showing microphthalmia and cleft lip/palate

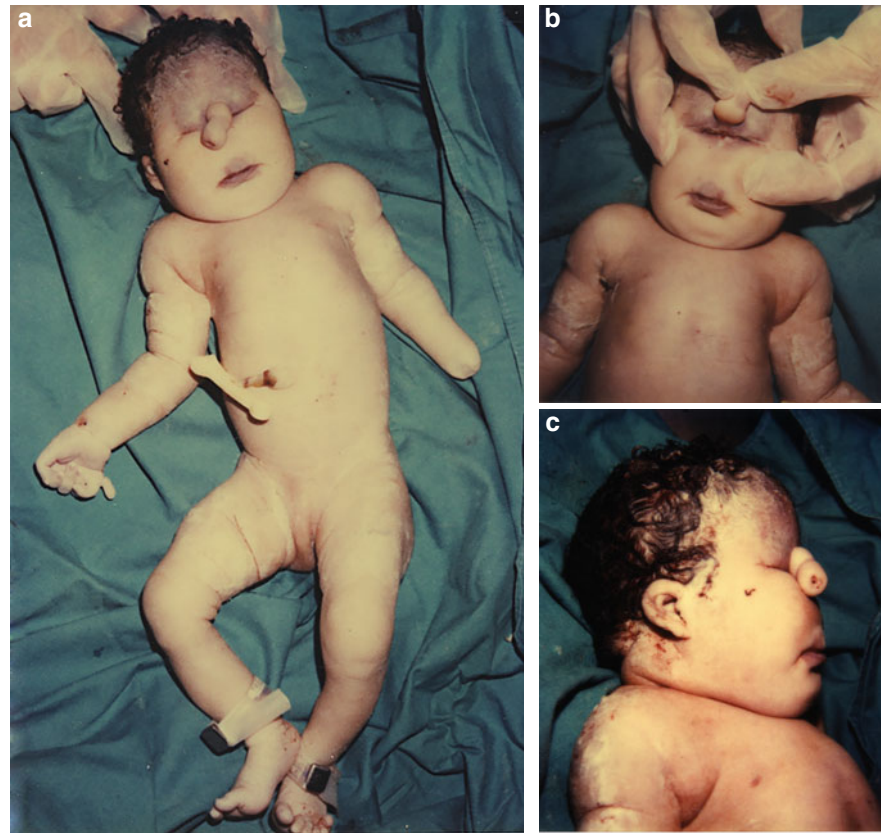
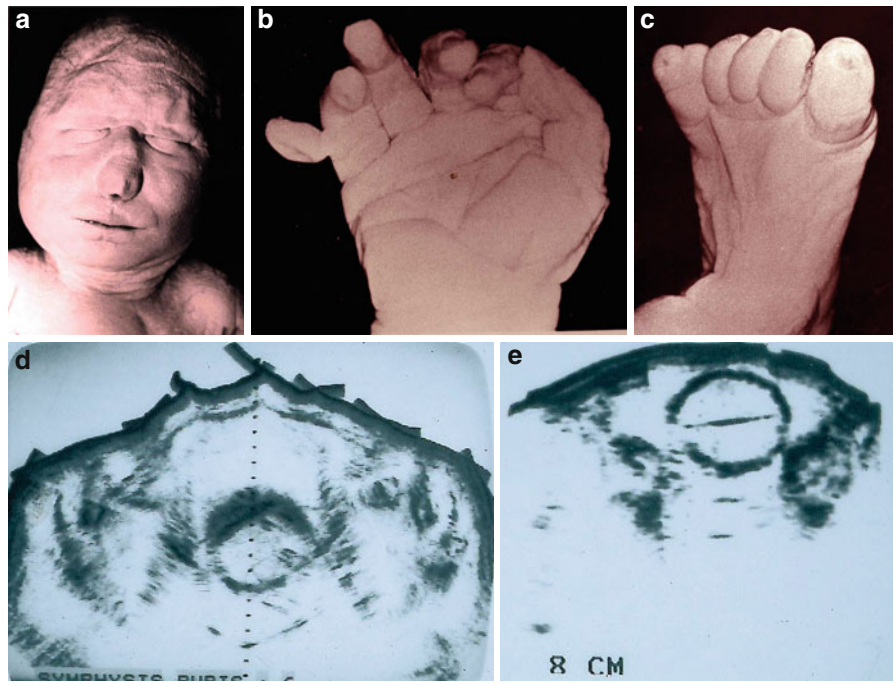


Fig. 7 (**a**–**c**) A neonate with trisomy 13 showing ethmocephaly, transverse reduction of the left forearm, and polydactyly of the right hand and both feet

Fig. 8 A child with trisomy 13 associated with premaxillary dysgenesis, hypotelorism, cleft nose, and smooth philtrum

Fig. 9 An infant with trisomy 13-Klinefelter syndrome showing hypotelorism and a single nostril (holoprosencephaly)

Fig. 10 (**a**–**e**) A neonate with trisomy 13 showing similar facial features. In addition, the infant has polydactyly. Prenatal ultrasound examination showed microcephaly, scalp edema, and holoprosencephaly (a normal ultrasound at the same gestation is given here)



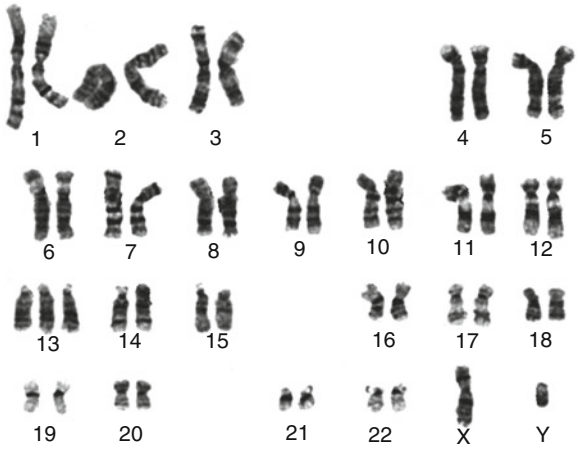


Fig. 11 Trisomy 13 karyotype (G-banded)

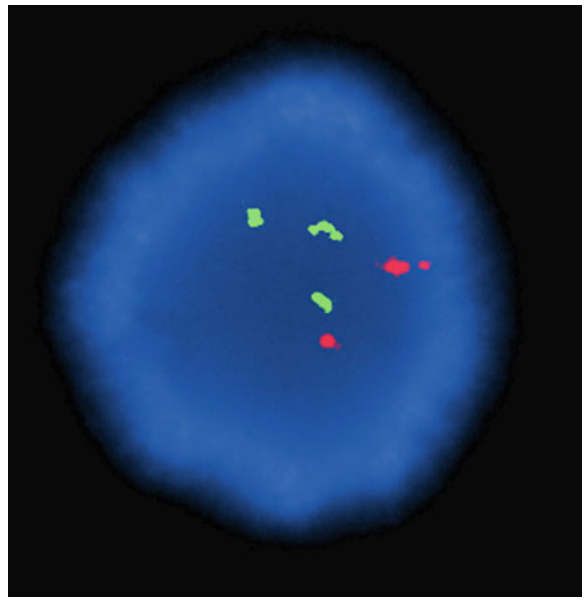


Fig. 13 Trisomy 13 shown by FISH analysis of interphase cells with three copies of the green signal (LSI 13/SpectrumGreen) representing three chromosome 13s and two copies of the red signal representing two chromosome 21s (LSI 21/SpectrumOrange)

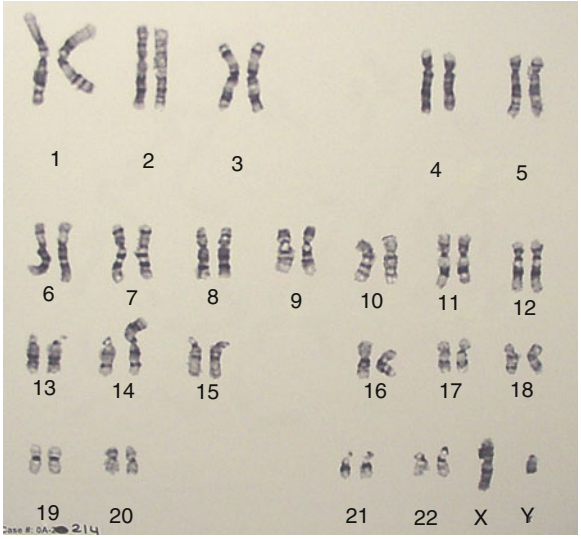


Fig. 12 Translocation of trisomy 13 karyotype [t(13q;14q)]

Trisomy 18 Syndrome

Edwards et al. and Smith et al. independently described trisomy 18 syndrome in 1960 (Edwards et al. 1960; Smith et al. 1960). It is the second most common autosomal trisomy after trisomy 21. Prevalence is approximately 1 in 6,000–8,000 live births.

Synonyms and Related Disorders

Edwards syndrome

Genetics/Basic Defects

1. Caused by an extra chromosome 18 resulting from nondisjunction in meiosis
   a. Maternal origin of an extra chromosome 18 in 90% of cases
   b. An error in maternal meiosis II is the most frequent cause of nondisjunction for chromosome 18, unlike all other human trisomies that have been studied, which show a higher frequency in maternal meiosis I.
   c. Increased incidence with advanced maternal age
2. Types of trisomy 18
   a. Full trisomy 18 in 95% of cases
   b. Rare mosaicism and translocation cases: translocation trisomy giving rise to partial trisomy 18 syndrome
3. Preponderance of females with trisomy 18 in live-borns (sex ratio 0.63) (sex ratio defined as the number of males divided by the number of females) compared to fetuses diagnosed prenatally (sex ratio 0.90) indicating a prenatal selection against trisomy 18 males after the time of amniocentesis (Nicolaidis and Petersen 1998)
4. The smallest extra region necessary for expression of serious anomalies of trisomy 18: Two critical regions, one proximal (18q12-q21.2) and one distal (18q22.3-qter), which work jointly to produce the typical trisomy 18 phenotype.

Clinical Features

1. Prenatal history (Chen 2011)
   a. Maternal polyhydramnios possibly related to defective fetal sucking and swallowing reflexes in utero
   b. Oligohydramnios secondary to renal defects
   c. Disproportionately small placenta
   d. Single umbilical artery
   e. Intrauterine growth retardation
   f. Weak fetal activity
   g. Fetal distress
2. Clinical history
   a. Apneic episodes
   b. Poor feeding
   c. Marked failure to thrive
3. Physical growth: profound growth retardation
4. Central nervous system (CNS)
   a. Inevitable profound delay in psychomotor development and mental retardation (100%)
   b. Neonatal hypotonia followed by hypertonia
   c. Jitteriness
   d. Apnea

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e. Seizures
f. Malformations
    i. Microcephaly
    ii. Cerebellar hypoplasia
    iii. Meningoencephalocele
    iv. Meningomyelocele
    v. Anencephaly
    vi. Hydrocephaly
    vii. Holoprosencephaly
    viii. Arnold-Chiari malformation
    ix. Hypoplasia or aplasia of the corpus callosum
    x. Defective falx cerebri
    xi. Frontal lobe defect
    xii. Abnormal gyri
    xiii. Migration defect
    xiv. Arachnoid cyst

5. Cranial
    a. Microcephaly
    b. Elongated skull
    c. Narrow bifrontal diameter
    d. Wide fontanels and cranial sutures
    e. Prominent occiput
6. Facial
    a. Microphthalmia
    b. Ocular hypertelorism
    c. Epicanthal folds
    d. Short palpebral fissures
    e. Iris coloboma
    f. Cataracts
    g. Corneal clouding
    h. Abnormal retinal pigmentation
    i. Short nose with upturned nares
    j. Choanal atresia
    k. Micrognathia/retrognathia
    l. Microstomia
    m. Narrow palatal arch
    n. Infrequent cleft lip and cleft palate
    o. Preauricular tags
    p. Low-set, malformed ears (faun-like with flat pinnae and a pointed upper helix)
7. Skeletal
    a. Severe growth retardation
    b. Characteristic hand posture, with clenched hands with the index finger overriding the middle finger, and the fifth finger overriding the fourth finger
    c. Camptodactyly
    d. Radial hypoplasia or aplasia
    e. Thumb aplasia
    f. Syndactyly of the second and third digits
    g. Arthrogryposis
    h. Rocker-bottom feet with prominent calcanei
    i. Talipes equinovarus
    j. Hypoplastic nails
    k. Dorsiflexed great toes
    l. Short neck with excessive skin folds
    m. Short sternum
    n. Narrow pelvis
    o. Limited hip abduction
    p. Severe kyphoscoliosis and tendency to spontaneous fracture of long bones emerging later
8. Cardiac malformations in more than 90% of infants with trisomy 18
    a. Ventricular septal defects
        i. Present in about two-thirds of cases
        ii. Large defect unlikely to undergo spontaneous closure
    b. Polyvalvular heart disease pulmonary and aortic valve defects)
    c. Double outlet right ventricle
    d. Atrial septal defects
    e. Patent ductus arteriosus
    f. Overriding aorta
    g. Coarctation of aorta
    h. Hypoplastic left heart syndrome
    i. Tetralogy of Fallot
    j. Transposition of great arteries
    k. Endocardial fibroelastosis
    l. Persistent left superior vena cava
    m. Absent right superior vena cava
    n. Dextrocardia
9. Pulmonary
    a. Pulmonary hypoplasia
    b. Abnormal lobation of the lung
10. Gastrointestinal
    a. Omphalocele
    b. Malrotation of the intestine
    c. Ileal atresia
    d. Common mesentery
    e. Meckel diverticulum
    f. Esophageal atresia with or without tracheoesophageal fistula
    g. Diaphragmatic eventration
    h. Prune belly anomaly
    i. Diastasis recti
    j. Abnormal lobulation of the liver

k. Absent or hypoplasia of gallbladder
l. Absent appendix
m. Accessory spleens
n. Exstrophy of cloaca
o. Pyloric stenosis
p. Common mesentery
q. Megacolon
r. Imperforate or malpositioned anus
s. Pilonidal sinus
t. Umbilical, inguinal, or diaphragmatic hernias

11. Genitourinary
    a. Micromulticystic kidneys
    b. Double ureters
    c. megaloureters
    d. Hydroureters
    e. Hydronephrosis
    f. Horseshoe kidneys
    g. Ectopic kidney
    h. Unilateral renal agenesis
    i. Cryptorchidism, hypospadias, and micropenis in males
    j. Hypoplasia of labia and ovaries, bifid uterus, hypoplastic ovaries, and clitoral hypertrophy in females
12. Endocrine
    a. Thymic hypoplasia
    b. Thyroid hypoplasia
    c. Adrenal hypoplasia
13. Dermatoglyphics
    a. Increased number of simple arches (6 or more) on the finger tips
    b. Transverse palmar crease
    c. Increased atd angle
    d. Clinodactyly of the fifth fingers with a single flexion crease
14. Prognosis
    a. Approximately 95–97.5% of conceptuses with trisomy 18 die in embryonic or fetal life.
    b. Only 30% of live fetuses at midtrimester amniocentesis surviving to term
    c. Five to ten percent of affected children survive beyond the first year.
    d. Rare reports of long survival into 20s
    e. High mortality rate secondary to cardiac and renal malformations, feeding difficulties, sepsis, and central apnea caused by CNS defects
    f. Severe psychomotor and growth retardation invariably present for those who survive beyond infancy.
    g. Milder nonspecific phenotype in mosaic trisomy 18 correlates with the proportion of normal cells in the body

Diagnostic Investigations

1. Conventional cytogenetic study to detect full trisomy, mosaic trisomy, or rare translocation type trisomy 18
2. Echocardiography for cardiac anomalies
3. Barium swallow for gastrointestinal anomalies
4. Ultrasound for genitourinary anomalies
5. Skeletal radiography
    a. Phocomelia
    b. Absent radius
    c. Tight flexion of the fingers with second over the third and the fifth over the fourth
    d. Talipes equinovarus
    e. Short sternum
    f. Hemivertebrae
    g. Fused vertebrae
    h. Short neck
    i. Scoliosis
    j. Rib anomaly
    k. Dislocated hips
6. Histopathological study of temporal bone (auditory organ) (Tadaki et al. 2003)
    a. External ear: arctation or atresia of external acoustic meatus (38%)
    b. Middle ear
        i. Anomalies of auditory ossicles (61%)
            a) Incus or malleus
            b) Stapes
        ii. Absence or aberration of tensor tympani muscle or its tendon (31%)
        iii. Complete absence or hypoplasia of stapedial muscle or its tendon (28%)
    c. Inner ear
        i. Hypoplasia of the ductus semicirculares (37%)
        ii. Shortened cochlea (22%)
        iii. Anomalies of stria vascularis (22%)
        iv. Absence or hypoplasia of lymphatic valve in utricle (21%)
        v. Enlargement of canaliculus cochleae (11%)
    d. Facial nerve: geniculate ganglion cells displaced into the internal auditory meatus (53%)

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. De novo full trisomy 18: 1% or less
      ii. Low-grade parental mosaicism has been reported in two occasions in sporadic cases of trisomy 18.
      iii. A parent being a balanced carrier of a structural rearrangement: increased recurrence risk pending on the type of structural rearrangement and the pattern of segregation
   b. Patient's offspring: unlikely to survive to reproduction
2. Prenatal diagnosis
   a. Prenatal screening in families without history of trisomy 18 using maternal serum markers
      i. Low human chorionic gonadotropin hCG) and low unconjugated estriol (uE3) in maternal serum during midtrimester: useful predictors for an increased risk for trisomy 18
      ii. Possible future first-trimester biochemical screening for trisomy 18: reduced levels of pregnancy-associated plasma protein A (PAPP-A) and free beta–human chorionic gonadotropin (beta-hCG) at 8–13 weeks gestation. The mean MOM in affected pregnancies was 0.25 for PAPP-A and 0.34 for free beta-hCG.
      iii. Screening for trisomy 18 using a combination of maternal age, PAPP-A, and beta-hCG: reported to achieve a detection rate of 76.6% with a false-positive rate of 0.5% (Biagiotti et al. 1998)
   b. Prenatal ultrasonography: The majority of fetuses with trisomy 18 have detectable structural abnormalities.
      i. First-trimester sonographic findings (Sepulveda et al. 2010)
         a) Nuchal translucency (77–91%)
         b) Absent/hypoplastic nasal bone (53%)
         c) Generalized subcutaneous edema (49%)
         d) Omphalocele (21%)
         e) Abnormal posturing of hands (6%)
         f) Megacystis (4%)
         g) Cardiac defect (4%)
         h) Pleural effusions (4%)
         i) Echogenic yolk sac (4%)
      ii. Oligohydramnios/polyhydramnios (12%)
      iii. Intrauterine growth retardation (29%)
      iv. Two-vessel umbilical cord (40%)
      v. CNS
         a) Abnormally shaped fetal head (strawberry or lemon) (43%)
         b) Microcephaly
         c) Dandy-Walker malformation (posterior fossa enlargement associated with cerebellar hypoplasia)
         d) Enlarged cisterna magna
         e) Choroid plexus cysts (43%)
         f) Neural tube defects (9%)
      vi. Micrognathia
      vii. Thickened nuchal skin fold
      viii. Cystic hygroma or lymphangiectasia (14%)
      ix. Omphalocele (20%)
      x. Esophageal atresia
      xi. Cardiac defects (37%): septal defects with polyvalvular disease
      xii. Renal anomalies (9%)
         a) Polycystic kidneys
         b) Horseshoe and ectopic kidneys
      xiii. Limb abnormalities
         a) Clenched hands with overlapping index finger (89%)
         b) Forehand and hand abnormalities such as a short radial ray
         c) Rocker-bottom feet
         d) Club feet
   c. 3D/4DUS offers diagnostic advantages for most anomalies associated with trisomy 18, especially anomalies of the extremities and face (Zheng et al. 2008).
   d. Amniocentesis or CVS by conventional cytogenetic or FISH techniques
      i. Straight trisomy 18
      ii. Trisomy 18 mosaicism: 54% risk for an abnormal outcome, including phenotypically abnormal offspring, IUGR, or fetal demise. The risk is increased with increasing percentage of amniotic fluid trisomic cell line.
   e. Culturing fetal hematopoietic stem-progenitor cells from maternal blood during pregnancy: a new strategy holding great promise for noninvasive prenatal genetic diagnosis
3. Management
   a. Genetic counseling in prenatally diagnosed trisomy 18

i. Traumatic experience in the lives of all couples having a fetus with trisomy 18
ii. Emotional upheaval persisting for variable time periods after the diagnoses and the decisions concerning the pregnancy outcomes

b. Medical care of trisomy 18 infants
   i. Supportive
   ii. Treat infections
      a) Otitis media
      b) Upper respiratory infections (bronchitis, pneumonia)
      c) Urinary tract infections
   iii. Nasogastric and gastrostomy supplementation for feeding problems
   iv. Orthopedic management of scoliosis secondary to hemivertebrae
   v. Primarily medical management of congenital heart disease
   vi. Diuretic and digoxin for congestive heart failure
   vii. Referral for early intervention including physical and occupational therapy
   viii. Psychosocial management: Discuss implications, possible outcomes, and available supportive services in the community.
   ix. Severe developmental delay exhibited by long-term survivors presenting the greatest challenge to parental coping during the childhood years
   x. Informed and empathetic care to families undergoing a complex grieving process that combines both the reactive grief predominant in chronic illness and the preparatory grief associated with impending death (Van Dyke and Allen 1990)

c. Surgical care of trisomy 18 infants: Because of the extremely poor prognosis, surgical repair of severe congenital anomalies such as esophageal atresia or congenital heart defects is not likely to improve the survival rate of infants and should be discussed with families.

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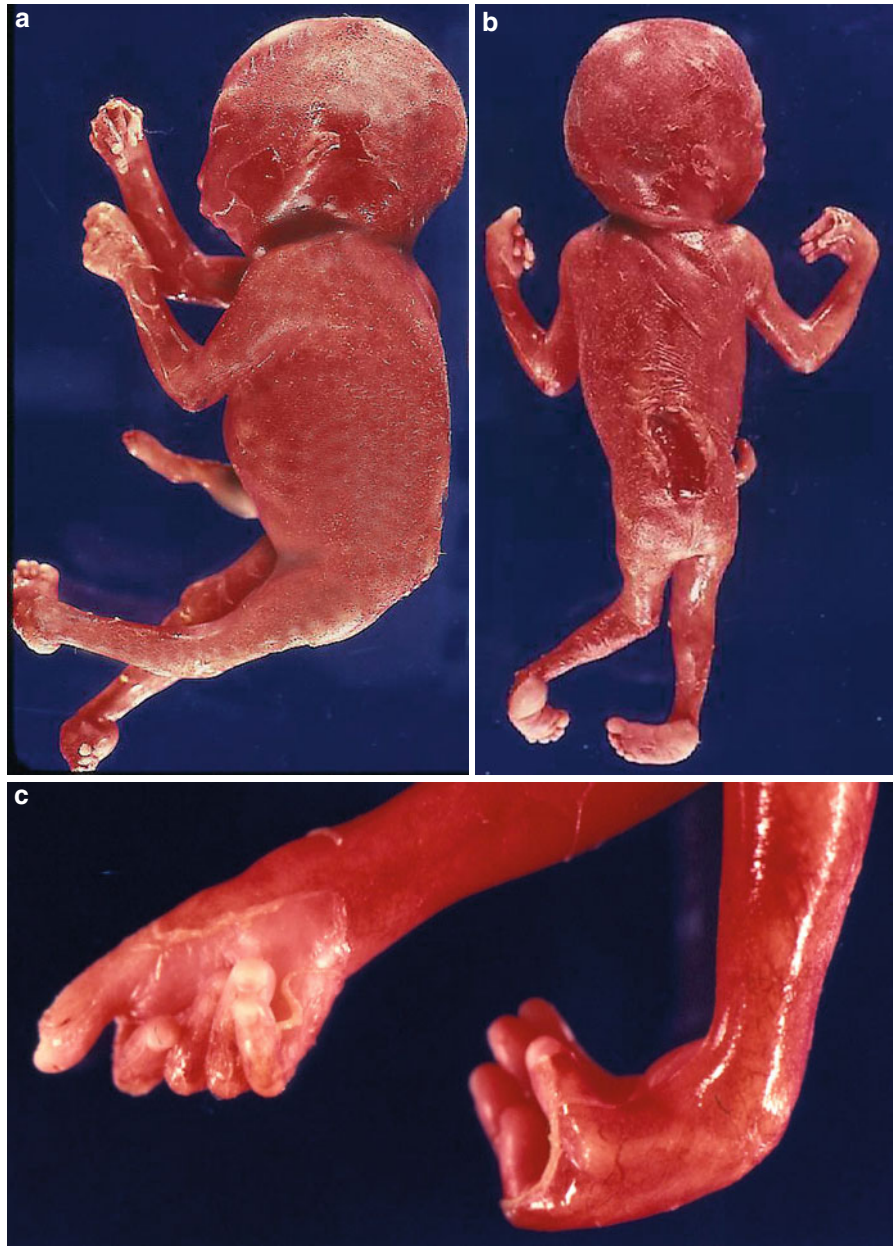

Fig. 1 (**a**–**c**) A fetus with trisomy 18 showing malformed and low-set ears, characteristic finger clenching pattern, spina bifida, hyperextended knee, and talipes equinovarus

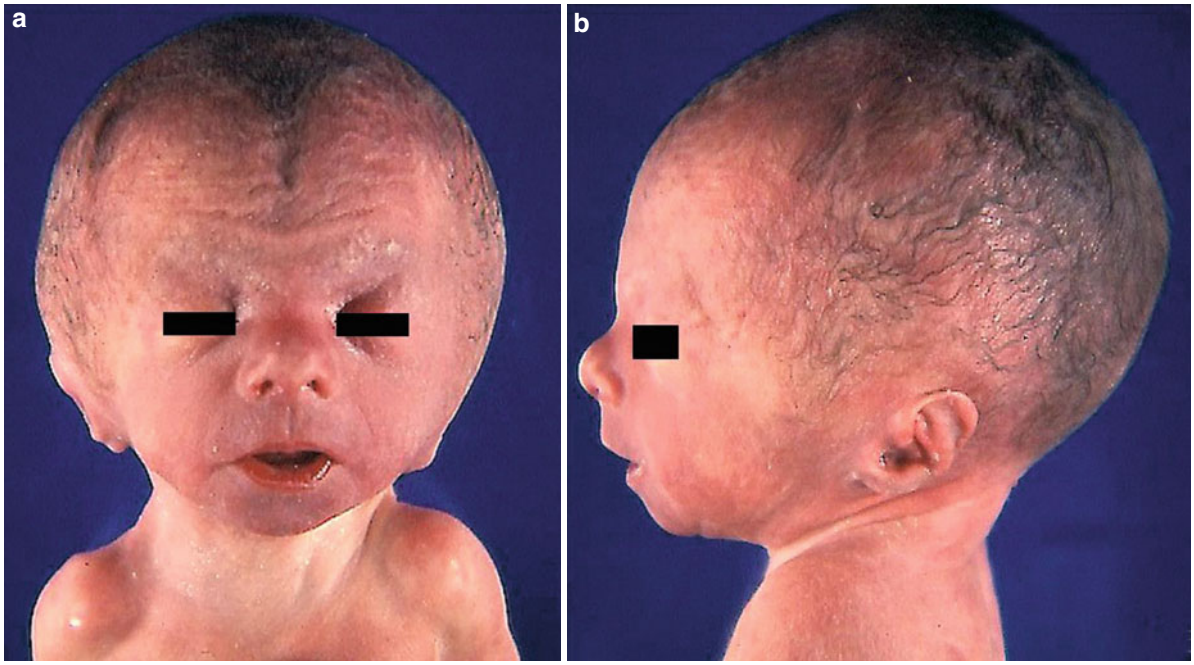

Fig. 2 (**a**, **b**) An infant with trisomy 18 showing small eyes, microstomia, low-set/malformed ears, and short neck

Fig. 3 An infant with trisomy 18 showing micro/retrognathia, short neck, and characteristic finger grasping pattern

Fig. 4 (**a**–**c**) Three infants with trisomy 18 showing reduction malformations of the upper extremities

Fig. 5 (**a**–**d**) Two infants with trisomy 18 showing small eyes, micro/retrognathia, and low-set/malformed ears

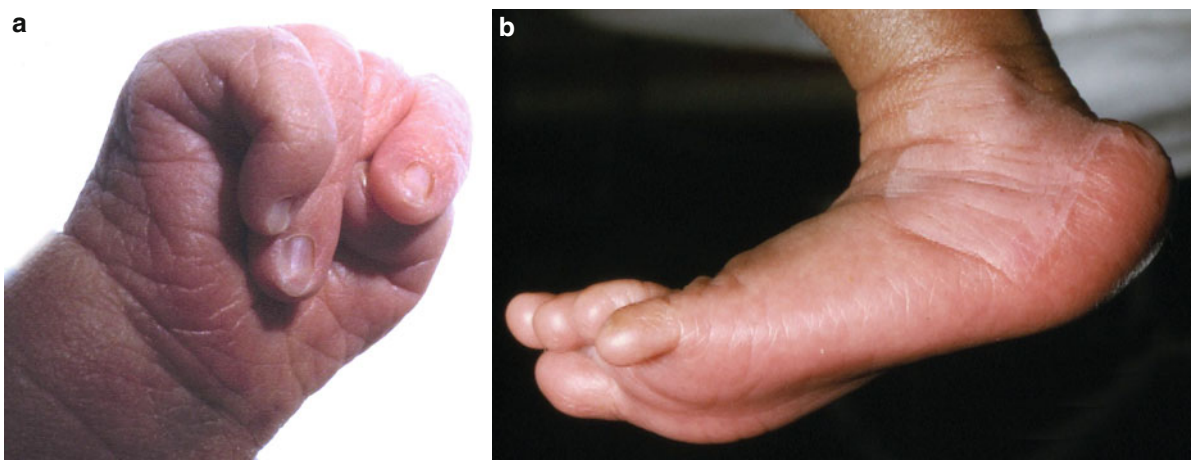

Fig. 6 (**a**, **b**) Typical hand grasping pattern (*left*) and rocker-bottom feet with prominent calcaneus (*right*) observed in trisomy 18

Fig. 7 Trisomy 18 karyotype (47,XY,+18)

Fig. 8 Translocation trisomy 18 karyotype [46,XX,+18,der (13)t(13;18)(q10;q10)]

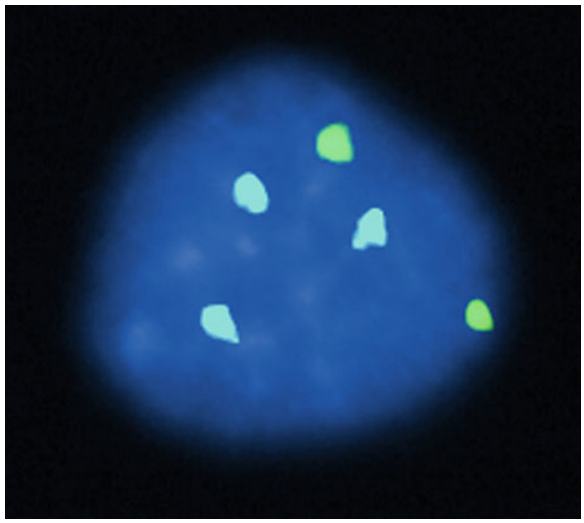

Fig. 9 Trisomy 18 shown by FISH (CEP X/SpectrumGreen, CEP 18/SpectrumAqua, Vysis/Abbott) on an uncultured amniocyte. Three copies of the aqua signal are present in the cells (CEP 18). Two copies of the green signal (CEP X) confirm a female fetus

Tuberous Sclerosis

Tuberous sclerosis is the second most common neurocutaneous syndrome after neurofibromatosis. The term "tuberous sclerosis" derived from the "tubers" (swellings or protuberances) and areas of "sclerosis" (hardening) of the cerebral gyri that calcifies with age. The classic description of the syndrome includes Bogt's triad: mental retardation, seizures, and adenoma sebaceum (a misnomer) or facial angiofibromas. Tuberous sclerosis affects about 1 in 6,000 newborns (Osborne et al. 1991).

Synonyms and Related Disorders

Tuberous sclerosis complex

Genetics/Basic Defects

1. Inheritance
   a. Autosomal dominant
      i. Almost complete penetrance
      ii. Extremely variable in its manifestations and severity
   b. Sporadic (new mutations) in two thirds of cases
2. Caused by mutations in either of the following two tuberous sclerosis complex (*TSC*) genes (Curatolo et al. 2008)
   a. *TSC1*
      i. Located on chromosome 9q34
      ii. Encodes protein, hamartin (TSC1), a protein implicated in regulating cell adhesion via interactions with cortical actin filaments and a plasma membrane binding protein ezrin-radixin-moesin, part of a Rho-mediated signaling pathway
      iii. Approximately 50% of tuberous sclerosis families show linkage to *TSC1*.
      iv. Mutations occurrence: 10–15% of sporadic cases
      v. Most described mutations in the *TSC1* gene result in a truncated protein.
      vi. Phenotype: less severe
   b. *TSC2*
      i. Located on chromosome 16p13.3
      ii. Encodes protein, tuberin (TSC2), a protein implicated in regulating cytoplasmic vesicle transport to the cell membrane
      iii. Approximately 50% of families show linkage to *TSC2*.
      iv. Mutation occurrence: 75–80% of sporadic cases
      v. Many mutations in the *TSC2* gene are large (contiguous) deletions, which may involve the *PKD1* gene, resulting in a severe phenotype called very early onset polycystic kidney disease.
      vi. Phenotype: more severe
3. Both *TSC1* and *TSC2*
   a. Have properties consistent with tumor suppressor genes functioning according to Knudson's "two-hit" hypothesis (Yeung 2003)
   b. The clinical variability occurs secondary to the random nature of the second "hit" in individuals carrying a germ line mutation.

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c. Loss of heterozygosity for *TSC1* or *TSC2* gene
   i. Suggests that 1 mutation is acquired embryonically and another is acquired later on somatically (two-hit hypothesis)
   ii. Observed in 41% of all hamartomas including renal angiomyolipomas, cardiac rhabdomyomas, and subependymal giant cell astrocytomas

4. Hamartin and tuberin
   a. Widely expressed in the brain
   b. May interact as part of a cascade pathway that modulates cellular differentiation, tumor suppression, and intracellular signaling
5. Mosaicism in tuberous sclerosis reported
   a. Somatic mosaicism: The mutation is not found in all cell lines.
   b. Gonadal mosaicism: The mutation found only in gonadal cells and is therefore transmitted to offspring while parents are spared from any disease manifestation.
6. Genotype-phenotype correlations (Dabora et al. 2001)
   a. Overlap of many clinical features exists among the patients with *TSC1* and *TSC2* mutations.
   b. Sporadic patients with TSC1 mutations
      i. On average, milder phenotypic manifestations compared with patients with TSC2 mutations
      ii. Lower frequencies of seizures
      iii. Lower frequencies of moderate to severe mental retardation
      iv. Fewer subependymal nodules and cortical tubers
      v. Less severe kidney involvement
      vi. No retinal hamartomas
      vii. Less severe facial angiofibroma
   c. Some features are rare or not seen at all in *TSC1* patients.
      i. Grade 2–4 kidney cysts or angiomyolipomas
      ii. Forehead plaques
      iii. Retinal hamartomas
      iv. Liver angiomyolipomas
   d. Both germ line and somatic mutations are less common in TSC1 than TSC2.
   e. Patients without mutation
      i. Milder than patients with TSC2 mutations
      ii. Somewhat distinct from patients with TSC1 mutations

Clinical Features

1. Characteristic cutaneous features (virtually 100% of cases) (Schwartz et al. 2007)
   a. Hypomelanotic macules ("ash-leaf spots") (87–100% of cases)
      i. One of the earliest skin lesions (often present at birth)
      ii. Commonly on trunk and buttocks, rarely on the face, and best appreciated by the Wood's fluorescence lamp
      iii. Not specific to tuberous sclerosis because they are seen in unaffected children
      iv. Smaller depigmented spots over the anterior shins: characteristically distributed in a "confetti" fashion (clustered skin lesions with a reticulated appearance)
   b. Shagreen patches (a form of collagenomas) (20–80%)
      i. Elevated discolored skin lesions commonly over lumbosacral region, observed in about 21% of patients
      ii. Age at presentation: birth to adulthood
   c. Facial angiofibromas (47–90%)
      i. One of the most common and specific cutaneous manifestations
      ii. Causing the most disfigurement among the skin lesions
      iii. Red to brown nodules, observed over the nose and cheeks in bilaterally symmetrical butterfly distribution. Rarely segmental tuberous sclerosis may present as unilateral facial angiofibromas.
      iv. Age of presentation
         a) Usually appear after 2 years of age
         b) Increase in size and number of facial angiofibromas with time
         c) Observed in about 80% of adults with tuberous sclerosis
      v. Chance of small and discrete papules of facial angiofibromas to become confluent and fungating lesions
   d. Forehead fibrous plaque (15%)
      i. Large fibromas without angiomatous appearance on the scalp or the forehead areas

ii. Yellowish-brown or skin-colored plaques of variable size and shape usually located on the forehead or scalp
iii. Present at any age and can be seen at birth or early infancy

e. Periungual fibromas (17–87%)
i. Skin-colored or reddish nodules seen on the lateral nail groove, nail plate, or along the proximal mail folds
ii. More commonly found on the toes than on the fingers
iii. Characteristically appear during puberty and persist through life

f. Café au lait spots: seen in 15–30% of patients with tuberous sclerosis

g. "Confetti-like" macules (2.8%)
i. Multiple, 1–2 mm white spots symmetrically distributed over extremities
ii. Present at the second decade or adulthood

h. Molluscum fibrosum pendulum (skin tags) (23%)
i. Multiple soft pedunculated skin growths on neck, rarely in axilla or groin
ii. More common during first decade of life, rarely during infancy

2. CNS abnormalities (the most common manifestations of the disorder)
a. Epilepsy
i. The major neurologic manifestation, affecting 85% of patients
ii. Onset usually at few months of age
iii. Typically with initial classic hypsarrhythmia and infantile spasms, which transform into adult-type partial complex or tonic-clonic seizures
iv. Carries a poor prognosis with cognitive impairment
v. Intractable seizures

b. Presence of cortical "tubers" (O'Callaghan 2008)
i. A pathognomonic sign
ii. Tubers are developmental abnormalities of the cerebral cortex.
iii. The lesions have lost the normal six-layered laminar architecture of the cerebral cortex and contain dysplastic neurones, astrocytes, and characteristic giant cells.
iv. Tubers can be identified in fetal life and persist throughout life.
v. Tubers do not increase in number after birth, although they may become more visible on magnetic resonance imaging as the brain myelinates in the first 2–3 years of life.

c. Subependymal nodules (abnormal neuronal and glial elements): the most common cerebral lesion

d. Cortical or subcortical white matter tubers (70% of cases)
i. Composed of abnormal giant astrocytes
ii. Found in 90% of patients with tuberous sclerosis
iii. Large cortical tubers may occasionally block the foramen of Monro resulting in hydrocephalus.

e. Subependymal giant cell astrocytomas
i. The most common CNS tumors (6–14%)
ii. Subependymal nodules, small hamartoma lining the ventricles, may calcify.
iii. A radiologically confirmed cortical tuber or calcified subependymal nodule are highly suggestive of tuberous sclerosis.
iv. Rare malignant transformation of these astrocytomas, accounting for 25% of deaths in tuberous sclerosis

f. Other abnormalities
i. Cerebral atrophy
ii. Cerebral infarct
iii. Cerebral aneurysm
iv. Arachnoid cyst
v. Chorea (rare manifestation) (Sha et al. 2009)

3. Developmental disorders (>50%)
a. Childhood
i. Learning disabilities
ii. Behavioral problems
iii. Pervasive developmental disorder
iv. Autism more common in childhood
v. Hyperactivity or attention deficit hyperactivity disorder (ADHD)
vi. Aggression

b. Adulthood: mental retardation present in less than 50% of the affected individuals

4. Ocular involvement (at least 50% of the patients)
a. Retinal and optic nerve astrocytic hamartomas (the most frequent manifestations)
b. Retinal phakoma

i. Astrocytomas of the retina
ii. Often called "mulberry lesions"
iii. Absence of the normal "red reflex" in the newborn suggests the presence of retinal phakoma.

c. Visual loss resulting from
i. Macular hamartoma
ii. Vitreous hemorrhage
iii. Papilledema or optic atrophy secondary to intracranial tumors

d. Rare sector hypopigmentation of the iris, vitiligo, or poliosis of the eyelid and eyelashes

5. Dental involvement: important findings
a. Pitting of the dental enamel
i. Invariably present in the permanent teeth
ii. Seen in the primary (deciduous) teeth (30%)
iii. Rarely produce symptoms

b. Gingival angiofibromas (50% of children; 70% of adults)

6. Neoplasms affecting heart, kidneys, lungs, and other organ systems
a. Cardiac rhabdomyomas (Caldemeyer and Mirowsk 2001)
i. The commonest cardiac tumors of childhood and are often associated with TSC
ii. The earliest diagnostic finding in some patients detected on prenatal sonography
iii. Detected by echocardiography, rarely causing problems
iv. Observed in two thirds of affected children. However, more than 80% of children with cardiac rhabdomyomas have tuberous sclerosis.
v. Usually resolve spontaneously or regress with age
vi. A rare cause of prenatal and neonatal cardiac failure, mostly from dysrhythmias
vii. Rare tumor obstruction to cardiac valves or chambers

b. Renal cysts or angiomyolipomas (70–80% of patients)
i. Bilateral multiple renal angiomyolipomas (70%)
a) Diagnostic of tuberous sclerosis
b) Renal angiomyolipomas are benign tumors but contain vascular tissue, which may cause bleeding, hypovolemic shock, and renal failure.
ii. Epithelial cysts (20%)
iii. Polycystic kidney disease (2–3%)
iv. Rare occurrence of renal cell carcinoma (<1%)
v. Malignant angiomyolipoma (<1%)
vi. Benign adenomatous hamartoma (oncocytoma) (<1%)
vii. Lymphangioleiomyomatosis of the renal sinus: rare

c. Pulmonary manifestations (Caldemeyer and Mirowsk 2001)
i. Lymphangio(leio)myomatosis (1–6% of patients)
a) Observed almost exclusively in young female patients, suggesting that a hormonal component is involved in the development of pulmonary sequelae (Lendvay and Marshall 2003)
b) Affects between 26% and 39% of women with TSC
c) Progressive, diffuse interstitial disease, detected by chest radiographs which show diffuse reticular pattern and multiple cyst lesions in the lungs
d) Often complicated by pneumothorax from rupture of subpleural pulmonary cysts
e) The end-stage disease shows "honeycomb" lungs.
f) No effective treatment that reverse the progression of the lung disease (one of the causes of early mortality in TSC patients (Hancock and Osborne 2002))
ii. Multifocal micronodular pneumocyte hyperplasia
a) Affects men and women
b) May accompany lymphangioleiomyomatosis

d. Hamartomas and polyposis of the stomach, intestine, and colon
i. Almost never cause significant symptoms
ii. Occasional GI bleeding leading to positive tests for fecal occult blood

e. Hepatic cysts and angiomyolipomas (up to 24%)
i. Asymptomatic and nonprogressive
ii. Marked female predominance

f. Vascular lesions (Salerno et al. 2010)
   i. Aneurysms
      a) Aorta
      b) Pulmonary artery
      c) Intracranial arteries (internal carotid, middle cerebral)
      d) Axillary artery
      e) Subclavian artery
      f) Iliofemoral artery
   ii. Stenotic-occlusive disease
      a) Aorta
      b) Common iliac artery
      c) Coronary artery
      d) Moyamoya disease
      e) Renal artery
      f) Mesenteric arteries
g. Arterial aneurysms reported in the brain, aorta, and axillary arteries
h. Musculoskeletal manifestations
   i. Sclerotic and hypertrophic lesions of bone
      a) Mostly an incidental finding
      b) Occasionally palpable and associated with pains
      c) Common locations including calvarium, pelvis, vertebrae, and long bones
   ii. Bone lucencies
      a) Nonspecific hamartomas
      b) Found in the phalanges of the hands and feet
      c) Usually asymptomatic
      d) Involvement in two thirds of patients

7. Pregnancy does not increase the risk of developing renal and pulmonary complications in women with tuberous sclerosis (Mitchell et al. 2003).
8. Diagnostic criteria of tuberous sclerosis complex (first proposed in 1992). The presence of one of the primary diagnostic criteria is considered sufficient to diagnose tuberous sclerosis complex.
   a. Primary features
      i. Facial angiofibromas
      ii. Multiple ungula fibromas (or periungual fibromas in the absence of trauma)
      iii. Cortical tuber (histologically confirmed)
      iv. Subependymal nodule or giant cell astrocytomas (histologically confirmed)
      v. Multiple calcified subependymal nodules protruding into the ventricle (radiographic evidence)
      vi. Multiple retinal astrocytomas (retinal hamartomas)
   b. Secondary features
      i. Affected first-degree relative
      ii. Cardiac rhabdomyoma (histologic or radiographic confirmation)
      iii. Other retinal hamartomas or achromic patch
      iv. Cerebral tubers (radiographic confirmation)
      v. Noncalcified subependymal nodules (radiographic confirmation)
      vi. Shagreen patch
      vii. Forehead plaque
      viii. Pulmonary lymphangiomyomatosis (histologic confirmation) (lymphangioleiomyomatosis)
      ix. Renal angiomyolipoma (radiographic or histologic confirmation)
      x. Renal cysts (histologic confirmation)
   c. Tertiary features
      i. Hypomelanotic macules (three or more ash-leaf spots)
      ii. "Confetti" skin lesions
      iii. Renal cysts (radiographic evidence)
      iv. Randomly distributed enamel pits in deciduous or permanent teeth
      v. Hamartomatous rectal polyps (histologic confirmation)
      vi. Bone cysts (radiographic evidence)
      vii. Pulmonary lymphangiomyomatosis (radiographic evidence)
      viii. Cerebral white-matter "migration tracts" or heterotropias (radiographic evidence)
      ix. Gingival fibromas
      x. Hamartoma of other organs (histologic confirmation)
      xi. Infantile spasms
   d. Diagnostic criteria
      i. Definitive: either 1 primary, 2 secondary, or 1 primary plus 2 tertiary features
      ii. Probable: either 1 secondary plus 1 tertiary or 3 tertiary features
      iii. Suspect: either 1 secondary or 2 tertiary features
9. The Tuberous Sclerosis Consensus Conference: devised the above clinical diagnostic criteria in 1998 (Roach et al. 1998; (Lendvay and Marshall 2003)

a. Major features
   i. Facial angiofibromas or forehead plaque
   ii. Nontraumatic ungual or periungual fibroma
   iii. Hypomelanotic macules (three or more)
   iv. Shagreen patch (connective tissue nevus)
   v. Multiple retinal nodular hamartomas
   vi. Cortical tuber
   vii. Subependymal nodule
   viii. Subependymal giant cell astrocytoma
   ix. Cardiac rhabdomyoma, single or multiple
   x. Lymphangiomyomatosis
   xi. Renal angiomyolipoma
b. Minor features
   i. Multiple, randomly distributed pits in dental enamel
   ii. Hamartomatous rectal polyps
   iii. Bone cysts
   iv. Cerebral white matter radial migration lines
   v. Gingival fibromas
   vi. Nonrenal hamartoma
   vii. Retinal achromic patch
   viii. "Confetti" skin lesions
   ix. Multiple renal cysts
c. Diagnostic criteria
   i. Definitive diagnosis: presence of two major features or one major feature plus two minor features
   ii. Probable diagnosis: presence of one major feature plus one minor feature
   iii. Possible diagnosis: presence of one major feature or two or more minor features

10. Prognosis
    a. The mild form of tuberous sclerosis: live full life without loss of function
    b. The severe form: significant morbidity and mortality from seizures, mental retardation, and associated cardiac, retinal, renal, and pulmonary pathology
    c. Association with sudden death (Byard et al. 2003; Noone et al. 2009)
       i. Cardiac arrhythmia
       ii. Epilepsy
       iii. Intratumoral hemorrhage
       iv. Additional complications
          a) Cardiac outflow obstruction
          b) Obstructive hydrocephalus
          c) Aneurysm rupture
          d) Spontaneous pneumothorax

Diagnostic Investigations

1. Cutaneous evaluation including Wood's lamp
2. Ophthalmologic evaluation for hamartomas
3. Echocardiography to identify rhabdomyomas
4. ECG for cardiac arrhythmias
5. EEG for seizures
6. Radiography of the skull (Caldemeyer and Mirowsk 2001)
   a. Calcification frequently seen in subependymal nodules and giant cell astrocytomas
   b. Less commonly seen in cortical and white matter tubers
   c. Calcification increases with the age of the patient.
7. Plain chest radiographic films: diffuse reticular pattern in lymphangiomyomatosis of the lung
8. Pulmonary CT scan
   a. Diffuse interstitial changes with infiltrates
   b. Cystic changes
9. Body CT (Avila et al. 2010)
   a. The number of sclerotic bone lesions seen at body CT is of value in the diagnosis of TSC and in the differentiation of patients with sporadic lymphangioleiomyomatosis from those with TSC/lymphangioleiomyomatosis.
   b. The CT finding of multiple sclerotic bone lesions might be added to the diagnostic criteria of TSC.
10. Renal ultrasound/CT/MRI
    a. Assess angiomyolipomas
    b. Assess renal cysts
11. Neuroimagings by MRI or CT of the brain
    a. Calcification best detected on computed tomography
    b. Magnetic resonance imaging more sensitive for detecting small subependymal nodules and cortical and white matter tubers, especially when not calcified
       i. Extent and number of cortical tubers
       ii. Subependymal gliomas
       iii. Dilated lateral ventricles
       iv. Hamartomatous foci
       v. Vascular dysplastic lesions such as aneurysms
       vi. Identify subependymal giant cell astrocytomas before occurrence of obstructive hydrocephalus

12. Histologic findings
    a. Angiofibromas
        i. Atrophic sebaceous glands with dermal fibrosis and dilation of some capillaries
        ii. "Glial" appearance of fibrosis due to the large size and stellate shape of the fibroblasts
        iii. Absence of elastic tissue in the angiofibromas
    b. Ungual fibromas
        i. Fibrosis
        ii. Rare capillary dilation
    c. Shagreen patches
        i. Increased dense sclerotic mass of broad collagenous bundles
        ii. Normal collagen bundles sometimes arranged in an interwoven pattern
        iii. Reduced elastic tissue
    d. Hypopigmented ash-leaf macule
        i. Normal melanocytes numbers with decreased pigmentation
        ii. Smaller melanosomes with defective melanization by electron microscopy
13. Molecular testing of the TSC1 and TSC2 genes: clinically available (Northrup and Au 2009)
    a. Complicated by the large size of the two genes, the large number of disease-causing mutations, and the high rate of somatic mosaicism (10–25%) (Sampson et al. 1997; Verhoef et al. 1999)
    b. Sequence analysis
    c. Deletion/duplication analysis: A deletion of the two contiguous genes (*TSC2* and *APKD1*) likely responsible if a child with tuberous sclerosis is found to have polycystic kidney disease

Genetic Counseling

1. Recurrence risk
    a. Patient's sib
        i. One to four percent recurrence risk (in case of unaffected parents) due to germ line mosaicism and nonpenetrance of the disorder
        ii. Fifty percentage if one of the parent is affected
    b. Patient's offspring: 50%
2. Prenatal diagnosis (Milunsky et al. 2009)
    a. Prenatal ultrasonographic detection of cardiac lesions consistent with rhabdomyoma
        i. Fifty percentage risk for tuberous sclerosis in the fetus
        ii. Cardiac rhabdomyomas (Bader et al. 2003)
            a) The most common cardiac tumor diagnosed in utero and in children
            b) Favorable natural history of tumors detected prenatally: Most tumors regress after the third trimester.
            c) In rare cases, there is progression in utero with a fetal demise risk of 4–6%.
    b. Prenatal diagnosis/preimplantation genetic diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.
3. Management
    a. Multidisciplinary team approach
    b. Early intervention programs
    c. Assess intellectual function and educational needs
    d. Psychiatric and behavioral problems (Muzykewicz et al. 2007)
        i. The most common formal diagnoses were anxiety disorders (28%), mood disorders (26%), adjustment disorders (21%), ADHD (21%), and mental disorders not otherwise specified due to general medical condition (42%).
        ii. Citalopram demonstrated efficacy in treating anxiety and depression.
        iii. Risperidone, in treating problematic behaviors
    e. Pharmacologic management of behavioral problems
    f. Treat cardiac failure or cardiac arrhythmias
    g. Anticonvulsants for seizure control
        i. Treatment for infantile spasm is difficult because it is often intractable to conventional antiepileptic drugs.
            a) ACTH among other anticonvulsant therapies with variable benefits
            b) Vigabatrin
        ii. Early control of seizures has a crucial role in preventing subsequent epileptic encephalopathy, and in reducing the cognitive/behavioral consequences of seizures, but does not guarantee for a normal mental outcome in children with TSC (Bombardieri et al. 2010).
    h. Rapamycin and clinical trials (Orlova and Crino 2010)

i. Rapamycin
   a) A macrolide antibiotic that has important regulatory effects on cell growth, proliferation, and inflammation via its inhibitory action on mammalian target of rapamycin
   b) Has been used as an immunomodulatory agent following organ transplantation and has a moderate-risk side effect profile
ii. Both preclinical and clinical trial data suggest that rapamycin may provide a possible therapy for TSC: The benefits may only be realized during active therapy.
   a) Reduction of angiomyolipomas volume
   b) Modest improvement of pulmonary function testing

i. Surgical care
   i. Laser treatment of facial angiofibromas
   ii. Removal of ungual fibromas by laser, diathermy, liquid nitrogen, or dermabrasion
   iii. CSF shunting to relief raised intracranial pressure
   iv. Epilepsy surgery: Unifocal onset seizures and mild to no developmental delay at the time of surgery are predictive of excellent long-term outcome.
      a) Focal cortical resection (tuberectomy)
      b) Lobar or multilobar resection
      c) Corpus callosotomy
   v. Vagus nerve stimulation
   vi. A partial nephrectomy or selective embolization preferable to total nephrectomy for treating angiomyolipomata
   vii. Cystic renal lesions rarely required surgery
   viii. Renal transplantation for end-stage renal insufficiency resulting from replacement of renal parenchyma by angiomyolipomas and growing cysts or from the removal of the kidneys for intractable hemorrhage (Papaioannou et al. 2003)
      a) Offers prolonged survival
      b) Appears to be the treatment of choice in such patients

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Fig. 1 (**a**, **b**) An ash-leaf spot is observed in a child affected with tuberous sclerosis, inherited from his mother who has characteristic facial angiofibromas with symmetrical "butterfly" distribution on the nasolabial folds and cheeks

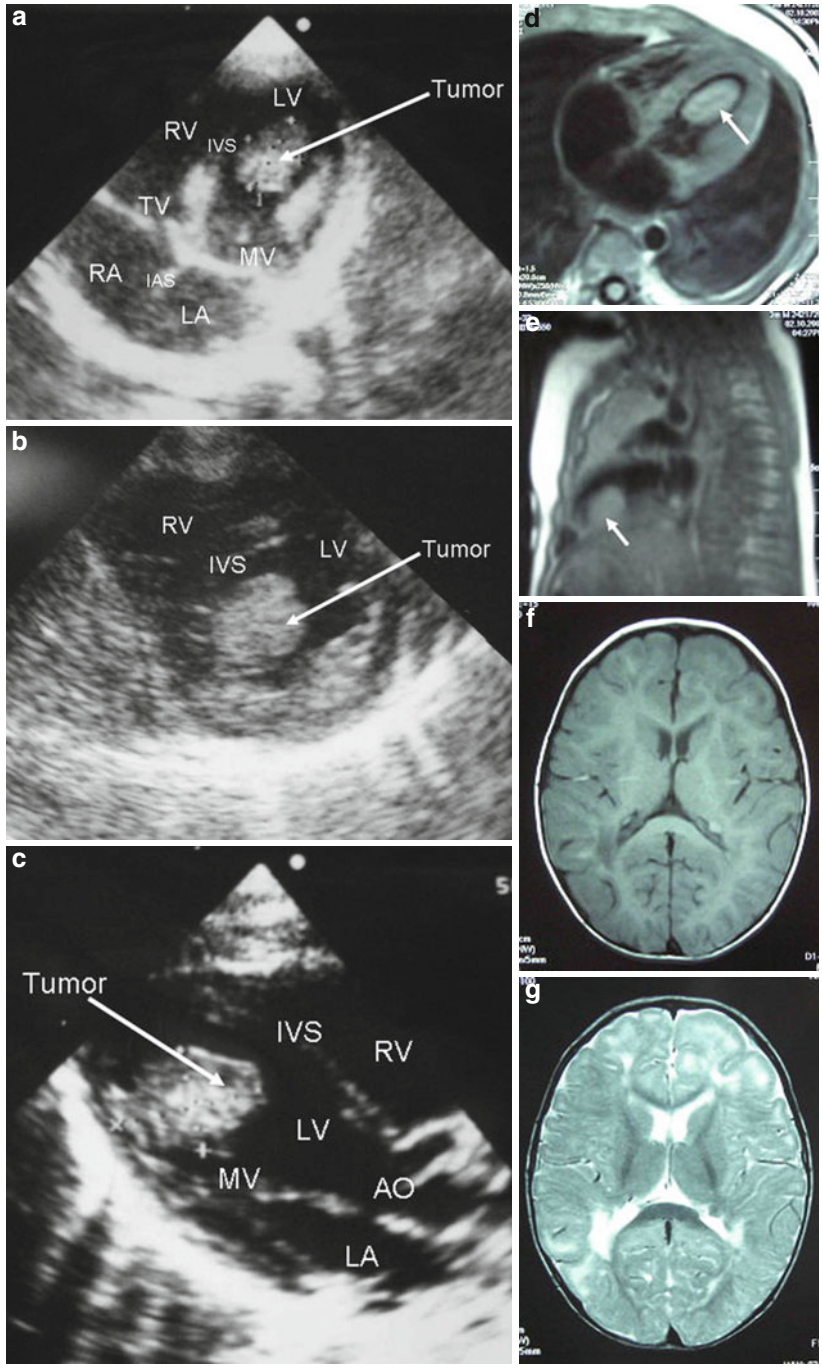

Fig. 2 A 3-month-old infant was found to have small angiofibromatous skin lesions on the cheek, two depigmented spots on the back, and a white round lesion in the left fundus. Echocardiography showed a tumor (measured 2 cm × 1 cm) in the left ventricular cavity (**a**, four chamber view; **b**, short axis view; **c**, long axis view). MRI with T1-enhanced images (**d**, **e**) showed the same rhabdomyoma (*arrow*) in the left ventricular cavity. T1-enhanced (**f**) and T2-enhanced (**g**) images of the brain showed many lesions at subcortical white matter indicated by high or low signals. Some lesions can be seen in the periventricular region. Abbreviations: AO *aorta*, IAS *interatrial septum*, IVS *interventricular septum*, LA *left atrium*, LV *left ventricle*, MV *mitral valve*, RA *right atrium*, RV *right ventricle*, TV *tricuspid valve*

Fig. 3 (**a**, **b**) Severe facial angiofibromas in symmetrical butterfly distribution over nose and cheek with a large forehead plaque. Some angiofibromas have become confluent and fungating lesions

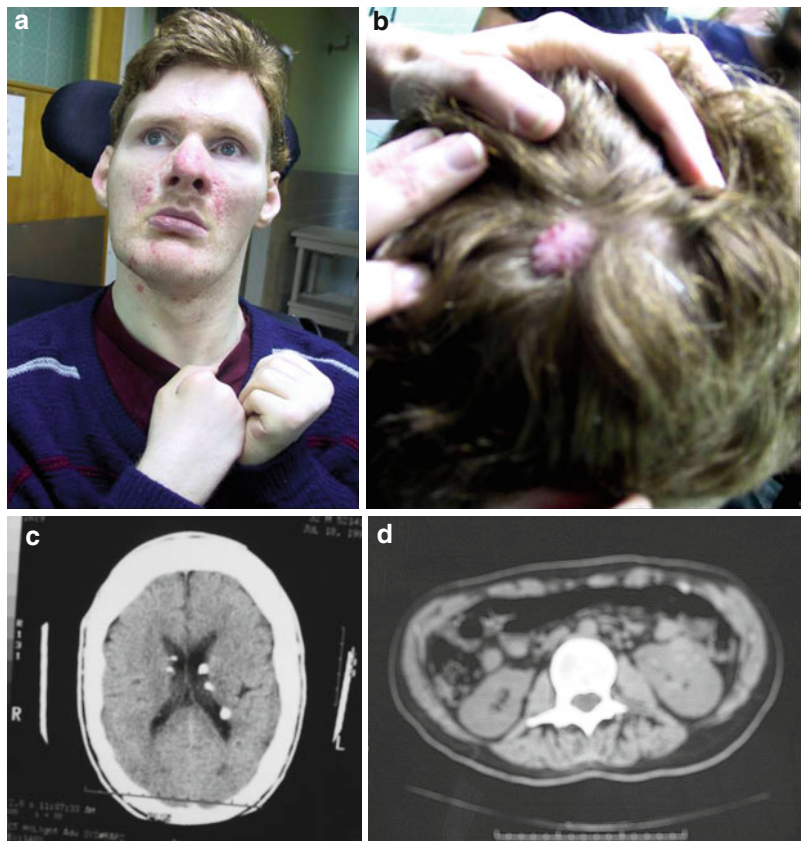

Fig. 4 (**a**–**d**) An adult with tuberous sclerosis showing typical facial angiofibromas and a scalp plaque. CT of the brain showed presence of calcified subependymal nodules. CT scan of the abdomen demonstrates an enlarged left kidney. Histologic examination of the tumor showed renal cell carcinoma

Fig. 5 (**a**, **b**) Two adults with tuberous sclerosis showing typical facial angiofibromas and mental retardation

Fig. 6 (**a**–**c**) An adult with tuberous sclerosis with typical facial angiofibromas and mental retardation. A plain skull X-ray film and a CT of the brain demonstrated intracranial calcifications

Fig. 7 (**a**, **b**) An adult with tuberous sclerosis showing typical facial features. Periungual (*fourth finger*) and ungual (*thumb*) fibromas were present

Fig. 8 (**a**–**c**) An adult with tuberous sclerosis showing typical facial angiofibromas, a scalp plaque, and a large depigmented lesion on the back

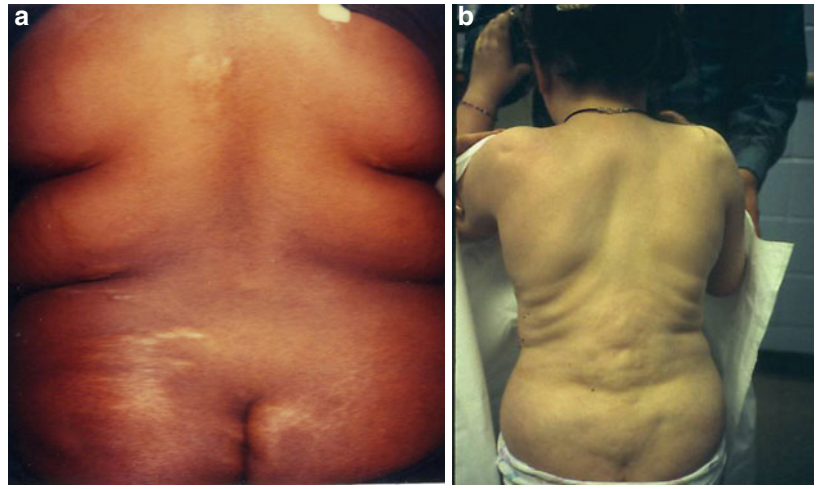

Fig. 9 (**a**, **b**) Shagreen patches are seen in upper back and lower back in two different patients with tuberous sclerosis

Turner Syndrome

In 1938, Turner reported a syndrome of sexual infantilism, short stature, webbed neck, cubitus valgus, and primary amenorrhea in seven female patients. Later in 1954, it was observed that the ovaries were usually replaced by streaks of stroma without follicles; hence, the name gonadal agenesis. Negative sex chromatin was discovered in 1954; only one X chromosome was demonstrated cytogenetically in these patients in 1959.

About 99% of 45,X fetuses abort spontaneously, usually before 28 weeks, and only 1% of these fetuses survive to term. Despite this, Turner syndrome is a relatively common chromosome disorder affecting 1 in 2,500 female live births. About 10% of all spontaneous abortuses have a 45,X karyotype.

Synonyms and Related Disorders

45,X Turner syndrome; 45,X/46,XX mosaic Turner syndrome; 45,X/46,X,r(X) ring chromosome X mosaic Turner syndrome; 46,X,i(X)(q10) isochromosome Xq syndrome

Genetics/Basic Defects

1. Caused by complete or partial X chromosome monosomy in all or some of the body cells
2. Short stature and skeletal manifestations (short fourth metacarpals, cubitus valgus, Madelung deformity, high-arched palate, and short neck) are attributed to haploinsufficiency of the *SHOX*, the short-stature homeobox-containing gene on the pseudoautosomal region of the sex chromosomes (Xp22 and Yp11.3). *SHOX* gene is also known as *PHOG* gene for pseudoautosomal homeobox-containing osteogenic gene, lying on the very tip of the short arm of both sex chromosomes (Binder et al. 2000).
3. Chromosome locus (Wolff et al. 2010)
   a. A majority of genes associated with the physical features observed in Turner syndrome are located on Xp (Xp11.2-p22) (Zinn et al. 1998)
   b. Loci contributing to ovarian function reside in Xq (Xq24) (Schlessinger et al. 2002)
4. Karyotype findings associated with Turner syndrome (Wolff et al. 2010)
   a. Prenatal
      i. Approximately 1–2% of conceptuses have a 45,X karyotype.
      ii. The fetuses typically have ultrasound findings such as cystic hygroma or nuchal thickening.
      iii. A majority of cases with mosaicism for a 45,X cell line and a cell line with a second structurally normal sex chromosome result in the birth of a child with a normal phenotype (Chang et al. 1990; Koeberl et al. 1995)
   b. Postnatal
      i. Apparently nonmosaic monosomy X is found in ~45% of patients with Turner syndrome postnatally.
      ii. A structural chromosome abnormality or mosaicism for 45,X and another cell line is found in the lymphocytes of the remaining patients with Turner syndrome
5. Presence of Y chromosome material (Wolff et al. 2010)

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a. Mosaicism for a cell line with a normal or abnormal Y chromosome is identified in 6–11% of patients with Turner syndrome with standard cytogenetic techniques.
b. Risk of developing gonadoblastoma (Cools et al. 2006)
   i. A gonadoblastoma is a neoplasm composed of germ cells and sex cord elements with an excellent prognosis if detected early.
   ii. Gonadoblastoma can progress to dysgerminoma with metastatic potential.
   iii. A gonadoblastoma susceptibility locus has been proposed for the pericentromeric region of the Y chromosome (Tsuchiya et al. 1995; Lau 1999)
   iv. The neoplasm does not appear to correlate with the presence of *SRY*.
   v. Presence of occult Y chromosome mosaicism
      a) Eight percentage of cases detected by molecular or standard cytogenetic techniques: Of these 12% of cases had gonadoblastoma
      b) Zero to four percentage of cases detected by FISH using a probe for the Y centromere (DYZ3) (Hanson et al. 2002; Wiktor and Van Dyke 2005)

6. Pathogenesis (Ogata and Matsuo 1995)
   a. Gonadal dysgenesis: Oocytes undergoing accelerated degeneration during the first meiosis, resulting in loss of nearly all oocytes by late childhood
   b. Somatic stigmata
      i. Lymph fluid stasis caused by lymphatic hypoplasia results in distension of the main and tributary lymphatic ducts and generalized lymphedema.
      ii. Distended lymphatics and lymphedema cause mechanical extension of surrounding tissues, giving rise to deformations recognized as lymphatic obstruction stigmata:
         a) Webbed neck
         b) Low posterior hairline
         c) Rotated auricles
         d) Puffy hands and feet
         e) Redundant skin
         f) Nail hypoplasia
         g) Whorl dominant finger tip pattern

7. Phenotype-karyotype correlation
   a. Absence or deletion of the short arm of the X chromosome correlates with Turner stigmata:
      i. Short stature
      ii. Broad chest
      iii. Widespread nipples
      iv. Webbing of the neck
      v. Peripheral lymphedema at birth
      vi. Short fourth metacarpals
      vii. Hypoplastic nails
      viii. Multiple pigmented nevi
      ix. Coarctation of the aorta
   b. Absence or deletion of the long arm of the X chromosome correlates with infertility and gonadal dysgenesis.
   c. The degree of mosaicism correlates with the presence of clinical features of Turner syndrome.
   d. Severe phenotype associates with a small or tiny ring X chromosome which lacks the *XIST* (X-inactive-specific transcript) at Xq13 (Cervantes et al. 2001):
      i. Loss of *XIST* results in functional X disomy for the sequences contained in the ring.
      ii. Some r(X), ascertained because of severe phenotypes, undergo X inactivation.

Clinical Features

1. Skeletal manifestations (Hall and Gilchrist 1990; Ogata and Matsuo 1995)
   a. Short stature (100%): an invariant feature in the 45,X Turner syndrome
   b. Characteristic growth pattern
      i. Intrauterine growth retardation
      ii. Progressive decline in growth velocity in childhood
      iii. Lack of pubertal growth spurt
      iv. Delayed growth cessation
   c. Cubitus valgus
   d. Madelung deformity of the wrist (a bayonet-like deformity of the wrist) with decreased extension and supination
   e. Hypoplastic nails
   f. Short fourth metacarpals
2. Characteristic craniofacial features
   a. Down slanting of the palpebral fissures
   b. Epicanthal folds

c. Occasional ptosis and strabismus
d. Midfacial hypoplasia
e. Broad nasal bridge
f. High-arched palate
g. Micrognathia
h. Rotated auricles

3. Teeth
   a. Crowding
   b. Malocclusion
4. Neck
   a. Short and broad neck
   b. Webbed neck (pterygium colli) with low posterior hairline from the resolution of the cystic hygroma that was present in fetal life
5. Chest
   a. Shield chest
   b. Increased internipple distance
6. Congenital heart defects (30%)
   a. Coarctation of the aorta
   b. Bicuspid aortic valve
   c. Aortic stenosis
   d. Aneurysm (aortic root dilatation)
   e. Cystic medial necrosis of the aorta
7. Vascular anomalies
   a. Multiple intestinal telangiectasia
   b. Hemangiomas
   c. Lymphangiectasia
   d. Venous ectasias
   e. Intermittent and recurrent gastrointestinal bleeding
   f. Protein-losing enteropathy secondary to gastrointestinal lymphangiomas
   g. Chylous fluid accumulation in the abdomen and chest
8. Peripheral lymphedema in the newborn infant involving dorsum of the hands and feet
9. Nail dysplasia
   a. Concave fingernails
   b. Upturned toenails
10. Skin
    a. Redundant skin
    b. Multiple pigmented nevi
    c. Tendency of hypertrophic scarring or keloid formation
11. Gonadal dysgenesis
    a. Sexual infantilism: one of the most common clinical findings
    b. Primary amenorrhea (the rule)
    c. Spontaneous menstruation occurring in about 5% of patients. Some of these women even give birth (3–5%).
    d. Delayed pubertal development in most patients
    e. Up to 30% of patients with at least some pubertal development indicating the presence of follicles in their ovaries in adolescence
    f. A high frequency of miscarriage reported among the spontaneous pregnancies of women with Turner syndrome
    g. Progressive ovarian failure
    h. Infertility/sterility
12. Genitourinary lesions
    a. Horseshoe and ectopic kidneys
    b. Ureteropelvic obstruction
    c. A double collecting system
    d. A bifid renal pelvis
    e. Hydronephrosis
    f. Vaginal agenesis: rare
13. Hypertension (common even without cardiac or renal malformations)
14. Conductive and sensorineural hearing losses
15. Autoimmune disease
    a. A markedly increased incidence of thyroid antibodies
    b. Autoimmune hypothyroidism
    c. Impaired serum glucose tolerance in 25–60% of patients
    d. Diabetes mellitus in 5% of patients
    e. An increased incidence of inflammatory bowel disease
       i. Regional enteritis
       ii. Ulcerative colitis
    f. Rheumatoid arthritis
    g. Acute hyperthyroidism: rare
16. Abnormal dermatoglyphics
    a. Predominant digital whorls
    b. Distal triradii
17. Psychosocial aspects
    a. Significantly higher verbal level than performance level attributed to a specific space-form perception deficit
    b. Arithmetic subtests: most difficult among verbal subtests
    c. Difficulty in performance
       i. Reading
       ii. Figure drawing

iii. Geometry
iv. Arithmetic

18. Presence of Y chromosome material in some cases of Turner syndrome
    a. A high risk of developing gonadoblastoma and dysgerminoma
    b. Requiring preventive removal of the dysgenetic gonads
19. Mosaic patients with a structurally abnormal X chromosome
    a. Classic Turner phenotype
        i. X-derived marker in majority of cases
        ii. Usually a large ring X chromosome that includes *XIST* not associated with a severe phenotype, although a low IQ or even mental retardation has been observed in some cases
    b. Severe phenotype
        i. Mental retardation
        ii. Dysmorphic features uncharacteristic of Turner syndrome
        iii. Observed in patients associated with a small or tiny ring X chromosome lacking the *XIST* gene at Xq13

Diagnostic Investigations

1. Endocrine study
    a. Very low estrogen levels
    b. Elevated pituitary gonadotrophins after puberty
2. Karyotype analyses
    a. 45,X
        i. Observed in 50% of cases
        ii. Maternal origin of the X chromosome in two thirds of cases
    b. Structurally abnormal sex chromosome, such as i(Xq)
    c. Mosaicism with a second cell line containing a normal or abnormal X or Y
        i. Most common forms of mosaicism (Saenger et al. 2001)
            a) 45,X/46,XX
            b) 45,X/46,X,i(Xq)
        ii. Containing a sex marker chromosome in about 20% of cases
            a) Sex marker chromosome: usually an X chromosome
            b) Second cell line containing a structurally abnormal Y chromosome in 6% of cases
    d. Determination of the chromosomal origin of sex marker chromosomes
        i. Fluorescence in situ hybridization (FISH)
        ii. Primed in situ labeling (PRINS) diagnostic for repetitive sequences in specific human chromosomes
    e. Painting probes and libraries and PCR to detect "hidden" mosaicism (Fernández-García et al. 2000; Oliveira et al. 2009)
        i. Classical alpha-satellite probes for the X (CEP-X) chromosome and Y chromosomes (CEP-Y) (Vysis)
        ii. Whole chromosome painting probes (WCP-X, WCP-Y) (Vysis)
        iii. XIST-digoxigenin (Oncor) hybridizing specifically to Xq13.2 indicating the X-inactivation center
        iv. DXZ4-biotin (Oncor) hybridizing specifically to a cluster of 50–100 copies of a 3-kb repeat in the Xq24 region
        v. Subchromosomal painting libraries (SCPL116 specific for the short arm of the X chromosome, SCPL102 specific for the long arm of the X chromosome)
        vi. Using PCR to detect Y chromosome–specific sequences
3. Identification of specific X and Y sequences
    a. Important for establishing phenotype-karyotype correlations
    b. Important for adequate genetic counseling
    c. PCR to identify the presence or absence of specific Y sequences
4. Echocardiography for cardiovascular malformations
5. Renal ultrasound for renal anomalies
6. Radiography
    a. Madelung deformity
        i. Prominent and dorsally dislocated but reducible distal ulna
        ii. Short and bowed radius
        iii. Carpal articular surface of the radius tilted in a volar and ulnar direction producing a triangular configuration and premature fusion of the ulnar side of the radial growth plate
    b. Short fourth metacarpals and metatarsals
    c. Short distal phalanges with tufting
    d. Carpal bone fusion
    e. Pes cavus

f. Irregular tibial metaphyses with mushroom projections on the medial surface of the proximal tibial metaphyses
g. Spine
   i. Schmorl's nodes (abnormalities of cartilaginous end plates)
   ii. Scheuermann's disease of the vertebrae (osteochondrosis of vertebral epiphyses in juveniles)
   iii. Scoliosis
   iv. Lack of lumbar lordosis
   v. Congenital hip dislocation
h. Skull
   i. Midfacial hypoplasia
   ii. An obtuse cranial base angle
   iii. Short cranial base
i. Osteoporosis

7. Other investigations
   a. Blood pressure measurement for hypertension
   b. Thyroid function
   c. Audiology for conductive and sensorineural hearing loss
   d. Orthodontic evaluation
   e. Orthopedic evaluation
   f. Glucose intolerance

Genetic Counseling

1. Recurrence risk: The mode of inheritance is sporadic.
   a. Patient's sib: low
   b. Patient's offspring: rarely pass to offspring due to infertility
2. Prenatal diagnosis
   a. Maternal serum screening
      i. Slightly decreased levels of α-fetoprotein and unconjugated estriol
      ii. Elevated hCG and inhibin A
   b. Ultrasonographic screening
      i. Fetal hydrops
      ii. Increased nuchal translucency
      iii. Fetal cystic hygroma
      iv. Coarctation of the aorta
      v. Left-sided cardiac defects
      vi. Brachycephaly
      vii. Lymphedema
      viii. Renal anomalies
      ix. Intrauterine growth retardation
      x. Polyhydramnios
      xi. Oligohydramnios
   c. Karyotype of fetal cells from amniocentesis or CVS using standard cytogenetic, FISH, or microarray analysis
      i. A karyotype consistent with diagnosis of Turner syndrome
      ii. Phenotype of the individual cannot be predicted based on the karyotype
      iii. Follow laboratory guideline recommendations for prenatal diagnosis of Turner syndrome (Wolff et al. 2010)
3. Management (Davenport 2010)
   a. Psychosocial counseling
      i. Degree of parental understanding and appropriate attitudes toward the patient with Turner syndrome depends, in general, on good family relationships, socioeconomic level of the family, and appropriate physician's counseling
      ii. Short stature: a major concern when entering school
      iii. Pubertal failure and sterility: major concerns to the parents and patients at pubertal age
      iv. Webbed neck less frequent concern cosmetically unless that defect is marked and visible
      v. Occasional parental rejection and over protectiveness
      vi. Child's adjustment to the disease influenced by parental personalities and their ability to cope with the implications of the syndrome
      vii. Development of a high degree of social competency permitting patients to be integrated into a society where they will be self-sufficient and self-sustaining
   b. Estrogen replacement therapy
      i. To induce near normal pubertal development
      ii. To prevent osteoporosis
      iii. To reduce the risk of developing cardiovascular disease
   c. Growth hormone (GH) therapy (with or without anabolic steroids) for short stature
      i. Standard of care for girls with Turner syndrome (Bondy 2007)
      ii. Girls treated with GH at 5.7 years (mean) averaged 7.2 cm taller than those in the control group (Stephure 2005)

d. Pregnancies among women with Turner syndrome: rare (Hovatta 1999; Cabanes et al. 2010; Mortensen et al. 2010)
   i. The most serious maternal complications
      a) Worsening of preexisting hypertension
      b) Aortic dissection
   ii. A high risk of miscarriages and stillbirths among spontaneous pregnancies
   iii. Seventy five percentage of spontaneous pregnancies: normal karyotype

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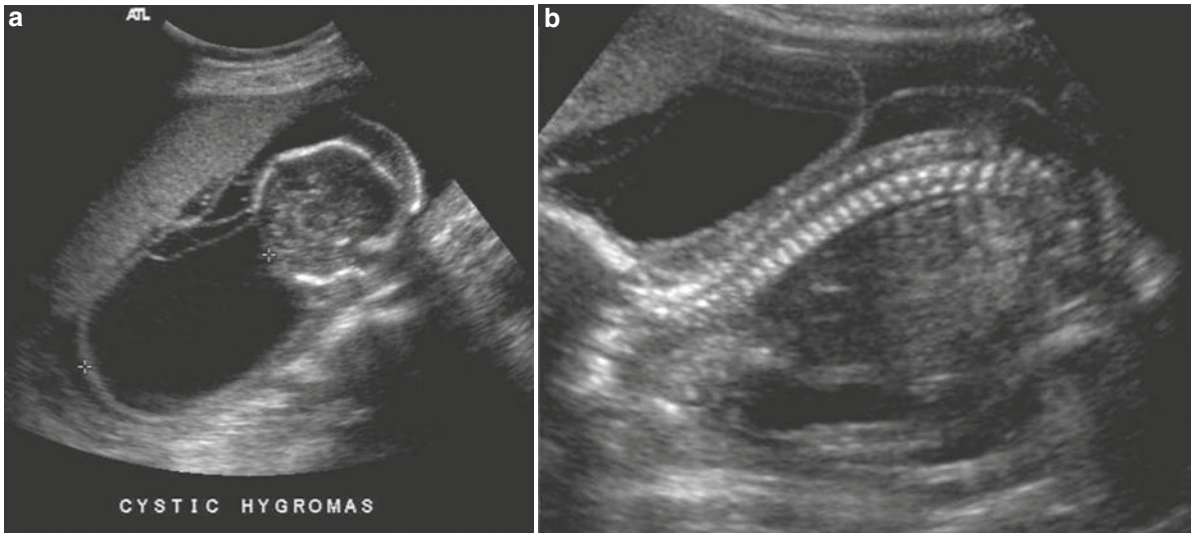

Fig. 1 (**a**, **b**) A multiseptated cystic hygroma is observed in a fetus with Turner syndrome at 18 weeks of gestation

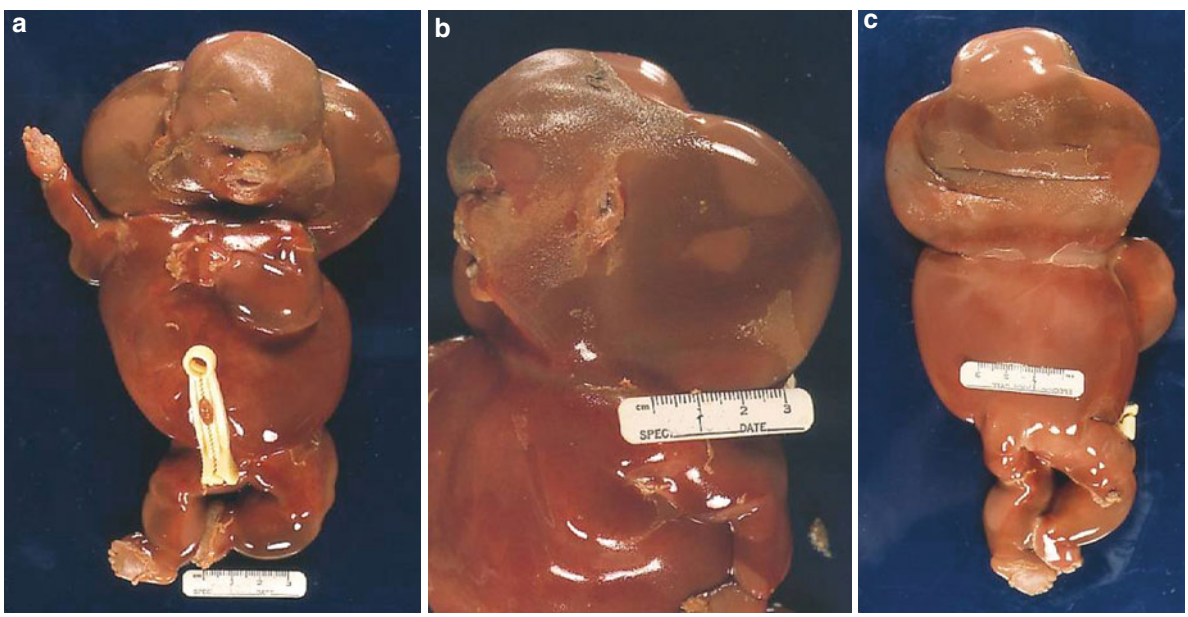

Fig. 2 (**a**–**c**) A 45,X fetus showing massive cystic hygroma and hydrops fetalis

Fig. 3 (**a**–**c**) A newborn with 45,X showing classic facial features, webbed neck, shield chest, and wide space between nipples

Fig. 4 (**a**, **b**) A 45,X newborn with classic facial features (epicanthal folds, down-slanting palpebral fissures, flat nasal bridge, receding chin, low-set/posteriorly rotated ears) and excessive nuchal skin folds

Fig. 5 (**a**, **b**) Two patients with Turner syndrome shield chest

Fig. 6 A patient with Turner syndrome showing short and webbed neck and low hairline

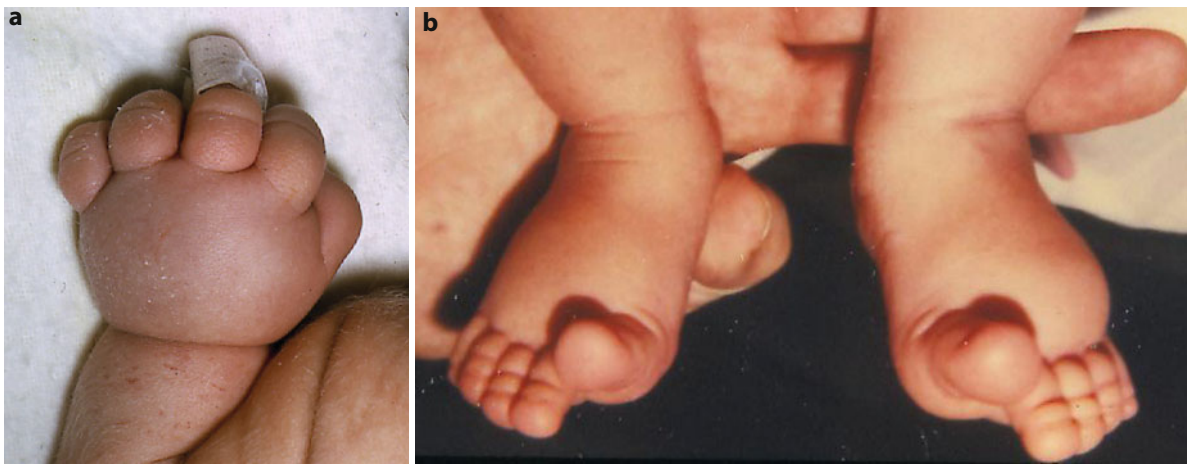

Fig. 7 (**a**, **b**) Two 45,X newborns with severe lymphedema of the dorsum of hand and feet and toenail hypoplasia

Fig. 8 (**a**–**d**) A 45,X girl showing short stature, classic facial features, severe webbed neck, shield-like chest, and widely spaced nipples

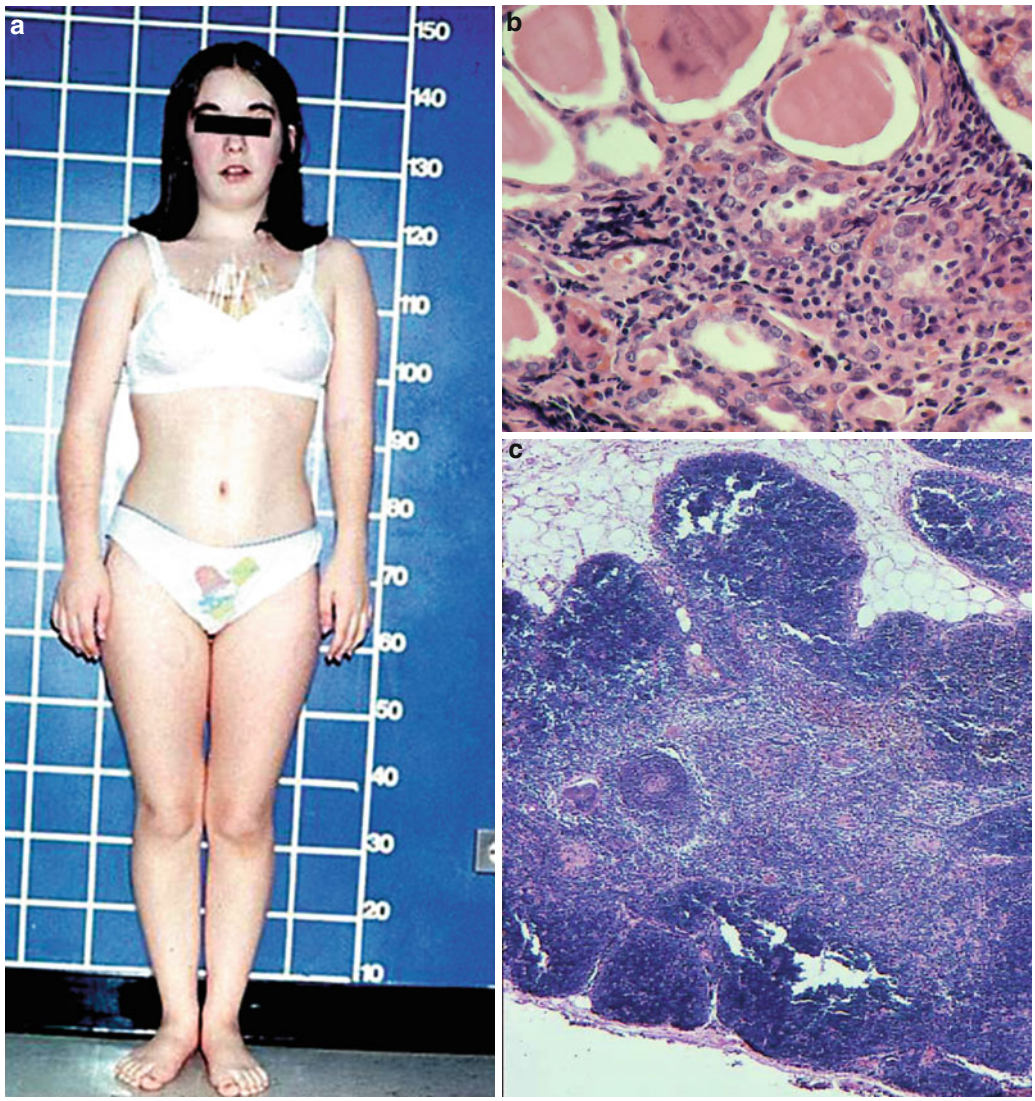

Fig. 9 (**a**–**c**) A 45,X/46,XX patient showing short stature, characteristic facial features, webbed neck, lymphocytic thyroiditis, and follicular formation of thymus medulla

Fig. 10 (**a**–**c**) An adult patient with 45,X/46,XX mosaic Turner syndrome showing webbed neck with low posterior hairline and short metacarpals, illustrated by hand radiograph

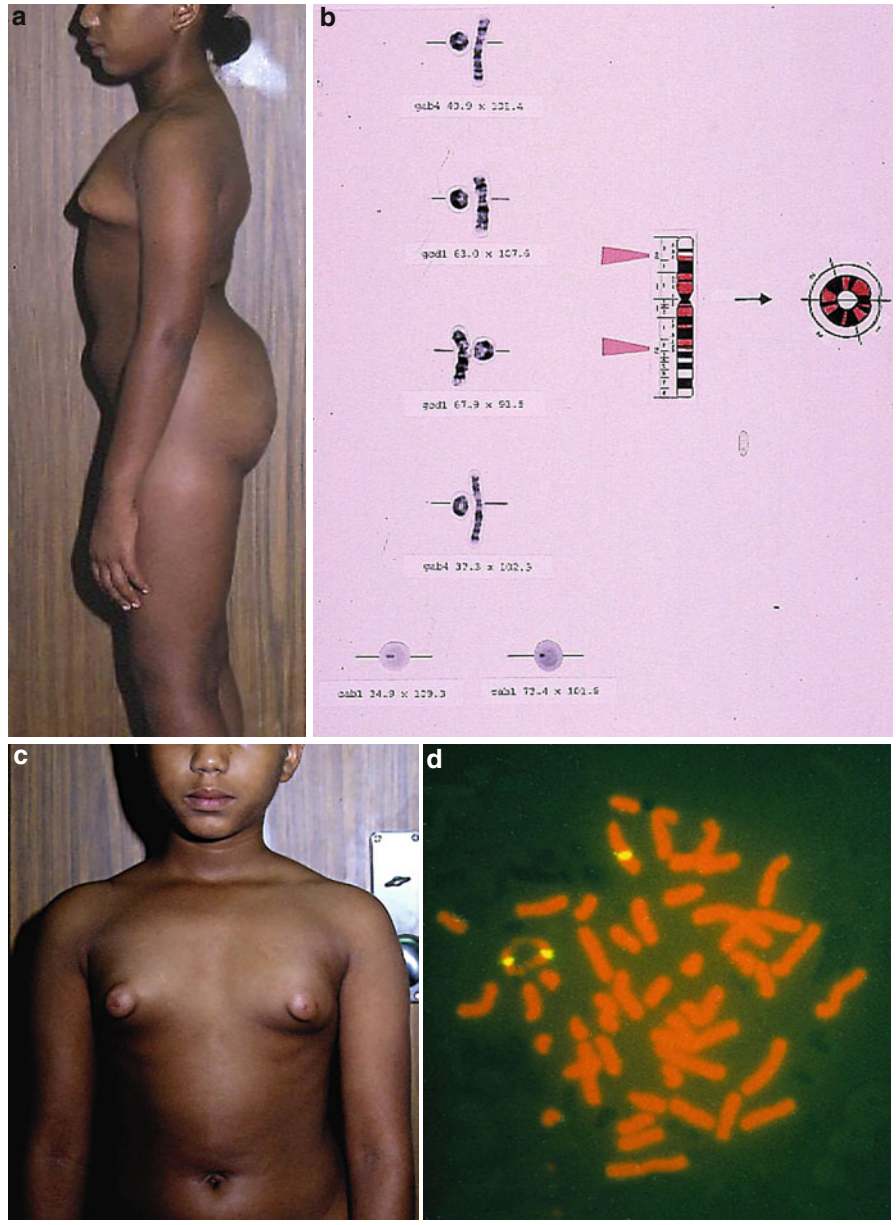

Fig. 11 (**a**–**d**) A girl with 45, X/46,X,r(X) ring chromosome X Turner mosaicism. The ring chromosome is illustrated by partial karyotype with ideogram and FISH with an X chromosome centromeric probe

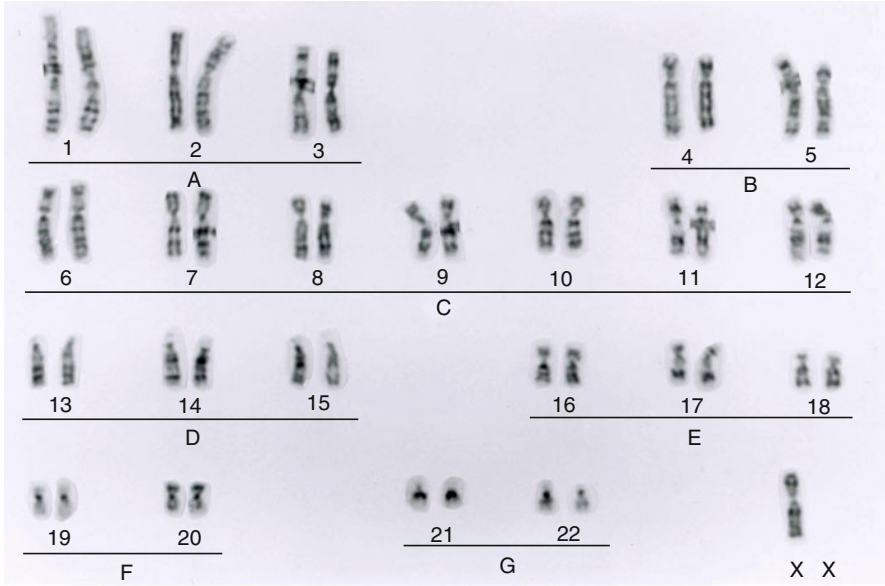

Fig. 12 45,X karyotype

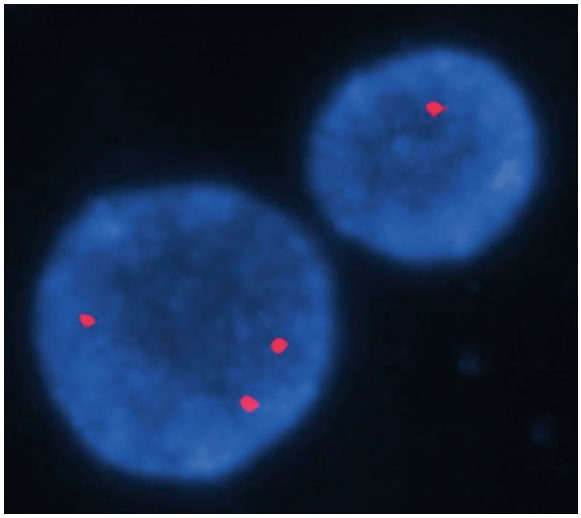

Fig. 13 FISH showing a mosaic fetus with XXX/X (CEP X/SpectrumOrange). Three copies of the orange signal are in the XXX cells and one copy in the monosomy X cells

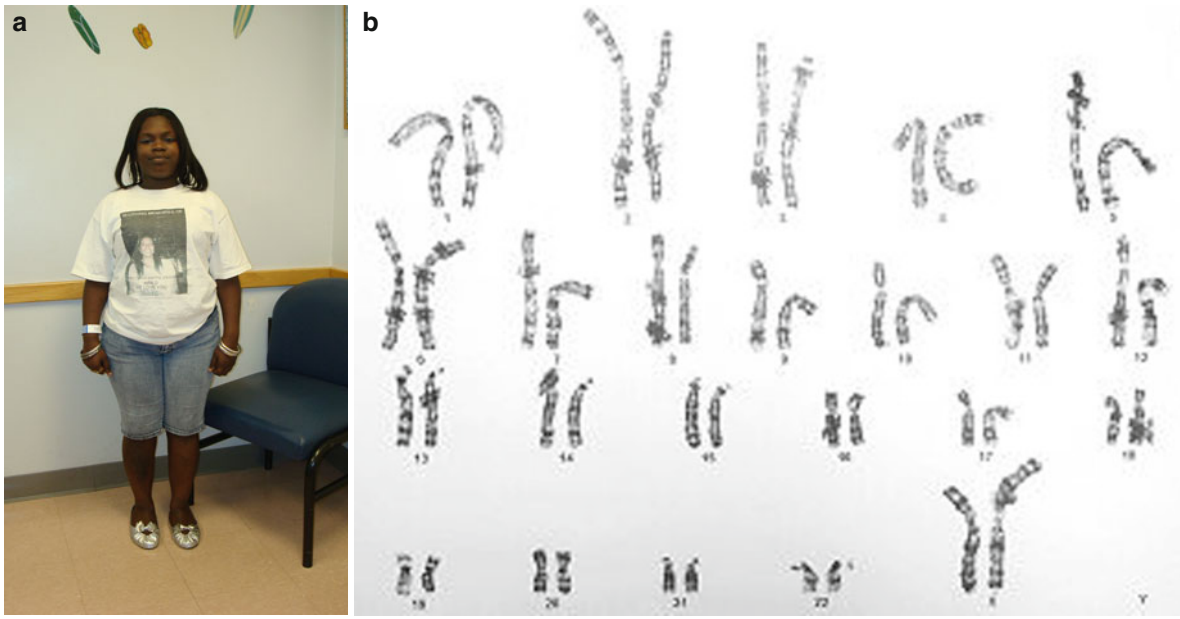

Fig. 14 (**a**, **b**) This 18-year-old adolescent girl was evaluated for absence of menarche. She was noted to have Turner stage II breasts, absence of axillary hair, and scanty pubic hair. However, she has average stature for her age. The karyotype shows 46,X, i(X)(q10) confirming the diagnosis of isochromosome Xq syndrome

Twin–Twin Transfusion Syndrome

Twin–twin transfusion syndrome results from imbalance in the net flow of blood leading to intrauterine blood transfusion from one twin to another twin as a serious complication in 10–30% of monochorionic diamniotic twin pregnancies (Banek et al. 2003; Weber and Sebire 2010).

Genetics/Basic Defects

1. Cause: a serious complication of monozygotic, monochorionic twin pregnancy through placental vascular anastomoses (unilateral arteriovenous anastomoses), resulting in transfusion of blood from one fetal twin to another twin (Banek et al. 2003)
2. Pathogenesis
   a. Imbalance in net blood flow through transplacental fetofetal transfusion, resulting in a discrepancy in blood volume distribution in two twins
   b. The donor twin
      i. Becoming hypovolemic, hypotensive, and oliguric
      ii. Leading to oligo-/anhydramnios and growth restriction
   c. The recipient twin
      i. Becoming hypervolemic, hypertensive, and polyuric
      ii. Leading to polyhydramnios and congestive heart failure

Clinical Features

1. Donor twin
   a. Birth weight: small for gestational age
   b. Pallor and anemic
   c. Poor peripheral perfusion
   d. Oligohydramnios in the amniotic sac secondary to hypovolemia and decreased urine output
   e. Stuck twin phenomenon (the twin appears in a fixed position against the uterine wall) resulting from severe oligohydramnios
   f. Hydrops fetalis secondary to anemia and high-output heart failure
2. Recipient twin
   a. Birth weight: larger at birth
   b. Plethoric and ruddy
   c. Jaundice
   d. Polyhydramnios in the amniotic sac secondary to hypervolemia and increased fetal urine output
   e. Hydrops fetalis secondary to hypervolemia
   f. Hypertension
   g. Hypertrophic cardiomegaly
   h. Right-sided heart failure with tricuspid regurgitation and right ventricular outflow tract obstruction
   i. Increased risk of cardiac malformations
   j. Intravascular coagulation
3. Staging of twin–twin transfusion syndrome (Bebbington 2010)
   a. Stage 1: Polyhydramnios in recipient sac (MVP >8 cm) and oligohydramnios in the donor sac (MVP <2 cm)

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   b. Stage 2: No visible bladder in the donor twin
   c. Stage 3: Doppler abnormality consisting of absent or reverse flow in the umbilical artery, reverse flow in the ductus venosus or pulsatile flow in the umbilical vein
   d. Stage 4: Ascites or hydrops in either fetus
   e. Stage 5: Demise of either fetus
4. Prognosis
   a. Premature delivery in case of mild to moderate twin–twin transfusion syndrome
   b. Guarded with possible serious maternal and fetal complications
   c. Antenatal death as well as neonatal death secondary to preterm delivery
   d. Survival rate for those diagnosed before 28 weeks: 20–45%
5. Antenatal factors that predict poor outcome
   a. Early gestational age at diagnosis with delivery before 28 weeks of gestation
   b. Fetal polyhydramnios requiring multiple therapeutic amniocenteses
   c. Fetal hydrops
   d. Absent or reversed diastolic flow in umbilical artery Doppler studies
6. Neonatal complications (Blickstein 1990)
   a. Neurologic sequelae in 25% of surviving twin in case of fetal demise in other twin
   b. Divergent intrauterine growth in association with subsequent physical and mental deficiencies in the smaller twins
   c. Thrombocytopenia suggested as the cause of cataracts, impaired hearing, and growth retardation of the donor twin
   d. Intrauterine growth deficiency of the brain and profound neonatal hypoglycemia implicated as reasons for cerebral impairment of the donor twin, resulting in subsequent lower intelligence compared with its co-twin
   e. Circulatory overload with heart failure if severe hypervolemia occurs
   f. Occlusive thrombosis due to hyperviscosity
   g. Polycythemia that may lead to severe hyperbilirubinemia and kernicterus
   h. Brain damage with cerebral palsy, microcephaly, or encephalomalacia
7. Maternal complications
   a. Secondary to multiple gestations
      i. Preeclampsia
      ii. Preterm labor
      iii. Hemorrhage
      iv. Diabetes
   b. Maternal mirror syndrome
      i. A rare complication associated with fetal hydrops
      ii. Also known as "Ballantyne syndrome" or "triple edema syndrome"
      iii. A syndrome of severe water retention that "mirrors" fetal hydropic changes
      iv. Frequent occurrence in the mid-trimester

Diagnostic Investigations

1. Difference in birth weight: inter-twin difference >20% (heavier twin = 100%) (Quintero 2003)
2. CBC to demonstrate inter-twin differences of hemoglobin level (difference ≥5 g/dL) (Quintero 2003)
   a. Anemia: frequently in donor twin at birth
   b. Polycythemia frequently in recipient twin at birth
3. Blood chemistry
   a. Hypoglycemia in either twins
   b. Hypocalcemia, hypoproteinemia in donor twin
   c. High creatinine in either twins with renal dysfunction
4. Thrombocytopenia in either twins
5. Hyperbilirubinemia in polycythemic recipient twin
6. Imagings
   a. Cranial ultrasound: intraventricular hemorrhage and periventricular leukomalacia in premature twins
   b. Chest radiography; pleural effusions and cardiomegaly in hydrops fetalis
   c. Echocardiography
      i. Myocardial dysfunction/hypertrophy
      ii. Valvular insufficiency
      iii. Pericardial effusion
   d. Renal ultrasound: abnormal renal echogenicity indicating hypoxic-ischemic cortical necrosis
   e. Abdominal ultrasound: Ascites in hydrops fetalis
7. Demonstration of transplacental vascular connections: an important criterion for the diagnosis of the twin–twin transfusion syndrome (Blickstein 1990)
   a. Donor twin
      i. Placenta
         a) Pale
         b) Swollen
         c) Atrophied

ii. Amniotic membrane showing amnion nodosum in the presence of oligohydramnios
b. Placenta of the recipient twin
i. Red
ii. Congested
iii. Hypertrophied
8. Surgical pathologic assessment of vascular anastomoses in monochorionic placentas with strong clinical correlation of placental types and occurrence of twin–twin transfusion (Bermúdez et al. 2002)
a. Type A (placenta without vascular anastomoses): 0%
b. Type B (placenta with only deep arteriovenous anastomoses): 81%
c. Type C (placenta with only superficial anastomoses): 1%
d. Type D (placenta with combined deep arteriovenous and superficial anastomoses): 18%
9. Sonographic criteria for determining chorionicity
a. Dichorionic
i. Separate placentas
ii. Well-visualized septum
b. Monochorionic diamniotic
i. One placenta
ii. A paper-thin, reflective hair-like septum (only small parts visible)
c. Dichorionic diamniotic: septum readily seen with a thickness similar to one wall of the umbilical cord

Genetic Counseling

1. Recurrence risk
a. Patient's sib: not increased unless in another pregnancy with monochorionic twinning (twin–twin transfusion syndrome affects 10–15% of monochorionic twins)
b. Patient's offspring: not increased unless in pregnancy with monochorionic twinning
2. Prenatal diagnosis (Blickstein 1990)
a. Ultrasonography
i. Divergent fetal size: striking differences in the sizes of the twins
a) Disparity in size of inter-twin abdominal circumference (difference >18 mm)
b) Disparity in size or in the number of vessels in the umbilical cords: The donor twin may have a single umbilical artery. The size of the umbilical cord of the recipient twin may be much larger than that of its co-twin.
ii. Divergent size of amniotic sacs (Quintero 2003)
a) Presence of polyhydramnios (largest pocket >8 cm) in one sac (the recipient twin persistently has a distended bladder and produces a large amount of urine)
b) Presence of oligohydramnios (largest pocket <2 cm or stuck twin) in other sac (the donor twin produces little urine)
iii. "Stuck twin" sign: a growth-retarded fetus tightly enwrapped within its membrane and trapped or stuck against the uterine wall due to oligohydramnios
iv. Determination of monozygosity
a) Like-sex twins
b) Monochorionic diamniotic placentation (absence of twin peak sign, thin separating membrane, and single placenta showing divergent echogenicity of the cotyledons supplying the two cords)
v. A hydropic placenta: a marker of anemia, even before the fetus itself becomes hydropic (de Laat et al. 2009)
vi. Evidence of hydrops in either twin
vii. Evidence of congestive cardiac failure in the recipient twin
viii. A sonographic staging classification for twin–twin transfusion syndrome allowing for the grading of the severity of the disease by standardized criteria (Quintero 2003)
a) Stage I: visible bladder of the donor twin, normal Doppler studies
b) Stage II: not visible bladder of the donor twin (during the length of examination, usually 1 h), not critically abnormal Doppler studies
c) Stage III: critically abnormal Doppler studies in either twin, characterized as absent or reverse end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus, or pulsatile umbilical venous flow
d) Stage IV: ascites, pericardial or pleural effusion, scalp edema, or overt hydrops of one or both twins
e) Stage V: presence of one or both demised twins

b. Echocardiography
   i. Possible advantages
      a) Assessment of cardiovascular adaptation to inter-twin transfusion
      b) Early recognition of deterioration
      c) Evaluation of antenatal management
   ii. Fetal heart rate monitoring: A silent, sinusoidal pattern in tracings of the fetal heart rate may indicate signs of fetal anemia.
   iii. Doppler studies
      a) Detection of arterio-arterial anastomoses in monochorionic twins
      b) Doppler velocimetry of the umbilical arteries: inter-twin differences in systolic/diastolic ratio >0.4 predicting growth discordancy of at least 350 g
   iv. Ultrasound-guided fetal blood sampling
      a) Establishing the diagnosis of monozygosity when blood group studies are performed on both twins
      b) Allowing an accurate antenatal assessment of the inter-twin hemoglobin difference and consequently establishing the diagnosis of twin–twin transfusion
      c) Revealing the degree of fetal anemia in the donor twin
c. Fetoscopy
   i. Plethora donor twin
   ii. Pale recipient twin

3. Management
   a. General approach
      i. Monochorionic twining at high risk for twin–twin transfusion syndrome
      ii. Requiring close obstetrical monitoring
      iii. Requiring specialized care in neonatal intensive care unit
   b. Postpartum therapies
      i. Directed towards the problems of each twin, such as prematurity, anemia, polycythemia, and hydrops fetalis
      ii. Severely anemic donor twin: requires packed red blood cell transfusions or partial exchange transfusions
      iii. Polycythemic recipient twin: requires partial exchange transfusion to lower serum hematocrit
   c. Prenatal therapies (van Gemert et al. 2001; Ropacka et al. 2002; Gardiner et al. 2003; Walker et al. 2007)
      i. Treating the mother with digoxin with favorable results when the recipient twin is showing signs of cardiac failure
      ii. Treatment options
         a) Prevent preterm labor and preterm premature rupture of the membranes from polyhydramnios (amniodrainage and septostomy)
         b) Isolate the twin circulations (cord ligation and selective laser photocoagulation)
      iii. Serial amniodrainage (amnioreduction): currently the most widely used therapy because it is simple and requires commonly available skills and equipment
         a) Removing large volumes of amniotic fluid from the recipient twin's sac
         b) Reducing the amniotic fluid volume, thereby reducing the risk of preterm labor or ruptured membranes
         c) Overall perinatal survival with serial aggressive amnioreduction: about 60% in uncontrolled published series
         d) Double survival rate (50%) and single survival rate (20%) in severe twin–twin transfusion syndrome presenting before 28 weeks of gestation
         e) Fail to address the underlying cause of twin–twin transfusion syndrome
         f) Complications: uterine contractions, premature rupture of membranes, chorioamnionitis, abruptio placenta, and inadvertent septostomy resulting in iatrogenic monoamniotic twins
      iv. Amniotic septostomy: intentionally puncturing the intertwine septum
         a) To create a hole in the intertwine membrane between the anhydramniotic donor's sac and the hydramniotic recipient's sac
         b) Restoring normal amniotic fluid pressure gradient, allowing fluid to move along a hydrostatic gradient from the hydramnios sac into the oligohydramnios sac
         c) Also an inadvertent occurrence during amnioreduction procedure
         d) Limited experience

v. Endoscopic laser coagulation of all placental vascular anastomosis (Wee and Fisk 2002)
   a) Reduces and abolishes intertwine transfusion by ablating chorionic plate anastomoses, producing functionally dichorionic pregnancies
   b) Proponents arguing that the procedure reduces the risk of neurological injury in survivors
   c) Overall survival rate (58%) with single survival of 32% and double survival of 42% for cases presenting prior to 18 weeks
   d) Rare fetal complications (relationship to the procedure not established): aplasia cutis, limb necrosis, amniotic bands, and microphthalmia/anophthalmia
vi. Selective feticide by cord occlusion (umbilical cord ligation): used as a last resort in cases in which both twins are at risk because of the serious condition of one twin
   a) Considered in case of monochorionic twin pregnancy in which one twin is a nonviable fetus, especially the condition is compromising the nonaffected fetus
   b) A typical example in twin reversed arterial perfusion sequence. The relatively normal twin risks high-output cardiac failure, complications of polyhydramnios, and death in utero.
   c) Another example of twin–twin transfusion syndrome, in which one fetus has major congenital anomalies or in utero–acquired abnormality, such as demonstrable cerebral lesions, terminal cardiac failure, or other conditions with a poor prognosis
   d) Benefits of selective termination of the affected twin: arrest the fetofetal transfusion process and protect the survivor
vii. In general, twin–twin transfusion syndrome diagnosed before 26 weeks of gestation has significantly better survival rates and fewer neurological sequelae after laser ablation therapy than amnioreduction. Twin–twin transfusion syndrome diagnosed after 26 weeks can best be treated by amnioreduction or delivery.

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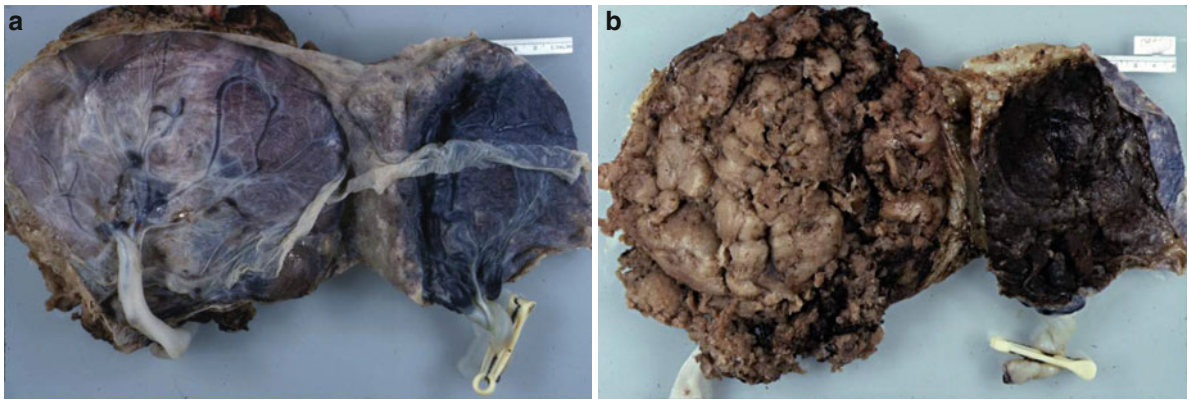

Fig. 1 (**a**, **b**) Diamniotic monochorionic twin placenta with features of twin–twin transfusion (the placental discs are not fused in this case): The placenta corresponding to the recipient twin (*right*) is small but plethoric and dark in color. The placenta of the donor twin (*left*) is large but anemic, pale, and edematous. The amniotic sacs were removed at the margins of the placental discs. The root of the thin monochorionic septum between the two sacs is shown on the fetal surface (first picture). The color difference between the two placentas is better shown on the maternal surface (second picture)

Fig. 2 The donor twin (*right*) showing smaller and pallor and the recipient twin (*left*) showing larger and plethoric at birth

Ulnar-Mammary Syndrome

Ulnar-mammary syndrome was originally described by Gilly in 1882 in a woman with mammary hypoplasia, inability to lactate, and absence of the third to fifth digits and ulna. Later in 1978, Pallister et al. reported a complex malformation syndrome in a young woman with abnormal development of ulnar rays, forearms, mammary gland tissue, axillary apocrine glands, teeth, palate, vertebral column, and urogenital system. Ulnar-mammary syndrome is a pleiotropic disorder affecting limb, apocrine gland, teeth, hair, and genital development.

Synonyms and Related Disorders

Pallister ulnar-mammary syndrome; Schinzel syndrome

Genetics/Basic Defects

1. Inheritance: autosomal dominant with variable expression
2. A gene for ulnar-mammary syndrome mapped to chromosome 12q23-q24.1
3. Caused by mutations that disrupt the DNA-binding domain of the T-box gene, *TBX3*
4. Mutations in human *TBX3* alter limb, apocrine, and genital development in ulnar-mammary syndrome (Bamshad et al. 1997).
5. No obvious phenotypic differences between those who have missense mutations and those who have deletions or frameshifts

Clinical Features

1. Posterior limb defects
   a. Widely variable
   b. Ulnar ray defects in most patients
      i. Hypoplasia of the terminal phalanx of the fifth digit
      ii. Hypoplasia or complete absence of the ulna and third, fourth, and fifth digits
   c. Postaxial digital duplications
   d. Camptodactyly
   e. Digital fusion
2. Apocrine gland abnormalities
   a. Mammary gland abnormalities: variable
      i. Hypoplasia to aplasia of the mammary glands and hypoplasia of the nipples
      ii. Accessory nipples
      iii. Inability to nipple feed
      iv. Normal breast development and lactation
   b. Decreased ability to sweat
   c. Reduced body odor
   d. Absent axillary perspiration
   e. Sparse axillary hair
3. Genital abnormalities: hypogenitalism
   a. Affected males
      i. Delayed puberty
      ii. Diminished to absent axillary hair
      iii. Micropenis
      iv. Cryptorchidism
      v. Small testes
      vi. Shawl scrotum
      vii. Reduced fertility
   b. Affected females
      i. Diminished to absent axillary hair
      ii. Imperforate hymen in some affected females

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4. Dental abnormalities
   a. Misplaced teeth
   b. Absent teeth
   c. Hypodontia
5. Other abnormalities
   a. Delay puberty
   b. Short stature
   c. Obesity
   d. Scanty lateral eyebrows
   e. Subglottic stenosis
   f. Pyloric stenosis
   g. Renal agenesis/malformation
   h. Pulmonary hypoplasia
   i. Inguinal hernia
   j. Anal atresia/stenosis
   k. Musculoskeletal abnormalities
      i. Short forearms
      ii. Hypoplastic humeri, scapulae, and clavicles
      iii. Hypoplastic pectoralis major muscles
      iv. Short, stiff, and crooked terminal phalanges of fourth to fifth toes
6. Differential diagnosis
   a. Hand-foot-uterus syndrome
      i. Autosomal dominant disorder
      ii. Allelic to ulnar-mammary syndrome speculated
      iii. Manifestations similar to ulnar-mammary syndrome include the following:
         a) Digital hypoplasia
         b) Carpal fusion
         c) Supernumerary nipples
         d) Genital anomalies
   b. Split hand/split foot syndrome: a causal relationship to ulnar-mammary syndrome suggested
   c. Scalp-ear-nipple syndrome: overlapping manifestations with ulnar-mammary syndrome
      i. Mammary hypoplasia
      ii. Diminished axillary perspiration
      iii. Dental abnormalities
      iv. Digital syndactyly: characteristic limb anomaly found in this syndrome (vs limb deficiency or duplications in ulnar-mammary syndrome)

Diagnostic Investigations

1. Radiography
   a. Short and stiff fifth finger
   b. Absent fifth finger ray
   c. Absent fourth finger ray
   d. Absent fourth to fifth finger rays
   e. Absent third to fifth finger rays
   f. Camptodactyly
   g. Hypoplastic/absent/deformed ulna
   h. Hypoplastic/absent/deformed radius
   i. Hypoplastic humerus, scapula, clavicle, and pectoralis major muscle
   j. Absent xiphisternum
   k. Postaxial polydactyly
   l. Short, stiff fourth and fifth toes
2. Endocrine investigations for hypogenitalism
3. Mutation analysis
   a. Missense mutations (L143P and Y149S)
   b. Nonsense mutation (Q360TER, S343TER)
   c. Splice-site mutations (IVS2 + 1G → C, IVS6 + 2T → A) producing a truncated protein product
   d. Frameshift mutations of small duplications

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased unless a parent is affected
   b. Patient's offspring: 50%
2. Prenatal diagnosis
   a. Ultrasonography and fetoscopy: possible to pregnancy at risk with presence of obvious fetal skeletal anomalies
   b. Mutation analysis of amniocytes and CVS: possible to families with identified mutation causing ulnar-mammary syndrome
3. Management
   a. Orthopedic management of limb defects
   b. Orchiopexy for cryptorchidism
   c. Testosterone management for hyogonadism in male patients
   d. Bottle feeding of infants born to mothers who has hypoplastic or absent nipples

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Fig. 1 A newborn (**a**, **b**) with ulnar mammary syndrome showing ulnar hypoplasia (missing fourth and fifth fingers) (**c**), ectrodactyly, syndactyly, and hypoplasia of the breast and nipples (**d**). The infant also had cryptorchidism, anal atresia, pulmonary hypoplasia, pyloric stenosis, and bilateral renal hypoplasia

Urofacial Syndrome

Urofacial syndrome, also known as Ochoa syndrome is characterized by severe voiding dysfunction and peculiar facies, i.e., inversion of facial expression with grimacing while smiling (Ochoa and Gorlin 1987; Ochoa 1992, 2004).

Synonyms and Related Disorders

Ochoa syndrome

Genetics/Basic Defects

1. Autosomal recessive inheritance based on:
   a. Affected siblings
   b. Normal parents
   c. Presence of consanguinity
2. Mutations with a loss of function in the *Heparanase 2* (*HPSE2*) gene were identified in all urofacial syndrome patients originating from Colombia, the United States, and France (Pang et al. 2010)
   a. HPSE2 encodes a 592 aa protein that contains a domain showing sequence homology to the glycosyl hydrolase motif in the heparanase (*HPSE*) gene, but its exact biological function has not yet been characterized.
   b. Complete loss of HPSE2 function in urofacial syndrome patients suggests that HPSE2 may be important for the synergic action of muscles implicated in facial expression and urine voiding.
3. Biallelic mutations in *HPSE2* gene on chromosome 10q23-q24, predicted to abolish activity of heparanase 2, cause urofacial syndrome in families from different ethnic groups (Daly et al. 2010).

Clinical Features

1. Characteristic facial expression
   a. Inversion of the facial expression when attempting to smile or laugh
   b. Facial grimace while smiling
   c. Smile looking like weeping
   d. Peculiar facial expression on smiling
2. Urinary manifestations
   a. Bladder dysfunction
      i. Intermittent urinary flow
      ii. Residual urine after voiding
      iii. Enuresis
      iv. Polyuria
   b. Urinary tract infection
   c. Hydronephrosis
3. Constipation
4. The urinary abnormalities may lead to renal deterioration and ultimate failure if untreated.

Diagnostic Investigations

1. Renal ultrasonography
2. Renal scan
3. Voiding cystourethrogram (VCUG)
4. Urodynamic studies

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is a carrier or affected

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2. Prenatal diagnosis: not yet reported
3. Management (Aydogdu et al. 2010)
   a. Intermittent urinary catheterization
   b. Appendicovesicostomy may be required for continent urinary diversion.
   c. Nocturnal bladder emptying with an indwelling nighttime catheter for polyuria
   d. Antibiotic prophylaxis
   e. Anticholinergic therapy
   f. Intravesical botulinium toxin injection
   g. Bowel management
   h. Augumentation cystoplasty

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Fig. 1 This 7-year-old girl presented with vague abdominal discomfort associated with nausea, nonbilious vomiting, and weight loss for past 8–10 weeks duration. Abdominal CT revealed bilateral hydronephrosis. Note the "grimace" facial appearance after smiling

Fig. 2 Patient's CT scan of the abdomen showed bilateral hydronephrosis

Fig. 3 Patient's VCUG showed smooth bladder wall

VATER (VACTERL) Association

VATER association is an acronym for the following nonrandom association of defects: *V*ertebral defects, *A*nal atresia, *T*racheoesophageal fistula with *E*sophageal atresia, and *R*enal or *R*adial defects. VACTERL association is an expanded acronym to include *C*ardiac defects and *L*imb defects. Diagnosis of VACTERL association is made if three out of the seven above defects are present in an infant. The incidence is estimated to be 1.6 cases in 10,000 live births.

Genetics/Basic Defects

1. Etiologic heterogeneity
   a. Isolated cases in most cases
   b. Reports of rare familial cases (single gene disorders)
   c. Reports of chromosome abnormality cases
   d. Recognized syndromes or phenotypes
   e. Observed more frequently in infants of diabetic mothers
2. Pathogenesis: suggestion of a defective mesodermal development during embryogenesis due to a variety of causes, leading to overlapping manifestations (Khoury et al. 1983)
3. Molecular basis of VACTERL association
   a. Report of a family in which a female infant was born and died at age 1 month due to renal failure. The mother and sister later developed classic mitochondrial cytopathy, associated with the A-to-G point mutation at nucleotide position 3,243 of mitochondrial DNA (Damian et al. 1996).
   b. Mitochondrial NP 3243 point mutation considered not a common cause of VACTERL association (Damian et al. 1996)
   c. Sonic hedgehog in the human: a possible explanation for the VATER association (Arsic et al. 2002)
   d. Recently, microdeletions of the FOX gene cluster at 16q24.1, comprising four genes, *FOXF1*, *MTHFSD*, *FOXC2*, and *FOXL1*, were reported to cause a phenotype resembling VACTERL association, with vertebral anomalies, gastrointestinal atresias (esophageal, duodenal, and anal), congenital heart malformations, and urinary tract malformations, as well as a rare lethal developmental anomaly of the lung, alveolar capillary dysplasia (Shaw-Smith, 2010)

Clinical Features

1. *V*ertebral anomalies
   a. Hemivertebrae
   b. Fused vertebrae
   c. Hypersegmentation of the vertebrae
   d. Hypersegmentation of the ribs
   e. Scoliosis
   f. Sacral anomalies
   g. Incomplete pedicle
   h. Sternal anomalies
2. *A*nal and urachal anomalies
   a. Anal atresia with or without fistula
   b. Persistent urachus

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3. *C*ardiac anomalies
   a. Ventricular septal defects
   b. Patent ductus arteriosus
   c. Tetralogy of Fallot
   d. Transposition of the great arteries
   e. Other cardiovascular anomalies
      i. Right aortic arch
      ii. Double aortic arch
      iii. Coarctation of the aorta
      iv. Dextrocardia
      v. Total anomalous pulmonary venous drainage
      vi. Left superior vena cava
      vii. Congenital mitral stenosis
      viii. Right anomalous coronary artery
      ix. Single umbilical artery
4. *T*racheoesophageal fistula
5. *E*sophageal atresia
6. *R*enal anomalies
   a. Renal agenesis/dysgenesis
   b. Ectopic kidney
   c. Horseshoe kidney
   d. Ureteral/urethral anomalies
   e. Hydronephrosis
   f. Renal ectopia
   g. Vesicoureteral reflux
   h. Posterior urethral valves
   i. Ureteropelvic junction obstruction
7. *L*imb defects
   a. Radial aplasia/dysplasia
   b. Hypoplastic thumbs
   c. Triphalangeal thumb
   d. Preaxial polydactyly
   e. Syndactyly
   f. Radioulnar synostosis
8. Other associated abnormalities
   a. Failure to thrive
   b. Short stature
   c. Wide cranial suture
   d. Large fontanel
   e. Potter facies
   f. Ear anomalies
   g. Cleft palate
   h. Gastrointestinal anomalies
      i. Malrotation
      ii. Meckel diverticulum
      iii. Duodenal atresia
      iv. Pyloric atresia
      v. Ileal atresia
      vi. Pancreatic heterotopia
      vii. Vermiform appendix agenesis
      viii. Omphalocele
      ix. Inguinal hernia
   i. Genital anomalies
      i. Hypospadias
      ii. Cryptorchidism
      iii. Bifid scrotum
      iv. Micropenis
   j. Neurological anomalies
      i. Tethered cord
      ii. Spinal dysraphia
      iii. Occipital encephalocele
   k. Anomalies more commonly associated with CHARGE association

Diagnostic Investigations

1. Radiography for vertebral and limb defects
2. Echocardiography for congenital heart defects
3. GI investigation for TE fistula or esophageal atresia
4. Renal ultrasonography for renal dysplasia
5. Urological evaluation of urogenital defects
6. Chromosome analysis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: low recurrence risk unless in a single gene disorder
   b. Patient's offspring: low recurrence risk unless in a single gene disorder
2. Prenatal diagnosis by ultrasonography revealing multiple congenital anomalies compatible to VACTERL association
   a. Vertebral anomalies
   b. Anorectal anomalies
   c. Congenital heart defects
   d. TE fistula or esophageal atresia
   e. Renal anomalies
   f. Limb defects
3. Management
   a. Medical care
   b. Surgical care
      i. TE fistula and/or esophageal atresia
      ii. Major cardiac defects
      iii. Urogenital anomalies
      iv. Skeletal and limb defects

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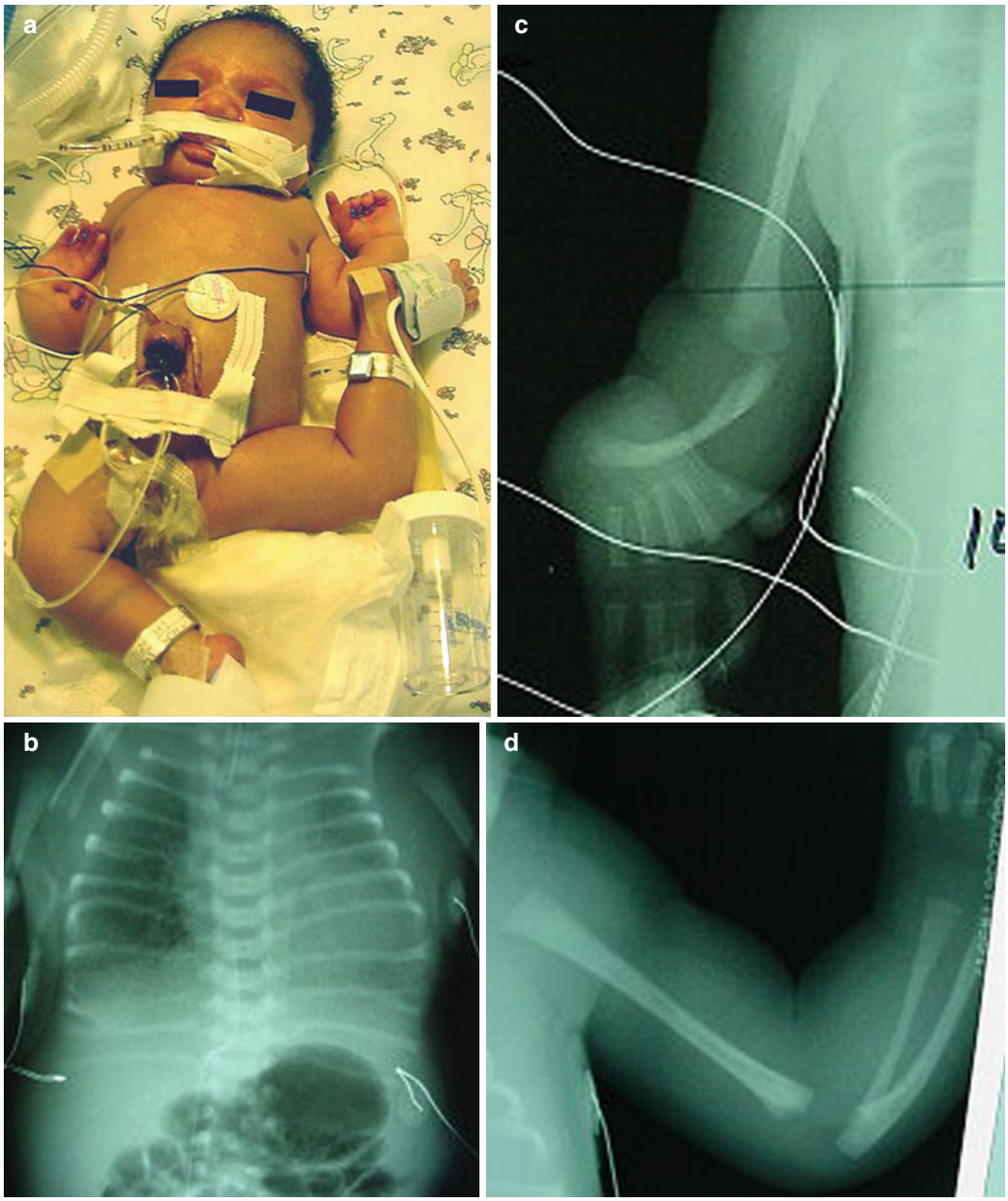

Fig. 1 (**a**–**d**) An infant with VATER association showing club hands, abnormally rotated left lower limb, fused/split ribs, hemivertebrae, radial aplasia on the right, and radioulnar fusion on the left elbow

Fig. 2 (**a**, **b**) A child with VATER association showing club hands and missing thumbs. Radiograph showed absence of the first phalanges and metacarpals and radial aplasia

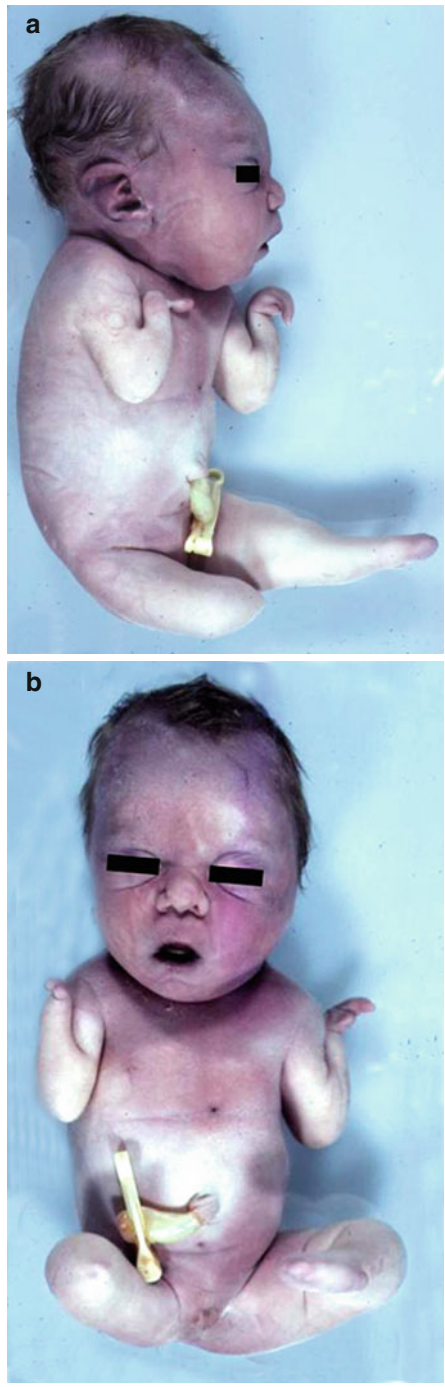

Fig. 3 (**a**, **b**) A male neonate with VATER association showing phocomelia, rudimentary external genitalia, and anal atresia, congenital heart anomalies (type 2 truncus arteriosus, tricuspid valve atresia, ventricular septal defect, large atrial septal defect), type 1 tracheoesophageal fistula, nonlobated lungs, agenesis of kidneys and ureters, malrotation of bowel, and vesicocolonic fistula were demonstrated in the necropsy

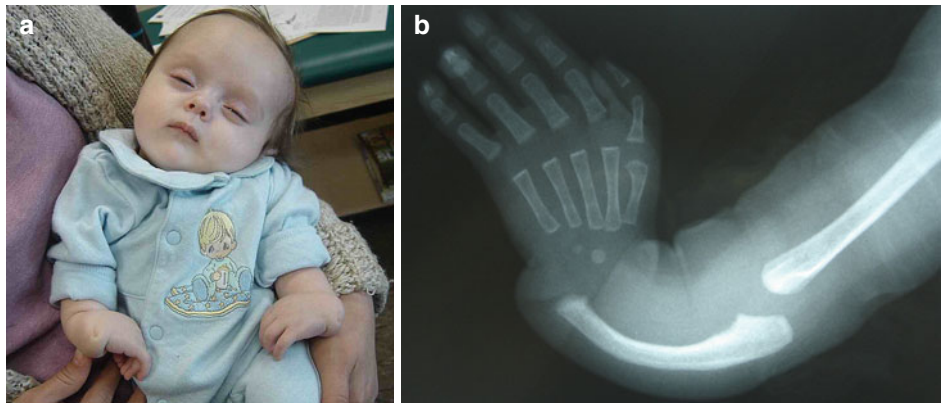

Fig. 4 (**a**, **b**) An infant with club hands and radial aplasia, illustrated by a radiograph

Fig. 5 (**a**–**c**) A girl with VATER association showing a remnant left thumb, anal atresia, and colostomy

Von Hippel–Lindau Disease

Von Hippel-Lindau disease (VHL) is a rare hereditary cancer syndrome. The prevalence is estimated at 1 in 85,000 with an incidence of 1 in 45,500 live births (Friedrich 2001).

Synonyms and Related Disorders

Angiomatosis retinae; Von Hippel-Lindau syndrome

Genetics/Basic Defects

1. Inheritance (Schimke et al. 2009)
   a. Autosomal dominant
   b. Reduced penetrance (95% penetrance at age 60)
   c. Positive family history in up to 80% of cases
   d. Sporadic new mutation in about 20% of cases
   e. Parental mosaicism described
2. Molecular pathogenesis of VHL disease
   a. VHL disease
      i. Caused by deletions or mutations in a tumor suppressor gene, the *VHL* gene, located on chromosome 3p25-26, which encodes an ubiquitin ligase that is involved in the cellular response to hypoxia
      ii. Two-hit theory of Knudson in a familial cancer syndrome such as VHL disease (Lubensky et al. 1998)
         a) Prediction of the genotype of each neoplasm which consists of an allele with an inherited germ line mutation and loss of the second wild-type allele through allelic deletion
         b) Loss of heterozygosity at chromosome 3p at the *VHL* gene region has been demonstrated in different VHL disease-associated tumors
      iii. A germ line mutation in the *VHL* gene (Hes et al. 2003)
         a) Predisposes carriers to tumors in multiple organs
         b) Consistently detected in 100% of classic families with more than one affected family member or classic sporadic patients with multiple VHL-related tumors
         c) Missense mutations leading to an amino acid substitution in *VHL* gene product pVHL, observed in 40% of the families with an identified *VHL* gene germ line mutation
         d) Microdeletions, insertions, splice site, and nonsense mutations, all predicted to lead to a truncated protein: observed in 30% of the families
         e) Large deletions including deletions encompassing the entire gene: account for the remaining 30% of the *VHL* gene germ line mutations
      iv. Somatic mutations (Hes et al. 2003)
         a) Independent somatic alteration of both alleles of the VHL tumor suppressor gene leading to tumorigenesis in nonfamilial (VHL-related) tumors

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   b) Somatic VHL gene mutations and allele loss: frequent events in sporadic clear cell renal cell carcinomas and sporadic central nervous system hemangioblastoma, uncommon in sporadic (i.e., nontumor syndrome associated) pheochromocytoma
b. *VHL* gene
   i. Mapped on chromosome 3p25
   ii. Involved in blood vessel formation by regulation of the activity of hypoxia-inducible factor (HIF)-1α
c. Patients with VHL disease
   i. With a positive family history: have inherited an inactive *VHL* allele from an affected parent
   ii. Without a positive family history: have a parent who is mosaic for a *VHL* mutation, presumably as the result of a de novo mutation during early development
d. Angiogenesis of VHL tumors: critical role of inactivation of *VHL* gene
   i. Overexpression of vascular endothelial growth factor (VEGF) resulting in hypervascularization
   ii. Negative regulation of hypoxia-inducible mRNAs including VEGF mRNA by VHL protein
e. Tumor development in VHL disease
   i. Linked to inactivation or loss of the remaining wild-type *VHL* allele in a susceptible cell, leading to loss of the *VHL* gene product pVHL
   ii. Inactivation of *VHL* gene contributing to tumorigenesis of the VHL tumor since VHL protein is required for the downregulation of transcription activity of certain genes

Clinical Features

1. Great variation in the clinical presentation with variable age of onset (Schimke et al. 2009)
2. Classification of VHL disease (Schimke et al. 2009; Sano and Horiguchi 2003)
   a. VHL type 1
      i. Typical VHL manifestations such as hemangioblastomas of the CNS and/or retina and clear cell renal cell carcinomas
      ii. Without pheochromocytoma
      iii. Truncating or null mutations in the VHL gene (deletions or frameshift, nonsense, or splice site mutations) observed in approximately 96–97% of patients with type 1 VHL
   b. VHL type 2
      i. With pheochromocytomas
      ii. Missense mutations observed in 92–98% of patients with type 2 VHL
   c. Subtypes of type 2 VHL
      i. VHL type 2A
         a) VHL without predisposition to renal cell carcinoma and pancreatic neuroendocrine tumor
         b) Specific mutations (Y98H, Y112H, V116F, L188V) in the *VHL* gene conferring an increased risk for VHL disease
      ii. VHL type 2B
         a) VHL with predisposition to renal cell carcinoma and pancreatic neuroendocrine tumor
         b) Specific mutations (R167Q, R167W) in the *VHL* gene conferring an increased risk for VHL disease
      iii. VHL type 2C
         a) VHL with only pheochromocytoma manifestation
         b) Specific mutations (V155L, R238W) in the *VHL* gene conferring an increased risk for VHL disease
3. Tumors/cysts linked to VHL disease, typically develop in the second, third, and fourth decades of life
   a. Retinal angioma/hemangioblastoma
      i. Responsible for the first manifestation of VHL in 50% of the patients
      ii. Retinal lesions
         a) Formerly called retinal angiomas
         b) Histologically identical to hemangioblastomas
         c) Identified in about 70% of the patients
         d) Bilateral in about 50% of the patients
         e) Multiple in about 66% of the patients
      iii. Complications when the condition is unrecognized and untreated at early stage
         a) Majority of retinal angiomas eventually hemorrhage
         b) Resulting in massive exudation and retinal detachment
         c) Ultimate development of neovascular glaucoma and blindness

b. Cerebellar hemangioblastomas (80% of CNS hemangioblastoma) (Friedrich 2001)
   i. The most common initial manifestation (34.9%)
   ii. Cumulative occurrence: 60.2%
   iii. The most common cause of death (47.7%)
   iv. Symptoms and signs
      a) Headache
      b) Slurred speech
      c) Nystagmus
      d) Positional vertigo
      e) Labile hypertension (without pheochromocytoma)
      f) Vomiting
      g) Wide-based gait
      h) Dysmetria
c. Spinal hemangioblastoma (20% of CNS hemangioblastoma) (Friedrich 2001)
   i. More specific for VHL disease
   ii. About 80% of cases are caused by VHL.
   iii. Cumulative occurrence (14.5%)
   iv. Symptoms and signs
      a) Pain
      b) Sensory and motor loss secondary to cord compression
d. Renal lesions
   i. Renal cysts: precursor lesions to clear cell renal cell carcinomas (75% of patients with VHL) which is a frequent cause of death
   ii. Hemangioblastoma
   iii. Renal cell adenoma
   iv. Renal cell carcinoma (20–40%)
e. Pheochromocytomas (tumor of adrenal medulla)
   i. Type 1 families
      a) Absence of pheochromocytomas
      b) Most type 1 families are affected by deletions or premature termination mutations
   ii. Type 2 families (7–20% of families)
      a) Presence of pheochromocytomas
      b) Most type 2 families are affected by missense mutations.
   iii. Arg238trp and arg238gln mutations: associated with a 62% risk for pheochromocytoma
   iv. Location of tumors
      a) Usually located in one or both adrenal glands
      b) May present anywhere along the sympathetic axis in the abdomen or thorax (paragangliomas) or head and neck (chemodectomas)
   v. Symptoms and signs
      a) Sustained or episodic hypertension
      b) Asymptomatic
f. Pancreatic lesions
   i. Type of lesions
      a) Simple pancreatic cysts
      b) Serous cystadenomas
      c) Pancreatic neuroendocrine tumors
   ii. Rarely causing endocrine or exocrine insufficiency unless the lesion is extensive
   iii. Occasionally causing biliary obstruction secondary to cysts in the head of the pancreas
g. Liver lesions
   i. Hemangiomas
   ii. Cyst
   iii. Adenoma
   iv. Carcinoid of the common bile duct
h. Splenic lesions
   i. Hemangiomas
   ii. Cyst
i. Pulmonary lesions
   i. Hemangiomas
   ii. Cyst
j. Bladder hemangioblastoma
k. Endolymphatic sac tumors of the inner ears (labyrinth)
   i. Tinnitus or vertigo
   ii. Deafness
l. Papillary cystadenomas of the epididymis in males
   i. Relatively common in males
   ii. Unilateral: rarely causing problem
   iii. Bilateral: infertility
m. Papillary cystadenomas of the broad ligament in females: much less common
n. Skin lesions
   i. Nevus
   ii. Café au lait spot
o. Bone lesions
   i. Hemangioma
   ii. Cyst

4. Diagnosis of VHL disease usually made on clinical grounds (Sanfilippo et al. 2003)
   a. A positive family history of VHL disease plus one of the following lesions (hemangioblastoma or visceral lesion):
      i. Retinal hemangioblastoma
      ii. Cerebellar hemangioblastoma

iii. Pheochromocytoma
iv. Renal cell carcinoma
v. Multiple pancreatic cysts

b. A negative family history of VHL disease needs one of the following (Friedrich 2001):
i. Two or more retinal or cerebellar hemangioblastomas, or
ii. One hemangioblastoma plus one visceral tumor

5. Prognosis
a. Life expectancy: <50 years
b. Most common causes of death
i. Renal cell carcinoma
ii. Cerebellar hemangioblastoma
c. Improved prognosis in patients with:
i. Earlier diagnosis
ii. Regular monitoring for predictable complications
iii. Followed by early interventions

Diagnostic Investigations

1. Biochemical test: elevated urinary catecholamines (VMA, metanephrine, and total catecholamine) suggesting pheochromocytoma even in the absence of hypertension
2. Eye examinations (Sanfilippo et al. 2003)
a. Ophthalmoscopy
b. Fluorescein angiography, a valuable tool useful in detecting subclinical fundus lesions
3. Radiography for rare associated bone cysts and osseous hemangiomas
4. Ultrasound examinations
a. Evaluation of the epididymis and broad ligament
b. Screening of the kidneys
5. CAT scan
a. To document the presence of CNS and visceral tumors
i. CNS hemangioblastomas
a) Cystic lesions (75%)
b) An enhancing lesion with multiple cystic areas (15%)
c) An enhancing solid mass (10%)
ii. Retinal hemangiomas too small to be depicted on CT scans, the diagnosis mainly dependent on the results of an ophthalmoscopic examination
iii. Papillary endolymphatic sac tumors presenting as a thin peripheral rim of calcification, representing the expanded cortex of petrous bone
b. Low sensitivity in the detection of renal cell carcinoma associated with VHL
i. Not reliable in differentiating cystic renal cell carcinomas, cancers within a cyst, and atypical cysts
ii. Impossible to differentiate a renal cell adenoma from a renal cell carcinoma
6. MRI to document the presence of CNS and visceral tumors
a. MRI appearances of a CNS hemangioblastoma: a well-demarcated cystic lesion with a highly vascular mural nodule that always abuts on the pia mater
b. Spinal hemangioblastomas: intramedullary tumors in most patients (75%) but may be radicular (20%) or intradural extramedullary (5%)
c. Pheochromocytoma: high signal intensity on T2-weighted MRI, differentiating it from adrenal cortical nodules
d. Endolymphatic sac tumors: high signal intensity with T1 imaging on MRI as a mass on the posterior wall of the petrous part of the temporal bone
7. Radionuclide studies
a. To provide an indication of metabolic activity of CNS tumors by positron emission tomography (PET) with 2-[fluorine 18]-fluoro-2-deoxy-D-glucose (FDG)
b. To detect bone metastases resulting from primary malignant tumor of bone of VHL
c. To assess renal function prior to resection of renal tumors
d. To detect pheochromocytoma using iodine-131 metaiodobenzylguanidine (^{131}I MIBG)
8. Angiography
a. Hemangioblastoma: a hypervascular lesion with intense and prolonged early enhancement of the mural nodule associated with dilated feeding vessels
b. Endolymphatic sac tumors
i. Hypervascular on angiography and the blood supply is derived from the external carotid artery

ii. Large tumors with an additional blood supply from the internal carotid artery and posterior circulation

9. Histologic features of VHL tumors (Sano and Horiguchi 2003)
   a. High degree of vascularization
   b. Presence of a clear cell component
10. NIH group recommendation for monitoring VHL patients and family members (Friedrich 2001)
   a. Birth to 2 years
      i. Annual physical examination
      ii. Annual ophthalmologic examination
   b. 2–10 years: urinary catecholamines every 1–2 years
   c. 11–19 years
      i. Biannual MRI of the brain and spine
      ii. Annual ultrasound examination of abdomen
      iii. CT scans of abdomen every 6 months if renal cysts or tumor present
   d. 20–59 years: annual CT scan of abdomen
   e. 60 years and above without VHL
      i. MRI of the brain and spine every 3–5 years
      ii. CT scan of the abdomen every other year
   f. Not necessary to monitor the family members identified previously with an empiric risk of 50% of being affected but are found not to have inherited the mutation
11. Molecular genetic analysis
   a. Considered standard for the evaluation of patients and families with suspected VHL disease: detects mutations in nearly 100% of affected individuals
   b. Clinical testing
      i. Sequence analysis
      ii. Deletion/duplication analysis
   c. Identification of *VHL* gene germ line mutations
      i. Identification of constitutional *VHL* gene deletions by FISH using probes from the *VHL* gene critical region in 3p25.3
         a) Offers a comprehensive way to screen for the presence of germ line deletions because it enables visualization of individual cells
         b) May identify mosaicism or cryptic translocation events that cannot be readily detected by other molecular strategies in patients with submicroscopic germ line deletions and a normal karyotype
         c) Enable to identify a de novo mosaic for the *VHL* gene deletion
      ii. Molecular diagnosis accomplished in virtually all families with classic VHL disease (families with multiple tumors) and in the majority of isolated patients with multiple VHL-associated tumors
         a) Qualitative and quantitative southern blotting to detect partial or complete gene deletions responsible for 28% of all cases
         b) DNA-sequence analysis of the protein-encoding region (all three exons) to detect point mutations in the remainder (72%) of the cases
   d. Mosaicism
      i. A potential cause for failure of molecular diagnosis in VHL
      ii. Individuals with mosaicism:
         a) Asymptomatic
         b) Manifesting as a single-system disease
         c) Manifesting as a multisystem disease
   e. Identification of a mutation in a proband allows the identification of mutation carriers among family members who do not yet exhibit any clinical manifestation of VHL

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. A small risk of having a sib with VHL since parental mosaicism accounts for some apparently sporadic or new cases of VHL
      ii. A 50% risk of having a sib with VHL disease if one of the parent is clinically affected or has a disease-causing *VHL* gene mutation
   b. Patient's offspring
      i. A 50% risk of inheriting the VHL disease-causing mutation
      ii. An individual mosaic for a disease mutation is at increased risk of having affected offspring, despite negative testing for the mutation by routine DNA diagnostic tests
2. Prenatal diagnosis available by molecular genetic testing of fetal DNA obtained from amniocentesis or CVS for pregnancies at 50% risk when the

disease-causing mutation has been identified in the affected parent

3. Preimplantation genetic diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family
4. Management
   a. Ocular management (Sanfilippo et al. 2003)
      i. Laser photocoagulation therapy or cryotherapy of retinal lesions
      ii. Several treatment strategies on the horizon that show promise for the ocular management of VHL disease
         a) Vascular endothelial growth factor (VEGF) inhibitors
         b) Use of radiotherapy, such as brachytherapy or linear accelerator–based radiosurgery
   b. In general, pancreatic NET with or without VHL disease shows a slow-growth phenotype and patients have a good prognosis. VHL patients at lower metastatic risk from pancreatic neuroendocrine tumor should be spared the risks of surgical resection (Tamura et al. 2010).
   c. Surgery: the mainstay of treatment for the tumors arising in patients with VHL disease (Sanfilippo et al. 2003)
      i. Renal cell carcinomas
         a) Partial nephrectomy or radiofrequency ablation to spare renal function if tumor involvement is not extensive
         b) Total nephrectomy often necessary for extensive tumor involvement
      ii. Resection of symptomatic brain stem hemangioblastomas, in general, is a safe and effective management strategy in patients with VHL disease. Most patients maintain their preoperative functional status, although long-term decline in functional status may occur due to VHL disease–associated progression (Wind et al. 2011).
      iii. Pregnant patients with spinal hemangiomas and VHL must be closely monitored for neurological compromise, as pregnancy can exacerbate both symptomatic and previously asymptomatic lesions. Patients must be evaluated on a case-by-case basis for surgical intervention, which should be carefully considered if clinical function begins to decline (Hayden et al. 2009).
   d. Stereotactic radiosurgery has been proposed as an alternative treatment strategy for CNS hemangioblastomas (Wind et al. 2011).

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Fig. 1 Retinal malformation secondary to von Hippel–Lindau disease

Fig. 3 A giant macroaneurysm of retinal vessels in a patient with von Hippel–Lindau disease

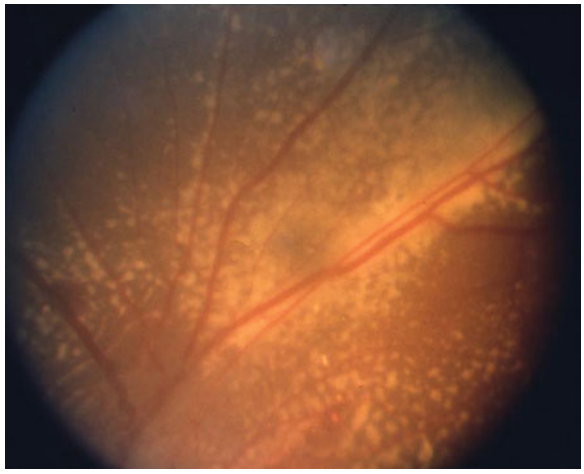

Fig. 2 Retinal exudates from vascular leakage in a patient with von Hippel–Lindau disease

Waardenburg Syndrome

Waardenburg syndrome is a rare autosomal dominant disorder characterized by patchy depigmentation, sensorineural hearing loss, and other developmental defects. There are four types of this syndrome. Types I and II are more common than types III and IV. The overall syndrome affects about 1 in 42,000 people (Waardenburg 1951).

Synonyms and Related Disorders

Klein-Waardenburg syndrome (Waardenburg syndrome with upper limb anomalies); Waardenburg syndrome with dystopia canthorum; Waardenburg syndrome with or without neurologic involvement; Waardenburg syndrome without dystopia canthorum; Waardenburg-Shah syndrome (Waardenburg syndrome with Hirschsprung disease)

Genetics/Basic Defects

1. Inheritance: genetic heterogeneity
   a. Autosomal dominant
      i. Type I (Waardenburg syndrome): presence of dystopia canthorum (lateral displacement of the inner canthi of the eyes in the presence of normal interpupillary distance)
      ii. Type II (Waardenburg syndrome with ocular albinism; absence of dystopia canthorum)
      iii. Type III (Klein-Waardenburg syndrome; presence of musculoskeletal abnormalities)
   b. Autosomal recessive: Type IV (Shah-Waardenburg syndrome or Waardenburg-Hirschsprung disease)
2. Cause (Read and Newton 1997)
   a. Type I and Type III: mutations in *PAX3* (paired box) gene on chromosome 2q35
   b. Type II
      i. Mutations in *MITF* (microphthalmia associated transcription factor) gene on chromosome 3p12-p14.1
      ii. Mutations in *SOX10* gene (encoding the Sry BOX10 transcription factor) on chromosome 22q13 (Bondurand et al. 2007; Iso et al. 2008)
      iii. Homozygous deletions of *SNAI2* in two patients (Sanchez-Martin et al. 2002)
   c. Type IV
      i. Mutations in the genes for endothelin-3 (*EDN3*) on chromosome 20q13.2-q13.3 or endothelin B receptor (*EDNRB*) on chromosome 13q22
      ii. Mutations in *SOX10* gene
3. Pathogenesis: None of the following theories explains all the features of Waardenburg syndrome (Dourmishev et al. 1999).
   a. Deficient neural crest theory
      i. Developmental abnormality of the neural crest as a cause of the disease
      ii. Supported by the association of Waardenburg syndrome with aganglionic megacolon
   b. As a part of the first arch syndrome theory
   c. A relationship of Waardenburg syndrome with status dysraphicus theory
   d. Intrauterine necrosis theory
4. Genotype-phenotype correlations: Specific mutations in the *PAX3* gene correlate with the expression of different features of Waardenburg syndrome.

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Clinical Features

1. Wide clinical spectrum
2. Facial appearance
   a. Dystopia canthorum (lateral displacement of the medial canthi)
   b. Bushy eyebrows with synophrys
   c. A narrow nose with prominent nasal root
   d. Marked hypoplasia of the nasal bone
   e. Short philtrum
   f. Short/retro positioned maxilla
3. Congenital sensorineural deafness (deaf-mutism): Waardenburg syndrome is the most common syndromal cause of deafness and is responsible for 2–3% of congenital deafness.
4. Pigmentary abnormalities
   a. Cutaneous pigmentary abnormalities
      i. Achromatic spots, with sharply defined irregular borders and containing scattered islands of hyperpigmention, resemble those of piebaldism.
      ii. Hyperpigmented macules on normally pigmented skin that have been described as a "patchy skin" and give the cases a "dappled appearance"
   b. Hair pigmentary abnormalities
      i. White forelock (may be evident at birth, soon afterwards, or develop later)
      ii. Premature graying of the scalp hair and of the eyebrows, cilia, or body hair
   c. Fundus pigmentary abnormalities
      i. Albinotic fundi (generalized decrease in retinal pigment)
      ii. Pigmentary mottling in the periphery
   d. Partial albinism
   e. Heterochromia (different color) of the iris
   f. Bilateral isohypochromia iridis (pale blue eyes)
   g. Ocular albinism (type II)
5. Musculoskeletal abnormalities (type III, Klein-Waardenburg syndrome) (Goodman et al. 1982)
   a. Ortho-osteomyo-dysplasia of the upper limbs
   b. Bilateral upper limb defects
   c. Flexion contractures
   d. Fusion of the carpal bones
   e. Syndactyly
6. Congenital aganglionic megacolon association (type IV, Shah-Waardenburg syndrome)
7. Occasional associated anomalies (da-Silva 1991)
   a. Cleft lip/palate
   b. Neural tube defects
   c. Facial asymmetry
   d. Facial palsy
   e. Hypokalemic periodic paralysis
   f. Preauricular pit
   g. Hypoplasia of the middle ear ossicles
   h. Blepharoptosis
   i. Microphthalmia
   j. Hypertelorism
   k. Iris coloboma
   l. Fixed dilated pupil, anterior lenticonus
   m. High-arched palate
   n. "Cupid bow" configuration of the upper lip
   o. Prognathism
   p. Microcephaly
   q. Mental retardation
   r. Esophageal atresia with tracheoesophageal fistula
   s. Imperforate anus
   t. Bifid spine
   u. Vertebral agenesis
   v. Absence of vagina and right adnexal uteri
   w. Syndactyly
   x. Cardiovascular anomalies
   y. Polythelia
   z. Urinary anomalies
   aa. Hyperkeratosis of palms and soles
   bb. Black forelock
   cc. Hyperpigmented skin lesions
8. Diagnostic criteria for Waardenburg type I and type II as proposed by the Waardenburg Consortium. To be affected with Waardenburg type I, an individual must have two major or one major plus two minor criteria. To be affected with Waardenburg type II, an individual should show two major features (with one major feature of an affected first-degree relative who should show two major features) (more stringent criteria by Liu et al. 1995) (Read and Newton 1997; Konno and Silm 2001).
   a. Major criteria
      i. Congenital sensorineural hearing loss
      ii. Pigmentary disturbances of iris
         a) Complete heterochromia iridium (two eye of different color)

b) Partial or segmental heterochromia (segments of blue or brown pigmentation in one or both eyes)
c) Hypoplastic blue eyes (characteristically brilliant blue in both eyes)
iii. Hair hypopigmentation (white forelock)
iv. Dystopia canthorum
v. Affected first-degree relatives
b. Minor criteria
i. Congenital leucoderma (several areas of hypopigmented skin)
ii. Synophrys or medial eyebrow flare
iii. Broad and high nasal root
iv. Hypoplasia of alae nasi
v. Premature graying of hair (scalp hair predominantly white before age 30)

Diagnostic Investigations

1. Audiologic evaluation for hearing loss
2. Histochemical studies of achromic skin
   a. Absent melanocytes
   b. Presence of only a few dihydroxyphenylalanine (dopa)-positive cells
3. Ultrastructural findings of depigmented skin
   a. Absence or dramatically reduced melanocytes
   b. Dendritic cells containing poorly melanized melanosomes
   c. Absence of melanosomes in the keratinocytes
4. Chromosome abnormalities observed in type I Waardenburg syndrome (Konno and Silm 2001)
   a. Inversion 2q35-q36.1
   b. Deletion 2q35-q36.2
   c. Del(2)(q34;q36.2)
5. Molecular studies of mutations for different types of Waardenburg syndrome (Konno and Silm 2001; Milunsky 2009)
   a. Testing methods
      i. Sequence analysis for gene mutations
      ii. Deletion/duplication analysis for gene deletions
   b. Different types of Waardenburg syndrome
      i. Waardenburg syndrome type I: *PAX3* gene mutation
      ii. Waardenburg syndrome type II: 15–20% of cases have heterozygous mutation in the *MITF* gene.
      iii. Waardenburg syndrome type III: interstitial deletion of chromosome 2 (2q35-q36.2) including the *PAX3* gene
      iv. Waardenburg syndrome type IV:
         a) Mutations in the gene encoding endothelin-3 (Edn 3) or one of its receptors, the endothelin-B receptor (Ednrb)
         b) Mutations in *SOX10*

Genetic Counseling

1. Recurrence risk
   a. Autosomal dominant inheritance
      i. Patient's sibs: not increased unless one of the parent is also affected or has germinal mosaicism (Kapur and Karam 1991)
      ii. Patient's offspring: 50%
   b. Autosomal recessive inheritance
      i. Patient's sibs: 25%
      ii. Patient's offspring: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis
   a. Possible when a mutation has been defined in the family
   b. Impossible to predict how severe the fetus will be affected
3. Preimplantation genetic diagnosis: available for families in which disease-causing mutation has been identified
4. Management (Konno and Silm 2001)
   a. No effective treatment available
   b. Photoprotection to protect the amelanotic areas from burning with sun exposure
      i. Sunscreens
      ii. Camouflage
         a) Hair dye
         b) Dermablend
   c. Autologous grafts or transplants of autologous cultured melanocytes used to repigment the areas of hypomelanosis (piebaldism)
   d. Important to diagnose and improve hearing loss: auditory habilitation with a cochlear implant with excellent prognosis (Cullen et al. 2006)
   e. Folate supplementation during pregnancy advisable for a fetus at risk for Waardenburg type I, although the risk for neural tube defect is low

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Fig. 1 (**a**, **b**) A 3-week-old infant with Waardenburg syndrome showing white forelock and vitiligo involving symmetrically anterior lower chest, anterior upper abdomen, lower legs, elbows, and fingers

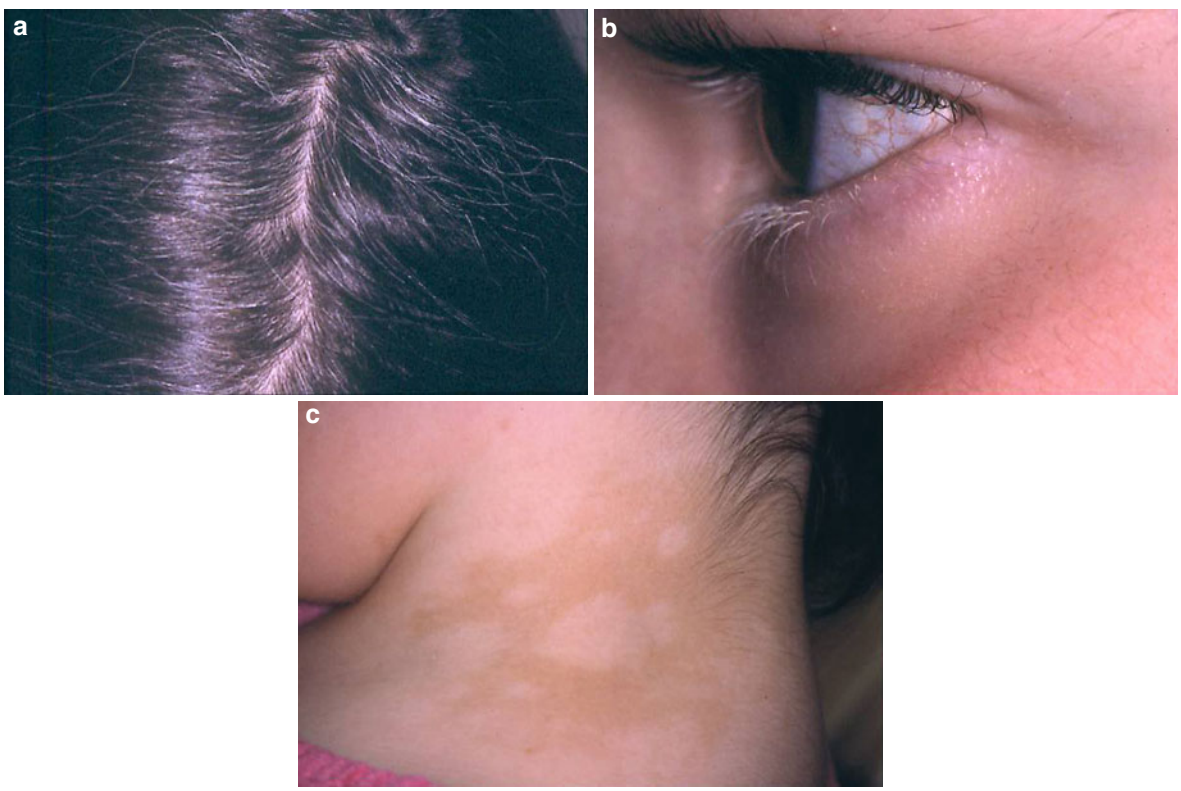

Fig. 2 (**a**–**c**) An adult patient with Waardenburg syndrome showing white forelock, white eyelashes, and patchy hyperpigmented macules on the neck

Fig. 3 A patient with Waardenburg syndrome. Notice grey forelock hair, broad-based brow, and increased interpalpebral space

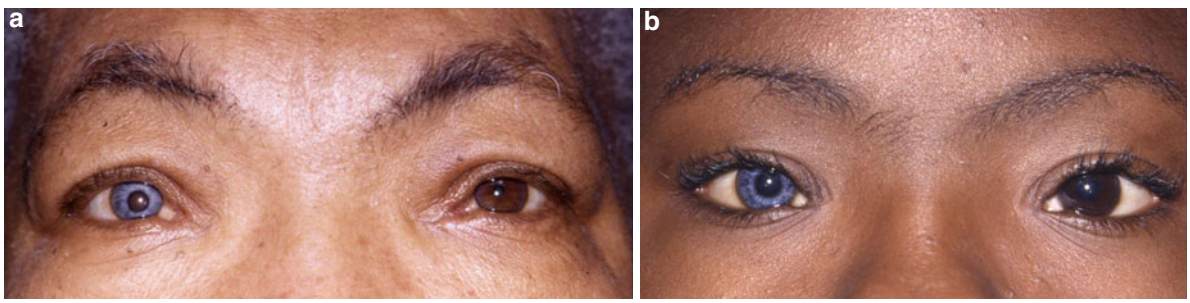

Fig. 4 (**a**, **b**) Two patients with Waardenburg syndrome showing iris heterochromia

Weill–Marchesani Syndrome

Weill–Marchesani syndrome (WMS), a rare connective tissue disorder, was first described by Weill in 1932 and further delineated by Marchesani in 1939 (Weill 1932; Marchesani 1939). It is also known as spherophakia-brachymorphia syndrome or congenital mesodermal dysmorphodystrophy.

Synonyms and Related Disorders

Congenital mesodermal dysmorphodystrophy; Glaucoma-lens ectopia-microspherophakia-stiffness-shortness syndrome; Spherophakia-brachymorphia syndrome

Genetics/Basic Defects

1. Despite clinical homogeneity, two modes of inheritance have been reported.
2. Autosomal dominant inheritance
   a. Caused by heterozygous mutations within the fibrillin-1 gene which is mapped to chromosome 15q21.1
   b. Autosomal dominant WMS and Marfan syndrome appear to be allelic conditions at the fibrillin-1 locus.
3. Autosomal recessive inheritance with occasional brachymorphism in heterozygotes
   a. Homozygosity mapping of an autosomal recessive WMS gene to chromosome 19p13.3–p13.2
   b. Missense *ADAMTS10* (a disintegrin-like and metalloprotease with thrombospondin motifs 10) mutation (c.73G>A; p.Ala25Thr) was recently identified to cause recessive Weill–Marchesani syndrome.
   c. ADAMTS10 is a member of the extracellular matrix protease family and is expressed in skin, fetal chondrocytes, and fetal and adult hearts.

Clinical Features

1. Unable to distinguish autosomal recessive and autosomal dominant WMS by clinical features alone
2. Proportionate short stature
   a. Heights of adult males: 142–169 cm
   b. Heights of adult females: 130–157 cm
3. Ophthalmological features
   a. Microspherophakia (small spherical lens): most important clinical feature of the syndrome
   b. Ectopia lentis: usually results in downward displacement of the lens
   c. Lenticular myopia: usually the first ophthalmologic finding and is progressive
   d. Secondary glaucoma
      i. Resulting from pupillary block in most cases due to forward movement of the lens or by dislocation of the lens into the anterior chamber
      ii. The most serious complication because it can lead to blindness
4. Presenile vitreous liquefaction has been described in a large family with autosomal dominant WMS.
5. Skeletal features
   a. Brachydactyly
   b. Enlarged interphalangeal joints
   c. Joints stiffness

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   d. Pectus excavatum
   e. Scoliosis
6. Occasional cardiac features
   a. Mitral valve prolapse
   b. Mitral valve insufficiency
   c. Mitral valve stenosis
   d. Pulmonary hypertension
   e. Subvalvular fibromuscular aortic stenosis
   f. Congenital pulmonic valve stenosis
   g. Patent ductus arteriosus
   h. Ventricular septal defect
   i. Prolonged QT interval
7. Normal intelligence

Diagnostic Investigations

1. Confirmation by molecular genetic testing in addition to clinical features
   a. *ADAMTS10* sequence analysis available clinically to identified homozygous mutations in autosomal recessive WMS
   b. Significance of mutations in *FBN1* in autosomal dominant WMS is unclear.
2. Carrier testing for relatives at risk requires prior identification of the disease-causing mutations in the family.
3. ECG to detect prolonged QT interval
4. Electron microscopy and immunological studies of skin fibroblasts from WMS patients suggest that the syndrome is associated with impairment of the extracellular matrix.

Genetic Counseling

1. Recurrence risk
   a. Patient's sib
      i. Autosomal dominant inheritance
         a) Fifty percent risk if one parent is affected
         b) Recurrence risk: small if neither parent is affected
      ii. Autosomal recessive inheritance: 25% affected; 50% carriers
   b. Patient's offspring
      i. Autosomal dominant inheritance: 50% risk
      ii. Autosomal recessive inheritance: 100% obligatory carriers for a disease-causing mutation in the *ADAMTS10* gene
2. Prenatal diagnosis: available for pregnancies at risk for autosomal recessive WMS provided prior identification of the disease-causing mutations in the family is known
3. Management
   a. Early detection and removal of an ectopic lens to decrease the possibility of pupillary block and glaucoma
   b. Medical treatment of glaucoma: difficult because of paradoxical response to miotics and mydriatics
   c. Surgical management of glaucoma
      i. Peripheral iridectomy to prevent or relieve pupillary block
      ii. Trabeculectomy in advanced chronic angle closure glaucoma
   d. Airway management: difficult during anesthesia because of stiff joints, poorly aligned teeth, and maxillary hypoplasia
   e. Periodic ophthalmic examinations for early detection and removal of an ectopic lens
   f. Avoid ophthalmic miotics and mydriatics to prevent inducing pupillary block.

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Fig. 1 (**a**–**c**) A 14-year-old female with Weill–Marchesani syndrome. She had short stature, spherophakia, and brachydactyly. She was again followed at 30 years of age with findings of short stature, shallow orbits, small eyes, myopia, brachydactyly, and enlarged and stiff interphalangeal joints. Her daughter has small lens/cornea, short stature, and brachydactyly

Williams Syndrome

In 1961, Williams et al. described children with a constellation of abnormalities including "unusual" facial features, growth retardation, supravalvular aortic stenosis, and cognitive impairment. In 1962, Beuren described a series of children with similar features, dental anomalies, peripheral pulmonary artery stenosis, and friendly personalities. Consequently, Williams syndrome is also known as Williams-Beuren syndrome. These characteristics are observed in virtually every patient with Williams syndrome, now known to be caused by a microdeletion of chromosome 7q11.23. The incidence of the syndrome is estimated to be between 1 in 20,000 and 1 in 50,000 live births.

Synonyms and Related Disorders

Chromosome 7q11.23 deletion syndrome; Williams–Beuren syndrome

Genetics/Basic Defects

1. Inheritance
   a. Sporadic new deletion in most cases
   b. Rare autosomal dominant transmission of microdeletion involving the Williams syndrome critical region in a few cases
2. Association of the elastin (*ELN*) gene disruption by chromosome translocation or partial deletion involving chromosome 7q11.23 and the supravalvular aortic stenosis: the first clue to the location of the Williams syndrome microdeletion
3. Caused by the haploinsufficiency of genes within a microdeletion of the long arm of chromosome 7 (7q11.23)
4. Deletions in the *ELN* gene (Osborne 1999; Donnai and Karmiloff-Smith 2000)
   a. Mechanism: deletions typically caused by unequal recombination during meiosis
   b. Deletion with equal frequency on the maternally or paternally inherited chromosome 7
   c. A total of at least 16 genes mapped within the commonly deleted interval
   d. *ELN* gene mapped approximately at the center of the deletion
   e. Responsible for supravalvular aortic stenosis and other vascular stenoses
   f. Possibly responsible for some of the connective tissue problems
      i. Lax joints
      ii. Premature aging of the skin
      iii. Joint contractures
      iv. A hoarse voice
      v. Bladder and bowel diverticula
      vi. Hernias
   g. Majority of patients with Williams syndrome with large deletion spans (approximately 1.5 Mb of DNA), which contain many genes that contribute to the additional clinical symptoms not seen in patients with isolated supravalvular aortic stenosis
   h. Genetic studies demonstrate that isolated nonsyndromic supravalvular aortic stenosis is associated with intragenic deletions within the *ELN* gene, while Williams syndrome involves deletions spanning the entire *ELN* gene (Lashkari et al. 1999).

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i. Other genes identified in the commonly deleted region: e.g., *LIMK1*, *CYLN2*, *GTF21RD1*, and *STX1A* (Jurado 2003)

Clinical Features

1. Characteristic dysmorphic facies, frequently referred to as elfin facies (100%). Effort must be made to curtail the use of "elfin facies" to denote a resemblance to a mythological creature since the term is not well received by family members (Lashkari et al. 1999; AAP 2001).
   a. Periorbital fullness
   b. Stellate lacy iris pattern
   c. Short nose with bulbous nasal tip
   d. Flat nasal bridge
   e. Prominent full cheeks
   f. Long philtrum
   g. Wide mouth
   h. Full lips
   i. Mild micrognathia
   j. Long narrow face and long neck in older children and adults
2. Cardiovascular diseases
   a. Supravalvular aortic stenosis (80%), often a progressive condition that may require surgical repair
   b. Generalized arteriopathy (narrowing of arteries secondary to abnormal elastin protein, an important component of elastic fibers in the arterial wall)
      i. Peripheral pulmonary artery stenosis often present in infancy and usually improves over time
      ii. Possible worsening over time of the coarctation of the aorta, renal artery stenosis, and systemic hypertension
      iii. Possible narrowing of any arterial wall since elastin protein is an important component of elastic fibers in the arterial wall
   c. Other congenital cardiac defects
      i. Mitral valve prolapse (11.6%)
      ii. Bicuspid aortic valve (15%)
      iii. Aortic hypoplasia
      iv. Septal defects
      v. Left ventricular hypertrophy
3. Variable mental retardation (75%)
4. Characteristic cognitive/behavioral profile (90%)
   a. Characteristic behavioral pattern
      i. Relative preservation of linguistic abilities
      ii. Gross deficiencies in visual-spatial processing and motor skills
   b. Motor disabilities affecting balance, strength, coordination, and motor planning
   c. Delayed speech acquisition, followed by excessive talking ("cocktail party" verbal abilities)
   d. Overfriendliness and an empathetic nature
   e. Uncontrollable loquacity
   f. Behavioral problems
      i. Hypersensitivity to sound (hyperacusis)
      ii. Sleep problems
      iii. Attention deficit/hyperactivity disorder (ADHD)
      iv. Anxiety
      v. Distractability
      vi. Inflexibility
      vii. Rituralism
5. Idiopathic infantile hypercalcemia (15%)
   a. Symptoms and signs of hypercalcemia (usually resolves during childhood)
      i. Extreme irritability
      ii. Vomiting
      iii. Constipation
      iv. Muscle cramps
   b. Possible lifelong persistence of abnormal calcium and vitamin D metabolism
   c. Hypercalcinuria predisposing to nephrocalcinosis
6. Other features
   a. Growth
      i. Postterm birth (>41 weeks)
      ii. Failure to thrive
      iii. Short stature (50%)
      iv. Hypothyroidism
      v. A premature and abbreviated pubertal growth spurt
   b. CNS
      i. Muscle hypotonia early
      ii. Muscle tone increases with age; hypertonia in some cases
      iii. Poor coordination
      iv. Awkward gait
      v. Chiari I malformation
      vi. Hyperreflexia of the lower extremities
   c. EENT
      i. Ocular findings
         a) Strabismus

b) Hyperopia
c) Stellate iris
d) Retinal vessel tortuosity
ii. Chronic otitis media
iii. Dental abnormalities
a) Hypodontia/Microdontia
b) Malocclusion
c) Overbite
d) Excessive interdental spacing
e) Small roots
f) High incidence of caries
iv. A hoarse or brassy voice
d. GI
i. Difficulty feeding
ii. Gastroesophageal reflux/vomiting
iii. Prolong colic
iv. Bowel diverticula
v. Hernias
vi. Rectal prolapse
vii. Constipation
viii. Peptic ulcers
e. Genitourinary (18%)
i. Bladder diverticula: the most common defects
ii. Renal artery stenosis
iii. Renal agenesis
iv. Duplicated kidneys
v. Horseshoe kidney
vi. Renal cysts
vii. Nephrocalcinosis
viii. Vesicouriteral reflux
f. Orthopedic problems
i. Low/hoarse voice
ii. Hernias
iii. Joint laxity mostly during infancy
iv. Joint contractures may develop by childhood and adolescence (50%).
v. Radioulnar synostosis
vi. Kyphosis
vii. Lordosis
viii. Scoliosis
ix. Hallux valgus
x. Hypoplastic nails
xi. Clinodactyly of fifth fingers

Diagnostic Investigations

1. Echocardiography for cardiac lesions
2. Ultrasonography
   a. Bladder and kidneys
   b. Intravascular ultrasound imaging: to detect vascular wall thickening with secondary lumen narrowing
3. Serum creatinine level
4. Blood calcium levels to detect hypercalcemia during early infancy
5. Thyroid function test
6. Ophthalmologic evaluation for strabismus and retinal vessel tortuosity
7. Urinalysis to detect hypercalcinuria
8. Renal ultrasound for possible nephrocalcinosis if hypercalcinuria is noted
9. Radiography: osteosclerosis of the metaphyses of long bones, the skull vault, or lamina dura of the alveolar bone in adolescence and adulthood, if overt hypercalcemia is present
10. Full cytogenetic studies
    a. Larger deletions detectable by standard cytogenetic techniques, especially by high-resolution chromosome analysis
    b. To rule out possible chromosomal rearrangements involving the 7q11.23 locus as well as any other cytogenetic abnormalities
11. Fluorescence in situ hybridization (FISH) with a cosmid probe corresponding to *ELN* for diagnostic testing: remains the most widely used laboratory test
    a. Ninety-nine percent of the patients with a hemizygous submicroscopic deletion of 7q11.23 detectable by FISH
    b. Cases undetectable by FISH
       i. Rare cases with a smaller deletion which does not fully encompass the FISH probe
       ii. Cases with phenocopies of Williams syndrome with same clinical phenotype produced by mutation or deletion of other gene(s)
       iii. Cases with a Williams syndrome–like phenotype associated with various cytogenetic rearrangements
12. Other diagnostic laboratory tests (Pober 2010)
    a. Microsatellite marker analysis
    b. Multiplex ligation-dependent probe amplification
    c. Quantitative polymerase-chain-reaction assay
    d. Array comparative genomic hybridization

Genetic Counseling

1. Recurrence risk
   a. Patient's sib (Lashkari et al. 1999)
      i. Recurrence risk low (<1%) (most cases are sporadic and neither parent is affected)
      ii. Presence of a small theoretical risk of germ line mosaicism in an unaffected parent (Kara-Mostefa et al. 1999)
      iii. If a parent is affected, the risk is 50%.
   b. Patient's offspring: 50% recurrence risk of having an affected offspring in individuals who have the deletion of the Williams syndrome critical region (parent-to-child transmission observed occasionally)
2. Prenatal diagnosis by amniocentesis or CVS
   a. Rarely utilized because most cases are sporadic and no prenatal indicators exist for low-risk pregnancies
   b. Utilized for pregnancies at 50% risk of having Williams syndrome
   c. FISH probe covering approximately 180 kb of the critical region deleted in the Williams syndrome including *ELN* gene, lim-kinase1 (*LIMK1*), and the D7S613 locus
3. Management
   a. Management of hypercalcemia (Lashkari et al. 1999)
      i. Limit high calcium food
      ii. Avoid preparations containing vitamin D
   b. Supravalvular aortic stenosis (a life-threatening component of the phenotype): surgically correctable
   c. Early dental care
   d. Education and vocational concerns
      i. Early daily learning activities and strategies
         a) Auditory cues
         b) Music activities, singing/rhyming songs, and toys with soft sounds
         c) Teaching communication skills through daily routines
         d) Use of language expansions and parallel talk
      ii. Special education for older children
      iii. Restrictive levels of care required for most adult patients
   e. Social and emotional concerns
      i. At increased risk for exploitation and abuse
      ii. Teaching of appropriate social skills
   f. Psychotherapy
      i. Verbally oriented psychotherapy
      ii. Group therapy

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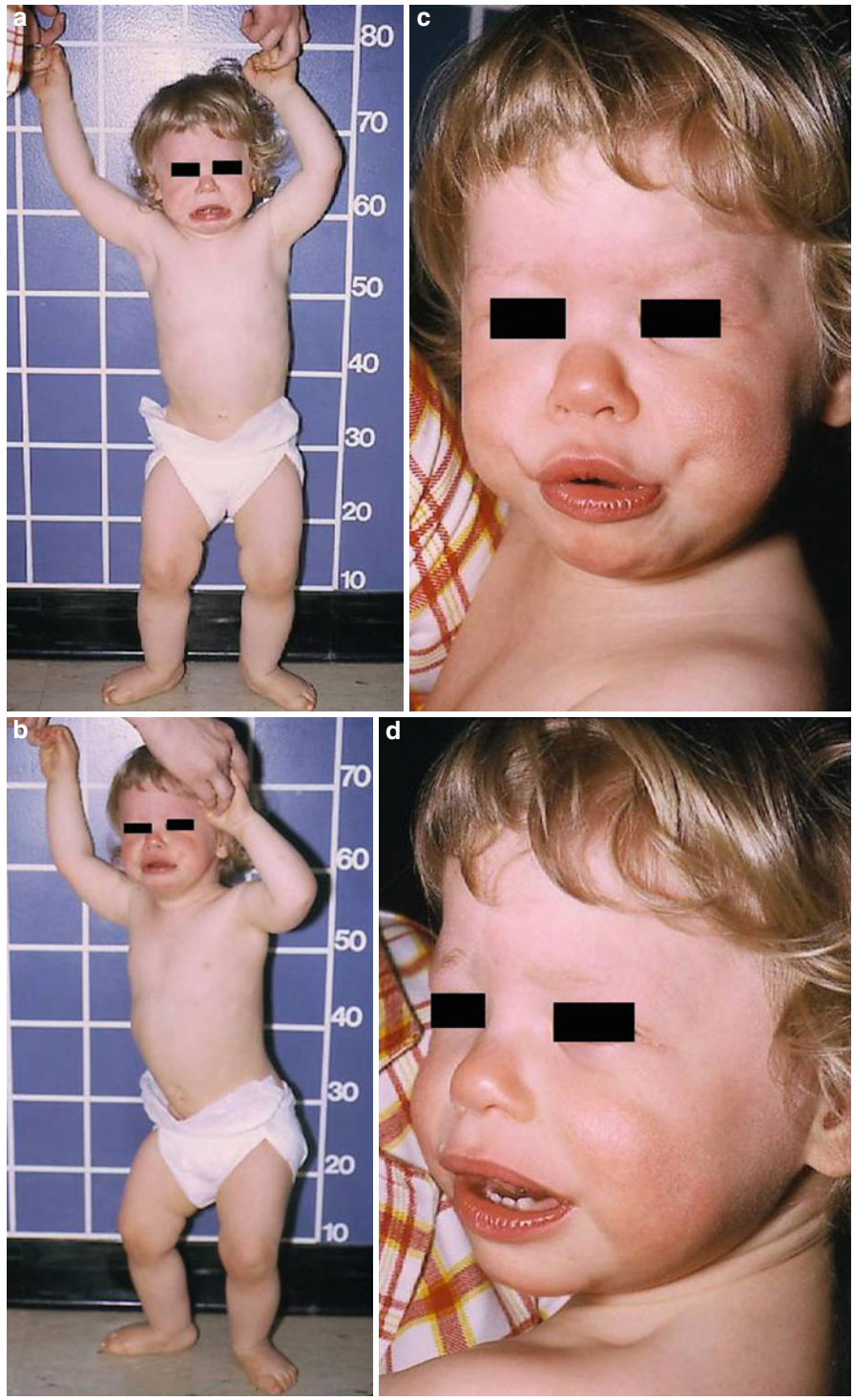

Fig. 1 (**a**–**d**) An infant with Williams syndrome showing periorbital fullness, stellate lacy iris pattern, flat nasal bridge, short nose with bulbous tip, wide mouth, and full cheeks and lips

Fig. 2 (**a**–**d**) A child with Williams syndrome showing similar features

Fig. 3 (**a**–**f**) Two young children with Williams syndrome showing characteristic facial appearance

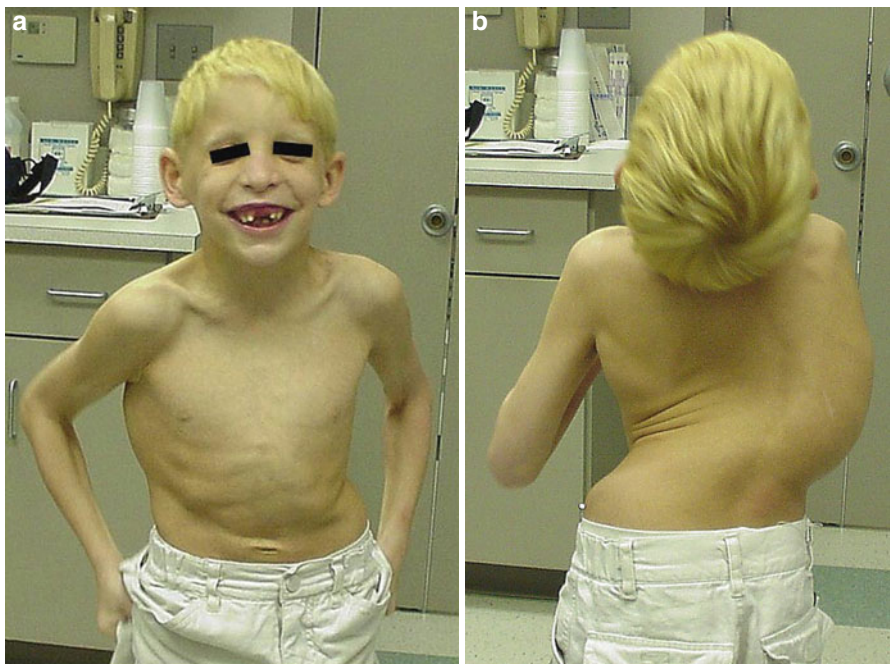

Fig. 4 (**a**, **b**) A child with Williams syndrome and severe scoliosis

Fig. 5 (**a**, **b**) An adult with Williams syndrome confirmed by FISH studies

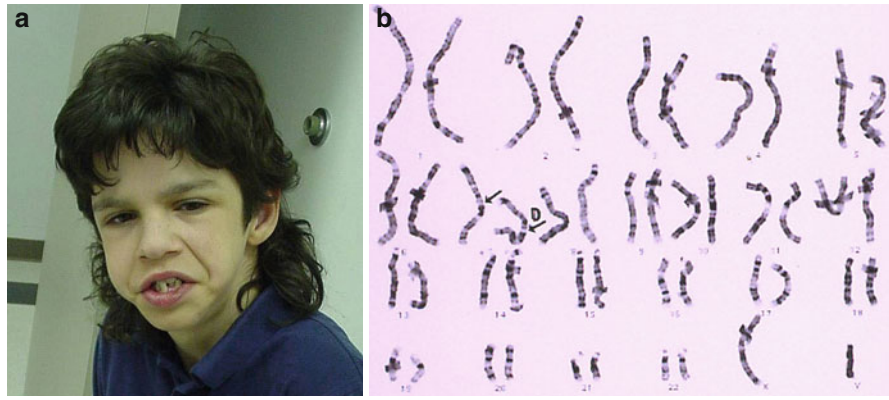

Fig. 6 (**a**, **b**) A child with Williams syndrome. A G-banded karyotype showing del(17q11) (*arrow* with D)

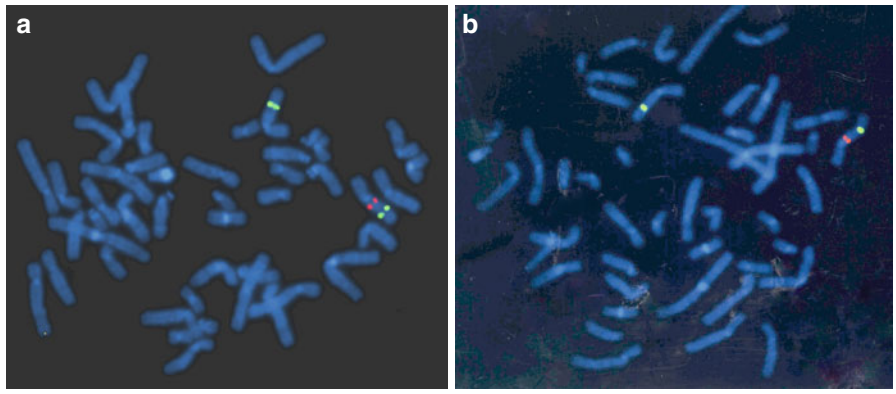

Fig. 7 (**a**, **b**) FISH showing the classic microdeletion seen in Williams syndrome (7p11.23) [LSI® Williams Syndrome (Elastin Gene) Region Probe, Vysis/Abbott]. The metaphase cells show only one chromosome 7 homologue with the orange signal (normal chromosome 7). The hemizygous deletion is shown on the chromosome with only the green loci [internal control probes for D7S486 and D7S522 (7q31)]

Wolf-Hirschhorn Syndrome

Wolf-Hirschhorn syndrome (WHS) is a chromosome 4p deletion syndrome, first described by Cooper and Hirschhorn in 1961, followed by the report of Wolf et al. in 1965 (Wolf et al. 1965). The incidence is estimated to be approximately 1 in 50,000 births.

Synonyms and Related Disorders

Chromosome 4p16.3 deletion syndrome; Pitt-Rogers-Danks syndrome

Genetics/Basic Defects

1. Caused by the deletion of the distal short arm of chromosome 4
   a. Variable size of the deletion
   b. Deletion of the terminal band (4p16.3): essential for full expression of the phenotype
   c. Identification of a 165 kb minimal critical region (WHSCR) within 4p16.3
   d. Mechanism of deletions
      i. De novo deletions (75%): interstitial deletion of preferential paternal origin in 85–90%
      ii. Deletions resulting from unusual cytogenetic abnormality (12%) such as ring chromosome 4
      iii. Deletions resulting from unbalanced product of a parental chromosomal rearrangement, usually of a reciprocal translocation (10–15%)
2. Types of chromosome abnormalities
   a. Detectable by conventional cytogenetic technique: large deletions
   b. Detectable only by molecular methods
      i. Terminal microdeletions
      ii. Interstitial microdeletions
      iii. Cryptic translocations
3. Genotype-phenotype correlation (Zollino et al. 2003, 2008)
   a. Patients with a large 4p16.3 deletion, averaging between 5 and 18 Mb: causing the widely recognizable WHS phenotype
      i. Severe mental and growth retardation
      ii. Major malformations
      iii. Seizures
      iv. Characteristic facial appearance with wide forehead, large and protruding eyes, hypertelorism, prominent glabella, down-turned mouth, and micrognathia
   b. Patients with a 4p16.3 microdeletion not exceeding 3.5 Mb
      i. Milder phenotype
      ii. Lack major congenital malformations
   c. Patients with a very large deletion exceeding 22–25 Mb, causing a severe phenotype that can hardly be defined as typical WHS
   d. Using genotype-phenotype correlation analysis in eight informative patients, Zollino et al. (2003) characterized the following distinctive WHS clinical signs that represent the minimal diagnostic criteria for this condition, and mapped this basic phenotype outside the currently defined WHSCR and designated as a new critical region, WHSCR-2.
      i. Presence of typical facial appearance
      ii. Mental retardation
      iii. Growth delay

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iv. Congenital hypotonia
v. Seizures

4. *LETM1*
   a. A gene deleted in WHS, encodes mitochondrial protein
   b. Current evidence suggests that at least some (neuromuscular) features of WHS may be caused by mitochondrial dysfunction.

Clinical Features

1. Maternal gestational history
   a. Intrauterine growth retardation
   b. Decreased fetal movements
   c. Small placenta
2. Developmental history
   a. Delayed psychomotor development
   b. Difficulty in ambulation, often with ataxic gait
   c. Seizures (50% of cases)
3. Behavior history
   a. Stereotypes
      i. Holding the hands in front of the face
      ii. Hand washing or flapping
      iii. Patting self on chest
      iv. Rocking
      v. Head shaking
      vi. Stretching of legs
   b. Absence of speech
   c. Babbling or guttural sounds, occasionally modulated in a communicative way
   d. Comprehension limited to simple orders or to a specific context
   e. Affect disorder that improves over time
   f. Walking with or without support
   g. Self-feeding
   h. Helps in dressing and undressing self
   i. Improved abilities and adaptation to new situations
   j. Communicative abilities and verbal comprehension with extension of the gesture repertoire and decreased occurrence of withdrawal and anxiety behaviors
4. Growth: Severe growth retardation (short stature)
5. CNS
   a. Profound mental retardation
   b. Microcephaly
   c. Seizures (50–100%)
   d. Congenital hypotonia with muscle hypotrophy particularly of the lower limbs
   e. Malformation (33%)
      i. Hypoplasia of cerebellum
      ii. Cavum or absent septum pellucidum
      iii. Agenesis of corpus callosum
      iv. Hypoplasia or absence of olfactory bulbs and tracts
      v. Microgyria
      vi. Migration defects
      vii. Hydrocephalus
6. Skull
   a. Frontal bossing
   b. High frontal hairline
   c. Hemangioma over forehead or glabella
   d. Scalp defect with or without underlying bony defect
7. Face: characteristic dysmorphic features collectively described as “Greek warrior helmet” facies (prominent glabella, hypertelorism, broad beaked nose, and frontal bossing)
8. Eyes
   a. Hypertelorism
   b. Down-slanting palpebral fissures
   c. Epicanthal folds
   d. Strabismus
   e. Coloboma
   f. Proptosis due to hypoplasia of orbital ridges
   g. Ectopic pupils
   h. Esotropia
   i. Ptosis
   j. Microphthalmia
   k. Megalocornea
   l. Sclerocornea
   m. Cataracts
   n. Hypoplastic anterior chamber and ciliary body of iris
   o. Persistence of lenticular membrane
   p. Hypoplastic retina with formation of rosettes
   q. Cup-shaped optic disks
   r. Congenital nystagmus
   s. Early-onset glaucoma
   t. Rieger anomaly
9. Nose
   a. Broad or beaked nose
   b. Nasolacrimal duct stenosis or atresia

10. Mouth
    a. Short upper lip
    b. Short philtrum
    c. Cleft lip or palate
    d. Bifid uvula
    e. Carplike mouth
    f. Micrognathia
    g. Retrognathia
11. Ears
    a. Low-set ears
    b. Large, floppy, or misshapen ears
    c. Microtia
    d. Preauricular dimples
    e. Chronic otitis media with effusion
    f. Sensorineural hearing loss
12. Cardiovascular
    a. Atrial septal defect
    b. Ventricular septal defect
    c. Persistent left superior vena cava
    d. Valve abnormalities
    e. Complex cardiac defects
13. Pulmonary
    a. Bilateral bilobed or trilobed lungs
    b. Lung hypoplasia secondary to diaphragmatic hernia
14. GI anomalies
    a. Diastasis recti
    b. Umbilical or inguinal hernias
    c. Accessory spleens
    d. Absent gallbladder
    e. Diaphragmatic hernia
    f. Intestinal malrotation
15. Genitourinary anomalies (25%)
    a. Hypoplastic kidneys
    b. Cystic dysplastic kidneys
    c. Unilateral renal agenesis
    d. Hydronephrosis
    e. Exstrophy of the bladder
    f. Hypoplastic external genitalia
    g. Cryptorchidism and hypospadias in males
    h. Hypoplastic müllerian derivatives (i.e., agenesis of vagina, cervix, or uterus; hypoplastic uterus; ovarian streaks) in females
16. Skeletal anomalies (60–70%)
    a. Long slender fingers with additional flexion creases
    b. Long narrow chest
    c. Hypoplastic widely spaced nipples
    d. Hypoplasia or duplication of thumbs and great toes
    e. Talipes equinovarus
    f. Hypoplasia of pubic bones
    g. Vertebral and rib anomalies
    h. Defective calvarium ossification
    i. Scoliosis
    j. Kyphosis
    k. Osteoporosis
    l. Delayed bone maturation
    m. Sacral dimple
17. Infection-prone, immunodeficiency
18. Malignant hematological disorders
    a. Myelodysplastic syndrome
    b. Leukemia
19. Dermatoglyphics
    a. Hypoplastic dermal ridges
    b. Transverse palmar creases (25%)
    c. Excess of digital arches
    d. t or t′
20. Pitt-Rogers-Danks syndrome (PRDS)
    a. Phenotypic overlap with WHS
        i. Prenatal and postnatal growth retardation
        ii. Microcephaly
        iii. Seizures
        iv. Developmental delay
        v. Facial features
            a) A wide mouth
            b) Short upper lip
            c) Flat philtrum
            d) Beaked nose
            e) Prominent eyes
            f) Maxillary hypoplasia
    b. Microdeletion of 4p16.3 detected in most cases
    c. Current evidence suggests that PRDS is not a separate clinical entity but may represent the milder end of the WHS spectrum (Battaglia and Carey 1998).
21. Fetal phenotype
    a. Major anomalies
        i. Intrauterine growth retardation
        ii. Microcephaly
        iii. Cleft palate
        iv. Corpus callosum agenesis
        v. Ventricular septal defect

vi. Diaphragmatic hernia
vii. Renal hypoplasia

b. Minor anomalies
i. Scalp defect
ii. Hypertelorism usually with a prominent glabella
iii. Pulmonary isomerism
iv. Common mesentery
v. Hypospadias
vi. Sacral dimple

22. Prognosis
a. Crude infant mortality rate: 17%
b. Mortality rate in the first 2 years: 21%
c. Cases with large de novo deletions are more likely to die than those with smaller deletions.
d. Follow-up of patients, spanning 23 years, showed a slow but constant evolution over time, in all areas (Battaglia et al. 2008).
i. There was an improvement of the motor, and the communicative skills, and of the verbal comprehension with extension of the gesture repertoire, and a reduction of isolation and anxiety
ii. Forty-five percent of patients were able to walk, either independently or with support (range: 2–12 years); 18% could help dressing and undressing themselves and doing simple household tasks
e. Causes of death
i. Birth anoxia
ii. Withdrawal of treatment after premature delivery
iii. Lower respiratory tract infections
iv. Sudden unexplained death
v. Congenital anomalies, such as congenital heart disease, dysplastic kidneys, renal hypoplasia, diaphragmatic hernia, and pulmonary hypoplasia

Diagnostic Investigations

1. Conventional cytogenetic studies: most common method to detect chromosome arm 4p deletions (60–70% of deletions)
2. High-resolution cytogenetic studies: to detect smaller deletions of chromosome band 4p16.3
3. Fluorescence in situ hybridization (FISH) using Wolf-Hirschhorn critical region probe: detecting >95% of deletions. Molecular cytogenetic studies using FISH allow the diagnosis to be made in patients with very small deletions or cryptic translocations. FISH uses genetic markers that have been precisely localized to the area of interest. The absence of signal from either the maternal or the paternal allele for the marker is indicative of monosomy for that chromosomal region.
4. Array comparative genomic hybridization (aCGH)
a. A new technology that can analyze the entire genome at a significantly higher resolution over conventional cytogenetics to characterize unbalanced rearrangements
b. 33 patients with WHS were analyzed using aCGH (South et al. 2008).
i. Observation of a much higher than expected frequency of unbalanced translocations (15/33, 45%)
ii. 7 of these 15 cases were cryptic translocations not detected by a previous karyotype combined with WHS-specific FISH
5. Immune workup
a. Common variable immunodeficiency
b. Immunoglobulin A (IgA) and immunoglobulin G2 (IgG2) subclass deficiency
c. IgA deficiency
d. Impaired polysaccharide responsiveness
e. Normal T cell immunity
6. Radiography
a. Delayed bone maturation
b. Microcephaly
c. Hypertelorism
d. Micrognathia
e. Anterior fusion of vertebrae
f. Fused ribs
g. Dislocated hips
h. Proximal radioulnar synostosis
i. Clubfeet
7. Echocardiography to detect heart defects
8. Renal ultrasound to detect renal anomalies
9. MRI and CT scans to demonstrate underlying brain pathology including agenesis of corpus callosum and ventriculomegaly
10. EEG for seizure monitoring
11. Swallowing study for feeding difficulty

12. Comprehensive audiologic and otologic evaluation to rule out possible hearing impairment
13. Ophthalmologic examination
14. Developmental testing
    a. Speech and motor evaluation
    b. Appropriate psychometric evaluation
15. Growth charts are available from 0 to 4 years of age, based on the study of 101 individuals (Anntonius et al. 2008). Use of these specific growth charts is recommended because standard growth charts are inapplicable for patients with WHS.

Genetic Counseling

1. Recurrence risk
    a. Patient's sib
        i. De novo deletion cases: no significant increased risk
        ii. Deletion resulting from a parental chromosomal rearrangement: increased risk for unbalanced product in offspring
    b. Patient's offspring: reproduction unlikely due to mental retardation
2. Prenatal diagnosis available to families in which one parent is known to be a carrier of a chromosome rearrangement by amniocentesis, CVS, or PUBS
    a. Ultrasonography to detect in utero manifestation of distinct phenotype
        i. Severe intrauterine growth retardation
        ii. Microcephaly
        iii. Hypertelorism, usually with prominent glabella
        iv. Micrognathia
        v. Cleft lip and palate
        vi. Diaphragmatic hernia
    b. Chromosome analysis
        i. Conventional karyotyping
        ii. FISH
        iii. Whole chromosome painting
3. Management
    a. Multidisciplinary team approach
        i. Early intervention program to improve motor development, cognition, communication, and social skills
        ii. Speech, physical, and occupational therapies
        iii. Appropriate school placement
    b. Manage feeding difficulties and failure to thrive
        i. Gavage feeding
        ii. Gastrostomy
        iii. Occasional gastroesophageal fundoplication
    c. Anticonvulsants for seizure control
    d. Orthopedic care for skeletal abnormalities
        i. Clubfoot
        ii. Scoliosis
        iii. Kyphosis
    e. Care for possible immunodeficiency

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Fig. 1 (**a**–**e**) A patient with Wolf–Hirschhorn syndrome at different ages showing characteristic facial features consisting of prominent glabella, hypertelorism, beaked nose, and frontal bossing, collectively described as "Greek warrior helmet" facies

Fig. 2 (**a**–**c**) A girl with WHS showing characteristic face and deletion of WHS locus (FISH)

Fig. 3 (**a**–**f**) Four children with WHS showing characteristic facial features of the syndrome

Fig. 4 (**a**–**d**) Two siblings with WHS showing characteristic features of the syndrome

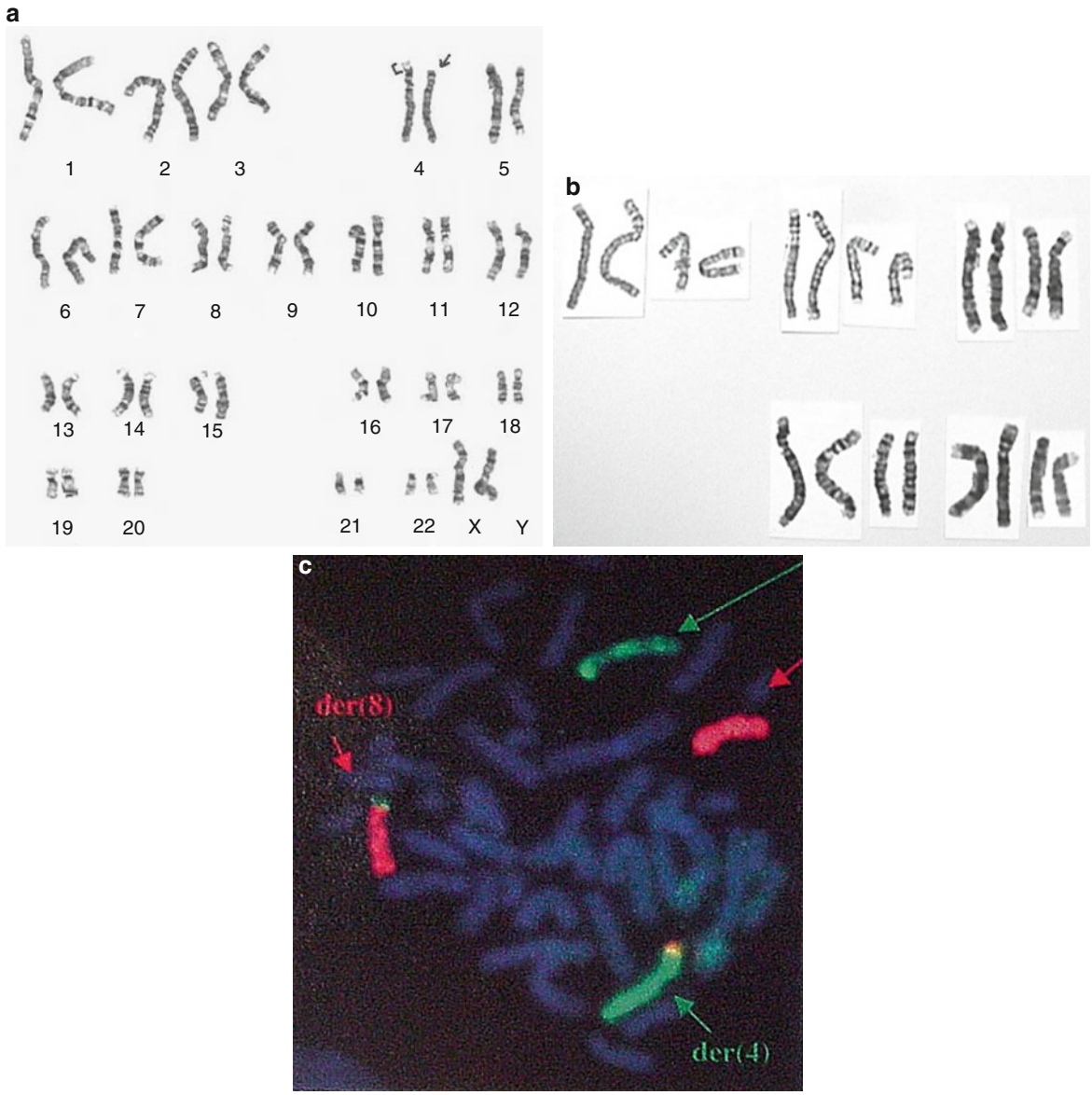
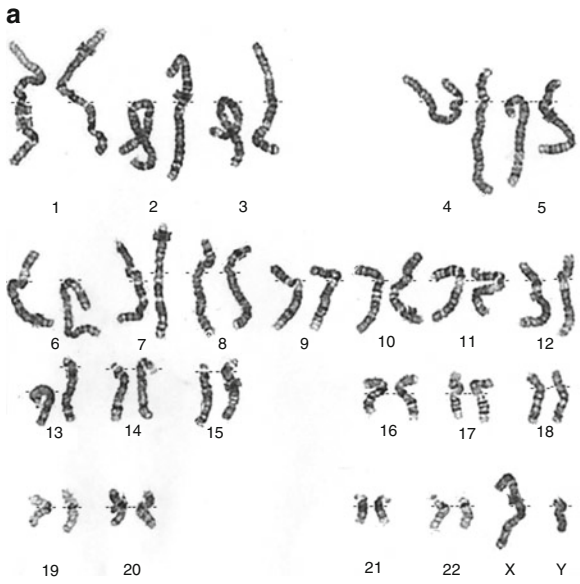


Fig. 5 (**a**–**c**) Karyotype of the sister showing deletion of 4p, derived from the mother with balanced translocation (4p;8p) (partial karyotypes). FISH analysis with whole chromosome paint specific for chromosome 4 (wcp4/SpectrumGreen) and chromosome 8 (wcp8/SpectrumOrange) demonstrated a t(4;8) in all metaphases analyzed. These results confirmed a reciprocal translocation between chromosome 4 and chromosome 8 in the mother



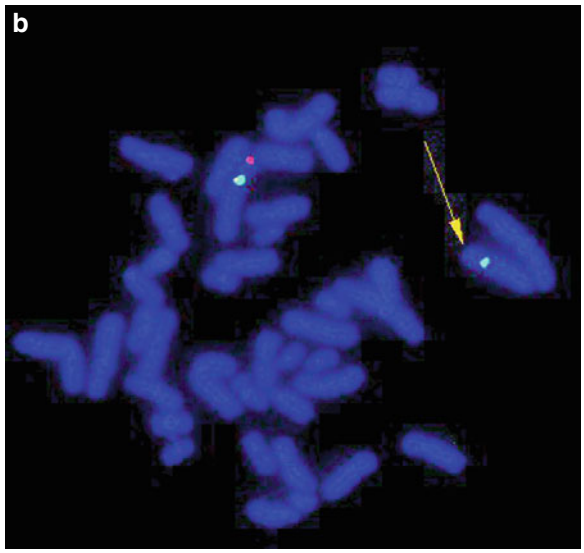


Fig. 6 (**a**, **b**) Karyotype and FISH of another patient with Wolf–Hirschhorn syndrome (4p-)

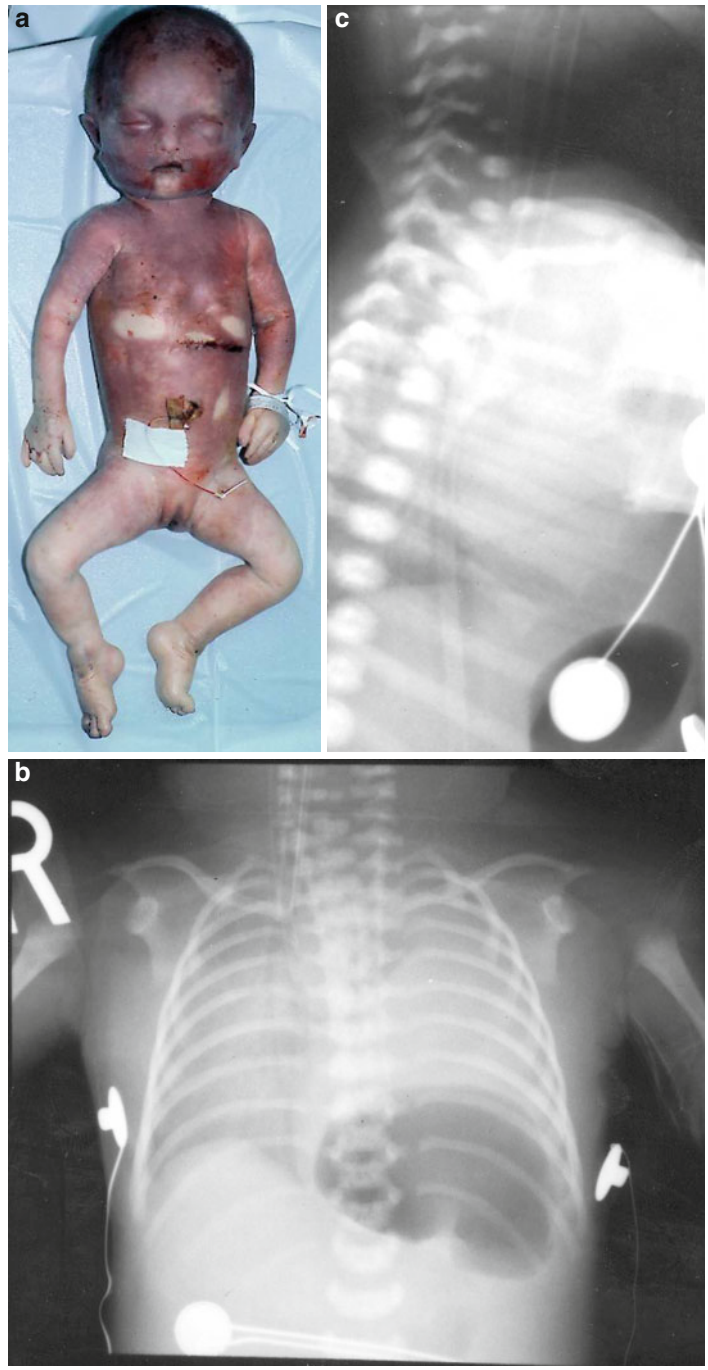


Fig. 7 (**a**–**c**) A fetus with WHS showing broad triangular-shaped nasal root, and the flat facial profile resembling "Greek warrior helmet." The radiographs show hypoplasia of the cervical vertebral bodies

X-Linked Agammaglobulinemia

X-linked agammaglobulinemia (XLA) was first described by Bruton in 1952 (Bruton 1952). It is a prototypical humoral immunodeficiency characterized by early onset of bacterial infections, profound hypogammaglobulinemia, and marked decrease of the peripheral B-lymphocyte population. Associated infections, particularly bacterial meningitis and pneumonia, are often life threatening.

Synonyms and Related Disorders

Agammaglobulinemia tyrosine kinase; B-cell progenitor kinase; Bruton-type agammaglobulinemia; Immunodeficiency 1

Genetics/Basic Defects

1. An X-linked recessive disorder
2. The responsible gene for XLA (named as Bruton's tyrosine kinase, *BTK*), mapped on Xq21.3-Xq22, is mainly involved in early B-cell maturation through its function in pre-B-cell receptor signaling pathway, and its absence causes an arrest in B-cell development.
3. Mutations in the *BTK* gene cause XLA.
4. No clear genotype phenotype correlation exists
5. Female XLA can result from heterozygous *BTK* gene abnormality and extreme nonrandom inactivation of X chromosome on which normal *BTK* gene is located.

Clinical Features

1. Presenting manifestations
   a. Infections in affected boys after the decline of passively transferred maternal antibodies: the major presenting feature
      i. Most frequently respiratory tract and gastrointestinal tract infections (91%), often protracted and recurrent, presenting as otitis media, pneumonitis, and diarrhea
      ii. Other common infections
         a) Conjunctivitis
         b) Sinusitis
         c) Skin infection
      iii. *S. pneumoniae* and *H. influenzae*: the most common organisms found prior to diagnosis and may continue to cause sinusitis and otitis after diagnosis and the initiation of gamma globulin therapy
      iv. Monoarticular or oligoarticular arthritis (20%) affecting large joints: the most common being knees, shoulders, ankles, wrists, and elbows
      v. Central nervous system infections (16%): meningitis/encephalitis
      vi. Septicemia (10%) excluding bacterial meningitis and associated bacteremia
      vii. Virtually, all patients had infections at more than one anatomic site and on more than one occasion.
   b. Neutropenia (10%): always occur in association with infection, and in all cases resolved after treatment with antibiotics and γ-globulin

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   c. Failure to thrive: a relatively infrequent occurrence
   d. Fever of unknown origin
   e. Complications of immunizations such as paralytic poliomyelitis following live virus vaccine and vaccinia gangrenosum following smallpox vaccination
2. Age at onset of symptoms
   a. By age 4 months (25%)
   b. By age 8 months (50%)
   c. By age 12 months (75%)
   d. By age 18 months (90%)
3. Chronic complications
   a. Chronic pulmonary disease (46%): the most frequent long-term complication of XLA
      i. Obstructive pulmonary disease (half of cases)
      ii. Combined obstructive and restrictive disease (half of cases)
   b. Sensory neurologic disorders
      i. Hearing loss (32%) as a consequence of chronic otitis media and meningoencephalitis
      ii. Delayed acquisition of speech (14%)
      iii. Learning disorders (15%)
      iv. Significant motor dysfunction as a consequence of encephalitis
         a) Hemiparesis
         b) Ataxia
         c) Diplegia
         d) Quadriplegia
4. Miscellaneous illnesses
   a. Dermatomyositis-like syndrome occurred in association with arthritis and with meningitis/encephalitis.
   b. Viral infections
      i. Disseminated enterovirus infection
      ii. Disseminated adenovirus infection
   c. Hematologic abnormalities: uncommon in treated patients
      i. Chronic Coombs' positive hemolytic anemia
      ii. Transient neutropenia and transient thrombocytopenia in conjunction with infection: resolved when the infection resolved
      iii. Insulin-dependent diabetes mellitus
5. Complications of γ-globulin therapy
   a. Rash
   b. Fever
   c. Apparent anaphylactic-like symptoms
   d. Acrodynia secondary to γ-globulin preparations containing mercury as a preservative
6. Causes of death
   a. Cardiorespiratory failure (38%): consequence of chronic pulmonary disease and cor pulmonale
   b. Severe viral infections (50%)
   c. Fulminant necrotizing hepatitis
   d. Aspiration as a consequence of poliomyelitis-related neurologic impairment
   e. Systemic staphylococcal infections

Diagnostic Investigations

1. Clinical clues to the diagnosis of XLA
   a. Chronic or recurrent nature of infections
   b. Infections at more than one anatomic location
   c. Family history of immunodeficiency
   d. An important clinical clue: absent or barely detectable tonsils and cervical lymph nodes
   e. About 60% of individuals with XLA are recognized as having immunodeficiency when they develop a severe, life-threatening infection such as pneumonia, empyema, meningitis, sepsis, cellulitis, or septic arthritis
2. Clinical laboratory findings in affected individuals
   a. Concentration of serum immunoglobulins
      i. The serum IgG concentration: typically less than 200 mg/dL
      ii. The serum concentrations of IgM and IgA: typically less than 20 mg/dL (Although decreased serum concentration of IgG and IgA can be seen in children with a constitutional delay in immunoglobulin production, low serum IgM concentration is almost always associated with immunodeficiency.)
   b. Antibody titers to vaccine antigens: Affected individuals fail to make antibodies to vaccine antigens like tetanus, *H. influenzae*, or *S. pneumoniae*.
   c. Lymphocyte cell surface markers: markedly reduced numbers of B lymphocytes (CD 19+ cells) in the peripheral circulation (<2% in almost all patients): the most distinctive laboratory finding
   d. Bruton's tyrosine kinase protein (measured by flow cytometry) is absent in most of the patients.
   e. Severe neutropenia: seen in about 10–25% of individuals at the time of diagnosis, usually

in association with pseudomonas or staphylococcal sepsis. Neutropenia is generally not seen after the initiation of gamma globulin therapy.

3. Molecular genetic testing
   a. Mutations in *BTK*: detectable by sequence analysis in approximately 90% of males with early-onset infections, hypogammaglobulinemia, and absent B cells
   b. Duplications or deletions in *BTK* gene: detectable by duplication/deletion analysis in 10% of affected males
   c. Molecular genetic testing of the *BTK* gene is the most reliable way to identify female carriers of XLA.
4. Diagnosis considered established only in those individuals who have a mutation in the *BTK* gene or who have a maternal uncle or cousin with absent B cells

Genetic Counseling

1. Recurrence risk
   a. Obligatory carriers: Mothers who have an affected son and one other affected relative in the maternal line (e.g., brother, uncle, nephew)
   b. Negative family history in 50% of affected males: two possibilities exist regarding his mother's carrier status and carrier risks of extended family members
      i. The mother is a carrier of a disease-causing mutation (80–85% of cases).
      ii. The mother is not a carrier and the affected male has a de novo disease-causing mutation (15–20% of cases).
   c. Patient's sib
      i. When the mother is a carrier
         a) A 50% chance of transmitting the *BTK* mutation by the mother in each pregnancy
         b) Male sibs who inherit the mutation will be affected.
         c) Female sibs who inherit the mutation will be carriers.
      ii. When the mother's carrier status is unknown and if the proband is the only affected individual in the family, the mother has an approximately 80% chance of being a carrier.
         a) Male sibs have a 40% chance of being affected.
         b) Female sibs have a 40% chance of being carriers.
      iii. When the mother is not a carrier (no evidence of her son's BTK disease-causing mutation present in DNA extracted from her leukocytes) and if the affected son represents a single case in the family, the male sibs are still at increased risk (<5%) of being affected because of the possibility of the presence of germ line mosaicism.
   d. Patient's offspring
      i. No sons will inherit the mutant allele and therefore will not be affected.
      ii. All daughters will inherit the mutant allele and will be carriers.
2. Prenatal diagnosis: available to pregnancies of women who are carriers
   a. The usual procedure: to determine fetal sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about 10–12 weeks of gestation or by amniocentesis usually performed at about 15–18 weeks of gestation
   b. If the fetal karyotype is 46,XY and if the disease-causing mutation has been identified in a family member, DNA from fetal cells can be analyzed for the known disease-causing mutation.
   c. Preimplantation genetic diagnosis (PGD): available for families in which the disease-causing mutation has been identified in an affected family member. However, the reliability of PGD for XLA has not yet been proven.
3. Management
   a. Gamma globulin replacement (weekly subcutaneous injection or intravenous infusion every 2–4 weeks) and aggressive use of antibiotics
      i. Improve the outlook for affected patients: a remarkable improvement in the health and well-being after therapy is started
      ii. Acute, life-threatening infections: rare in patients with XLA who are receiving intravenous gamma globulin
      iii. Chronic lung disease and enteroviral infections still develop in some patients.

b. Inactivated polio vaccine rather than live oral polio vaccine is given to children with XLA and their sibs.
c. Molecular genetic testing of at-risk male relatives as soon after birth as possible to ensure that gamma globulin replacement therapy is initiated in affected individuals
d. Adults with XLA: become productive members of society and excel in many areas despite the disease impacts on the daily lives

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Fig. 1 A 5-year-old boy was evaluated for immune deficiency because of recurrent respiratory tract infections (two pneumonias since late infancy) and one episode of meningitis. Recent immunoglobulin levels revealed IGA of <5 mg/dL (22–159), IGG of 115 mg/dL (141–1,135), and IGM of 11 mg/dL (47–200). Flow cytometry (immune deficiency panel) showed CD3, 92.9% (3,498); CD4, 43% (1,645); CD8, 46% (1,747); CD4/CD8, 1:1.1; CD19, 0.1% (4); and CD16 + CD56+, 6.2% (233). These findings are consistent of B-cell defect with normal T cell subsets and normal NK cells. Bruton's tyrosine kinase mutation analysis revealed a novel mutation in the splice site of exon 6 (g.58919 G > C). Previously, a mutation at this splice site (g.58919) G > A has been reported in the BTKBASE. The impact on protein structure and function for this mutation, assessed using a splice site prediction software, would be the same as that reported for g.58919 G > A. The patient currently receives intravenous immunoglobulin (610 mg/kg) and is responding well

Fig. 2 A 3-year-old male, a brother of the above patient, was also evaluated for immune deficiency because of recurrent upper respiratory infections in the first 2–3 months of life, three pneumonias in later infancy, and a pneumococcus meningitis recently. Recent immunoglobulin levels were IGA of <5 mg/dL, IGG of 184 mg/dL, and IGM of 10 mg/dL. Flow cytometry (immune deficiency panel) revealed CD3, 8% (1,979); CD4, 55% (1,365); CD8, 27% (679); CD4/CD8 ratio, 2:1; CD19+, 1.4% (34); and CD16+ CD56+, 11% (270). The patient currently receives intravenous infusion of immunoglobulin (680 mg/kg) and responds well

X-Linked Ichthyosis

X-linked ichthyosis is a relatively common genetic disorder of keratinization. It is the second most common type of ichthyosis after vulgaris. The incidence is estimated to be between 1 in 2,000 and 1 in 6,000 male live births.

Synonyms and Related Disorders

Placental steroid sulfatase deficiency; Steroid sulfatase deficiency

Genetics/Basic Defects

1. Inheritance
   a. X-linked recessive
   b. Usually affects males only
   c. Transmitted by carrier females (about 1 in 2,000 women are carriers of steroid sulfatase (STS) enzyme deficiency)
   d. Most apparently, sporadic cases appear to be inherited based on biochemical analysis (as their mothers showed low values of STS enzyme activity).
   e. Reports of a few affected female patients
2. Etiology (Janniger and Schwartz 2001)
   a. Caused by a deficiency of STS enzyme
   b. The *STS* gene
      i. Mapped on the distal part of the short arm of the X chromosome (Xp22.3)
      ii. Close to the pseudoautosomal region
      iii. Unlike most X-chromosome genes, the *STS* gene escapes the X-inactivation process.
3. Molecular defects
   a. Deletion of the entire steroid sulfatase (*STS*) gene: the most common molecular defect in X-linked ichthyosis (XLI) patients (observed in 90% of patients)
   b. Partial deletion or point mutation (observed in 10% of patients)
   c. The deletion of *STS* gene may occasionally extend to involve neighboring genes (interstitial and terminal deletions of Xp22.3), resulting in a contiguous gene defect and may be associated with the following conditions. Depending on the length of the deletion, these disorders occur independently from each other or in combination as a contiguous gene syndrome (Aviram-Goldring et al. 2000).
      i. Kallmann syndrome (hypogonadotropic hypogonadism and anosmia)
      ii. X-linked chondrodysplasia punctata
      iii. Short stature
      iv. Mental retardation
      v. Ocular albinism
      vi. Ichthyosis
4. Segregation analysis of paternal transmission of the affected X chromosome (Toral-Lopez et al. 2008): *STS* gene deletion may occur in male meiosis as a result of:
   a. An intrachromosomal event
   b. Recombination between S232 sequences on the same DNA molecule, or
   c. During the process of DNA replication

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Clinical Features

1. Cutaneous manifestation (Hernandez-Martin et al. 1999; Jasmi and Al-Khenaizian 2002)
   a. Generalized scaling of the skin (ichthyosiform hyperkeratosis)
      i. Early onset: usually at birth or within 4 months of life
      ii. Large, dark-brown polygonal scales
         a) Usually symmetrically distributed
         b) More prominent on the trunk and the extensor aspects of the limbs
         c) Usually the flexures less affected
      iii. Face usually free from scales, except in the preauricular areas, giving the classic "unwashed appearance," which is considered by many to be pathognomonic
      iv. Sparing palms and soles in most cases
   b. Normal nails and hair
   c. Seasonal influence
      i. Improve during the summer
      ii. Worsen during dry, cold weather
2. Extracutaneous manifestations
   a. Corneal opacities
      i. The most common extracutaneus features
      ii. Secondary to deposits of cholesterol sulfate crystals
      iii. Asymptomatic (not affecting the visual acuity)
      iv. Occurring in the posterior capsule of Descemet's membrane or the corneal stroma (Aviram-Goldring et al. 2000)
      v. More frequent during the second and third decades of life
      vi. Observed in 10–50% of affected males and carrier females
   b. Cryptorchidism
      i. Occurring in 10–20% of patients (versus the incidence of cryptorchidism in the normal population of 1%)
      ii. Possible mechanisms
         a) A deficit in the STS enzyme
         b) A genetic disturbance located on the short arm of chromosome X close to the *STS* gene
   c. Patients at an increased risk of testicular cancer development
   d. CNS manifestations
      i. Epileptic seizures
      ii. Reactive psychological disorders
   e. Clinical manifestations as a part of the contiguous gene syndrome expression
      i. Kallmann syndrome
      ii. Short stature
      iii. Mental retardation
      iv. X-linked chondrodysplasia punctata
   f. Other rare manifestations
      i. Pyloric hypertrophy
      ii. Congenital abdominal wall defect
      iii. Acute lymphoblastic leukemia
3. Steroid sulfatase deficiency during pregnancy in carrier females
   a. Leads to an overall decrease in the levels of estrogen
   b. Causes poor cervical dilatation and prolonged labor
   c. Frequently necessitates a caesarean section

Diagnostic Investigations

1. Direct biochemical demonstration of STS deficiency (undetectable levels of STS activity) from the following tissue (Hernandez-Martin et al. 1999; Jasmi and Al-Khenaizian 2002):
   a. Placenta
   b. Skin fibroblasts
   c. Leukocytes
   d. Keratinocytes
2. Demonstration of an increase in substrates of STS
   a. Dihydroepiandrosterone sulfate (DHEAS)
   b. Cholesterol sulfate
3. Electrophoresis: rapid migration of serum cholesterol sulfate (negatively charged and carried by low-density lipoprotein (LDL) particles) toward the positive pole during electrophoresis
4. Molecular genetic diagnosis yielding reliable results in most affected patients
   a. Detection of complete deletion of the STS gene in most patients
      i. Fluorescence in situ hybridization (FISH)
      ii. Southern blotting
      iii. Multiplex polymerase chain reaction (PCR)

b. Partial deletion by FISH: may provide a false negative FISH result
c. A very small number of cases carrying point mutations instead of deletions at the *STS* gene: undetectable by Southern blot or PCR
d. Carrier detection
   i. STS enzyme assay
   ii. FISH technique especially useful in carrier detection since the enzymatic assay often provides inconclusive results

Genetic Counseling

1. Recurrence risk
   a. Patient's sib (given that the mother is a carrier)
      i. 50% of male sibs affected
      ii. 50% of female sibs carriers
   b. Patient's offspring
      i. Affected male patients
         a) Male offspring normal
         b) All female offspring carriers
      ii. Affected female patients (heterozygous)
         a) 50% of male offspring affected
         b) 50% of female offspring carriers
      iii. Affected female patients (homozygous)
         a) All male offspring affected
         b) All female offspring carriers
2. Prenatal diagnosis
   a. Maternal plasma demonstrating low or undetectable estriol levels in routine maternal serum screening, which is associated with the following conditions (Braunstein et al. 1976; Kashork et al. 2002):
      i. Placental steroid sulfatase deficiency
      ii. Fetal death
      iii. Miscarriages
      iv. Anencephaly
      v. Fetal adrenal hypoplasia
      vi. High-dose corticosteroid therapy
      vii. Aneuploidies
         a) Down syndrome
         b) Triploidy
      viii. Smith-Lemli-Opitz syndrome in rare cases
   b. Maternal urine and plasma profile of affected fetuses indicating a primary placental sulfatase deficiency (low estriol levels) (Basler et al. 1992)
   c. Amniocentesis (Aviram-Goldring et al. 2000)
      i. Elevated sulfated steroids in the amniotic fluid
      ii. FISH to detect deletion in one copy of X chromosome at region Xp22.3 using steroid sulfatase probe
   d. Skin biopsy through fetoscopy to measure sulfated steroid
3. Management (Hernandez-Martin et al. 1999)
   a. Most patients have disease limited to the skin.
   b. Spontaneous improvement in most cases with age and during summer months and hardly require any treatment
   c. Attempt to diminish the abnormal cohesion of corneocytes by facilitating their separation in the milder forms
      i. Topical keratolytics
      ii. Emollients
      iii. Hydrating agents
   d. Retinoids for potential treatment in severely affected patients
   e. Liarozole, a imidazole derivative which inhibit cytochrome P450 to increase the level of endogenous retinoid acid by blocking its P450-dependent catabolism
   f. Examination of male patients to detect cryptorchidism which has an increased risk of testicular cancer

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Fig. 1 A sporadic case of X-linked ichthyosis showing thick, large, polygonal, dark-brown scales involving the extensor

Fig. 2 X-linked ichthyosis affecting three boys in a family

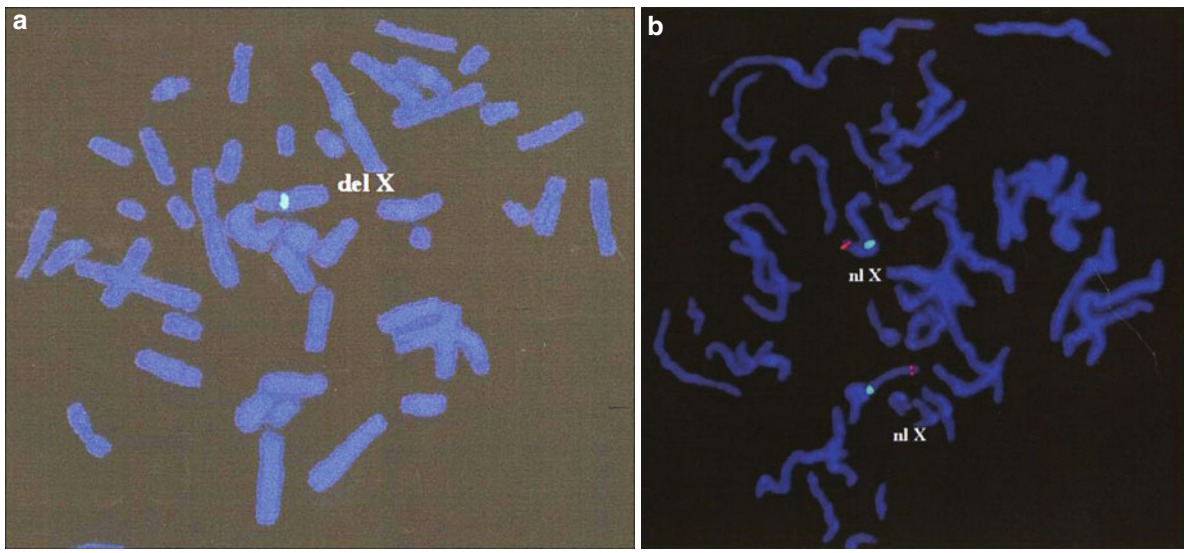

Fig. 3 (**a**, **b**) Abnormal FISH analysis showed a deletion in the steroid sulfatase critical region on the X chromosome [del(X)(p22.3p22.3)(STS-)] in a male fetus (*left photo*). The case was ascertained because of undetectable UE3 from maternal serum screen. The *right photo* (FISH) showed a normal XX control

XX Male

46,XX maleness (XX male syndrome) is a rare disorder occurring in about 1 in 20,000–25,000 newborn males (De la Chapelle 1972; Rajender et al. 2006). Three clinical categories of sex-reversed 46,XX individuals have been identified: (1) XX males with normal external or internal genitalia; (2) XX males with ambiguity, usually detected at birth by external genital ambiguities such as hypospadias, micropenis, or clitoromegaly; and (3) XX true hermaphrodites, who carry internal or external genital ambiguities detected at birth (Valetto et al. 2005). Recently, the term "46,XX testicular DSD (disorder of sex development)" has been proposed for XX male or XX sex reversal (Lee et al. 2006; Hughes et al. 2006; Hughes 2008).

Synonyms and Related Disorders

46,XX disorder of sex development; 46,XX sex reversal syndrome

Genetics/Basic Defects

1. Sex differentiation: Please see the chapter on XY Female Syndrome (Vilain 2009).
2. The *SRY* gene (Valetto et al. 2005)
   a. Located in the short arm of Y chromosome (Yp11.32) near the pseudoautosomal boundary of the Y chromosome
   b. Encodes the sex-determining region Y protein
   c. Has many predicted properties of the testis-determining factor (TDF) (Sinclair et al. 1990)
   d. XX transgenic mice carrying the murine *SRY* gene developed as phenotypic male mice (Koopman et al. 1991).
   e. Loss-of-function mutations in the *SRY* gene: can cause a complete sex reversal (genetically male individuals developing as XY females, presenting a streak gonad lacking germ cells) (Jager et al. 1990; Hawkins et al. 1992)
   f. The gene most commonly known to be associated with 46,XX testicular DSD
      i. Presence of Y chromosome material including *SRY* in some XX individuals: leads to testis determination and the development of a male phenotype
      ii. The majority of XX males carry the *SRY* gene as a result of an illegitimate XY chromosomal interchange during paternal meiosis (Fechner et al. 1993).
      iii. *SRY*-negative individuals resulting from *SRY* gene mutation
   g. Several genetic mishaps conceive the 46,XX male genotype (Rizvi 2008).
      i. An original 47,XXY configuration with the loss of the Y chromosome early in embryogenesis
      ii. A loss-of-function gene mutation on an autosomal chromosome or on the X chromosome that leads to an aberrancy in the testis differentiation pathway
      iii. Possibility that 46,XX males actually have a "hidden" cell line with a Y chromosome present ("cryptic mosaicism")
      iv. Translocation of the Y chromosome fragment containing the SRY gene to the short

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arm of an X chromosome or an autosome by unequal interchange between homologous regions during paternal meiotic division (Rego et al. 1996)
   a) The affected individual has male sexual characteristics because of the Y fragment, with the testis-determining factor, being located on the autosome or X chromosome, despite the XX sex chromosome pattern.
   b) If the translocation is in a "pseudoautosomal region" proximal to the SRY gene, there may be no significant outcome.
   c) Only if the translocation involves the SRY region of the Y chromosome then the X chromosome will "act" like a Y chromosome in determining the phenotypic gender of the person.
3. Pathogenesis of 46,XX sex reversal syndrome: currently not clear with the following hypotheses (Wang et al. 2009):
   a. Hypothesis of target gene mutation (Liu et al. 2005)
      i. The structural gene that determines human gender may be located in the autosome, which is regulated by the inhibition of X chromosome and the activation of Y chromosome.
      ii. 46,XX individuals, due to defects of the inhibition of X chromosome, result in spontaneous activation of the downstream gene in the absence of *SRY* gene, transform into 46,XX males.
   b. Hypothesis of overexpression of *SOX9* gene (SRY box-related gene 9 located in 17q24.3-q25.1): Upregulation of *SOX9* expression caused by chromosomal abnormalities or mediated by other bypass activation (e.g., PGD2) may result in the occurrence of the SRY-gene-negative 46,XX male patient.
   c. Hypothesis of Xp-Yp translocation: Abnormal exchange of the ends of X-Y chromosomes (Xp-Yp translocation) occurred during paternal sperm meiosis resulting in X-type sperm containing SRY gene, which could lead to 46,XX offspring when combining with eggs.
4. Approximately 85% of individuals with 46,XX testicular DSD (Queipo et al. 2002; Zenteno-Ruiz et al. 2001)
   a. *SRY* positive
   b. Phenotypically males with unambiguous male genitalia at birth
   c. Not diagnosed until puberty when they fail to proceed normally
5. Remaining 15% of individuals with 46,XX testicular DSD (Zenteno-Ruiz et al. 2001; Kusz et al. 1999)
   a. Genital ambiguity
   b. *SRY* positive in only a minority of cases
6. A proposed classification of causes of 46,XX disorders of sex development (DSD) (Hughes 2008)
   a. Disorders of gonadal (ovarian) development
      i. Gonadal dysgenesis
      ii. Ovotesticular DSD
      iii. Testicular DSD (e.g., *SRY*+, *dup SOX*9, RSP01)
   b. Androgen excess
      i. Fetal
         a) 3β-hydoxysteroiddehydrogenase 2 (HSD3B2)
         b) 21-hydroxylase (CYP21A2)
         c) P450 oxidoreductase (POR)
         d) 11β-hydoxylase (CYP11B1)
         e) Glucocorticoid receptor mutations
      ii. Fetoplacental
         a) Aromatase (*CYP19*) deficiency
         b) Oxidoreductase (*POR*) deficiency
      iii. Maternal
         a) Maternal virilizing tumors (e.g., luteomas)
         b) Androgenic drugs
   c. Other
      i. Syndromic associations (e.g., cloacal anomalies)
      ii. Müllerian agenesis/hypoplasia (e.g., MURCS)
      iii. Uterine abnormalities (e.g., MODY5)
      iv. Vaginal atresia (e.g., KcKusick-Kaufman)
      v. Labial adhesions

Clinical Features

1. Natural history (Vilain 2009)
   a. Approximately 80% of patients
      i. Present after puberty with normal pubic hair and normal penile size, but small testes, gynecomastia, and sterility resulting from azoospermia

ii. The small testes are usually soft but may become firmer with age.
iii. A minority have cryptorchidism and/or anterior hypospadias (Boucekkine et al. 1994).
iv. Gender role and gender identity are reported as male for the common, unambiguous presentation, but systematic psychosexual assessment has not been performed on a significant number of individuals with 46,XX testicular DSD.

b. Approximately 20% of patients: ambiguous genitalia noted at birth, typically penoscrotal hypospadias with or without chordee.
c. Untreated patients: similar to typical consequences of testosterone deficiency
i. Low libido and possible erectile dysfunction
ii. Decrease in secondary sexual characteristics, such as sparse body hair, infrequent need to shave, and reduced muscle mass
iii. Increase in fat mass with lower muscle strength
iv. Increased risk of osteopenia
v. Increased risk of depression

2. SRY-positive 46,XX males
a. Present after puberty
i. Shorter-than-average stature (De la Chapelle 1972)
ii. Gynecomastia
iii. Small testes
iv. Azoospermia
b. Rarely present with atypical genitalia and are less likely than individuals with *SRY*-negative 46,XX males to have gynecomastia (Ferguson-Smith et al. 1990; Boucekkine et al. 1994; Ergun-Longmire et al. 2005)
3. SRY-negative 46,XX males
a. Tend to present with ambiguous genitalia at birth, such as penoscrotal hypospadias and cryptorchidism
b. If untreated, almost always develop gynecomastia around the time of puberty
4. Genotype-phenotype correlations
a. Presence of *SRY* : often associated with the presence of normal male external genitalia
b. Absence of *SRY* : more often associated with ambiguous genitalia (Grigorescu-Sido et al. 2005)
c. Genotype-phenotype correlation: not entirely reliable because a small number of individuals with *SRY*-negative 46,XX males have normal external genitalia (Vilain et al. 1994; Zenteno et al. 1997; Kolon et al. 1998; Vernole et al. 2000; Abusheikha et al. 2001)
5. Long-term outcome: most had male sexual potential and male sex identity as long as testicular tissues were preserved (Kojima et al. 2009)
6. Differential diagnosis
a. Syndromic XX testicular DSD
b. Isolated XX testicular DSD
c. Sex chromosome abnormalities
i. Klinefelter syndrome
ii. 46,XX/46,XY
iii. 45,X/46,XY
d. Mosaic duplication of 17q23.1-q24.3 including *SOX9* gene
e. 46,XX ovotesticular DSD
f. 21-hydroxylase deficiency causing congenital adrenal hyperplasia
g. Prenatal exposure of a pregnancy to androgens with an XX karyotype can cause virilization resulting in an infant with ambiguous genitalia that may look similar to those of a male with 46, XX testicular DSD and genital ambiguity.
i. Externally administered androgens such as danazol
ii. Endogenously produced androgens by the mother

Diagnostic Investigations

1. Routine cytogenetic studies: 46,XX karyotype (Vilain 2009)
2. Endocrine studies
a. Hypergonadotropic hypogonadism secondary to testicular failure (Pérez-Palacios et al. 1981)
i. Moderately elevated basal serum concentrations of LH and FSH
ii. Usually decreased serum testosterone concentration
iii. HCG stimulation test
a) Low to subnormal testosterone response
b) Little or no elevation of serum testosterone concentration
b. Preservation of hypothalamic-pituitary axis: GnRH stimulation test shows a normal LH and FSH response (not warranted for diagnosis).

3. Testicular biopsies (De la Chapelle 1981)
   a. Decrease in size and number of seminiferous tubules
   b. Peritubular fibrosis
   c. Absence of germ cells
   d. Hyperplasia of Leydig cells
4. Molecular genetic testing
   a. Fluorescence in situ hybridization (FISH) using commercially available FISH probe to locate *SRY* gene on the short arm of one X chromosome
   b. PCR amplification
      i. Used when FISH fails to detect the *SRY* region
      ii. More likely to detect a small amount of Y chromosome translocated onto the X chromosome
      iii. To detect the Y chromosome material in an individual who is an XX-*SRY*-positive/XX-*SRY*-negative mosaic
   c. Comparative genomic hybridization (CGH) method to identify the small unbalanced chromosome rearrangement implicated in an XX male (Rigola et al. 2002)

Genetic Counseling

1. Recurrence risk (Vilain 2009)
   a. Patient's sib
      i. Sibs of a proband with *SRY* translocation to an X chromosome
         a) Proband with a de novo translocation (in most cases): has a low risk to XX sibs (<1%). No instances of germline mosaicism have been reported, but it remains a possibility.
         b) Proband with familial translocation (father carrying two copies of SRY, one translocated to his X chromosome and one on his Y chromosome): XX sibs will have 46,XX testicular DSD or XX true hermaphroditism; XY sibs will not be affected.
      ii. Sibs of a proband with *SRY* translocation to an autosome
         a) Proband with a de novo translocation: risk to sibs not increased
         b) Proband with familial translocation (father carrying an *SRY* gene translocated onto an autosome): XX sibs of a proband each have a 50% chance of inheriting the translocated *SRY* gene and will have 46,XX testicular DSD or XX true hermaphroditism.
      iii. Sibs of a proband with SRY-negative 46,XX testicular DSD: 25% risk
   b. Patient's offspring
      i. Men with SRY-positive 46,XX testicular DSD: infertile
      ii. Men with SRY-negative 46,XX testicular DSD: infertile
2. Prenatal diagnosis
   a. Available for pregnancies at risk for SRY-positive 46,XX DSD from fetal cells obtained by amniocentesis or CVS using FISH
   b. Fetal karyotype discordant with the phenotypic sex observed by ultrasound examination in most cases
   c. An *SRY*-positive result decreases but does not exclude the likelihood of ambiguous genitalia.
   d. Has been described in several cases (Margarit et al. 1998; Trujillo-Tiebas et al. 2006)
3. Management
   a. Testosterone replacement therapy: low-dose testosterone therapy: initiate after age 14 years
      i. Testosterone enanthate injection: preferred
      ii. Transdermal patches and gels
   b. Reduction mammoplasty for gynecomastia for:
      i. Failure of regression of gynecomastia after testosterone replacement therapy
      ii. Presence of gynecomastia causing psychological distress
   c. Male-to-female transsexual operation for an XX male patient who is eager to live as a female (Kurita et al. 2006)
      i. Resection of the penis
      ii. Repositioning of the urethra
      iii. Vaginal construction
   d. Calcium, exercise, vitamin D, biphosphonates, or calcitonin for osteopenia
   e. Psychological support

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Fig. 1 (**a**–**c**) A 19-year-old phenotypically male patient has been evaluated for slightly high-pitched voice, gynecomastia, cryptorchidism on the right, a small atrophic testis on the left, and penile hypospadias. Chromosome study revealed 46,XX

XXX Syndrome

Females with a 47,XXX karyotype were first described by Jacobs et al. in 1959. The incidence of 47,XXX among female newborns is approximately 1 in 1,000 live births (Pennington et al. 1980). It is the most common female chromosomal abnormality. As some individuals are only mildly affected or asymptomatic, it is estimated that only 10% of individuals with trisomy X are actually diagnosed (Tartaglia et al. 2010).

Synonyms and Related Disorders

Trisomy X syndrome

Genetics/Basic Defects

1. Etiology: An extra chromosome X is responsible for 47,XXX.
2. Mechanism of the origin for the 47,XXX condition
   a. Almost all 47,XXX result from maternal nondisjunction.
   b. Typically at meiosis I
   c. The risk of trisomy X increases with advanced maternal age.
   d. Postzygotic nondisjunction occurs in approximately 20% of cases.
3. The phenotype in trisomy X is hypothesized to result from overexpression of genes that escape X-inactivation, but genotype-phenotype relationships remain to be defined (Tartaglia et al. 2010).

Clinical Features

1. No specific phenotype exists in 47,XXX females (Chudley et al. 1990).
2. A higher incidence of minor anomalies
   a. Epicanthal folds
   b. Upslanting palpebral fissures
   c. Ear abnormalities
   d. Clinodactyly
3. Growth and development (Otter et al. 2010)
   a. Birth weights tend to be slightly lower than the general population.
   b. The physical phenotype shows earlier growth and longer legs.
   c. Taller in older children
   d. Relative microcephaly
   e. Hypotonia
   f. At risk for mild speech/language and motor delays and learning disabilities
   g. The behavioral phenotype often shows auditory processing disorders, disorders in language development, and problems in forming stable interpersonal relationships.
   h. Psychiatric disorders seem to be more common in triple X syndrome.
   i. Quality of life seems to increase after leaving school.
   j. Intelligence
      i. Normal range
      ii. Lower intelligence quotients (10–15 points) in comparison to unaffected sibs
4. Gonadal structures and function
   a. Heterosexual
   b. Normal secondary sexual characteristics

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c. Normal menstruation
d. Fertility usually normal
e. Late menarche
f. Occasional amenorrhea
g. Premature ovarian failure
h. Sterility with streak gonads

5. Congenital anomalies reported in a very small number of patients
   a. Urogenital tract abnormalities
   b. Brain abnormalities including seizures
   c. Skeletal abnormalities
   d. Congenital heart defects
   e. Craniofacial abnormalities
6. Adaptation status: variable (Harmon et al. 1998)
   a. At risk for intellectual and psychological problems
   b. 47,XXX women during adolescence and young adulthood
      i. Less well adapted
      ii. With more stress
      iii. With work, leisure, and relationship problems
      iv. With a lower IQ
      v. With more psychopathology when contrasted with the comparison group
   c. Most 47,XXX women
      i. Self-sufficient
      ii. Functioning reasonably well
7. Differential diagnosis prior to definitive karyotype results includes (Tartaglia et al. 2010):
   a. Fragile X
   b. Tetrasomy X
   c. Pentasomy X
   d. Turner syndrome mosaicism

Diagnostic Investigations

1. Chromosome analysis
2. Psychological and psychiatric evaluation when needed

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring (Dewhurst 1978)
      i. An increased risk of a cytogenetically abnormal child but the extent of the risk cannot yet be determined
      ii. Majority of offspring normal
2. Prenatal diagnosis by fetal karyotyping from amniocytes or CVS, followed by detailed ultrasonographic examinations of multiple organ systems to screen for possible associated congenital malformations (Bağci et al. 2010)
3. Management
   a. Infancy/toddler: assess milestones
   b. Childhood
      i. Assess school performance
      ii. Provide intervention if needed
         a) Speech/language therapy
         b) Physical/occupational therapy
         c) Educational remediation
   c. Adolescence: usually no intervention needed
   d. Adulthood: annual physical examination

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Fig. 1 (**a**, **b**) A girl with 47, XXX at different ages showing normal phenotype

Fig. 2 A girl with 47,XXX showing normal phenotype

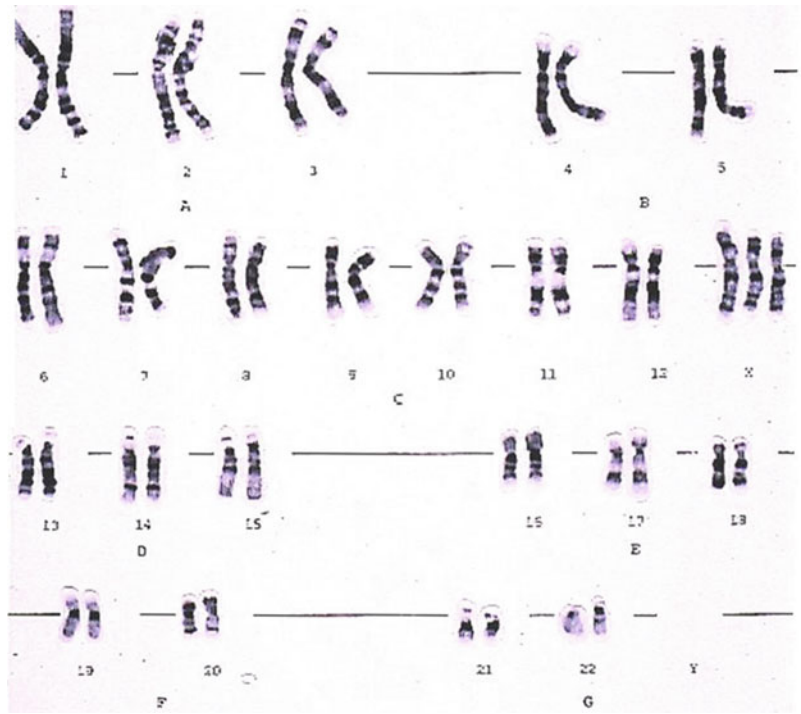

Fig. 3 47,XXX karyotype

XXXXX Syndrome

49,XXXXX (pentasomy X) is a rare sex chromosome aneuploidy. The birth prevalence of pentasomy X is estimated to be one in 85,000 females (Martini et al. 1993).

Synonyms and Related Disorders

49,XXXXX syndrome; Penta X syndrome

Genetics/Basic Defects

1. Etiology: three extra X chromosomes are responsible for the pentasomy X syndrome (Archidiacono et al. 1979).
2. Occurrence of a 49,XXXXX complement: secondary to sequential nondisjunctions in meiosis I and meiosis II in the mother
   a. Involves the survival of both X chromosomes in a single oocyte through both meiotic divisions (Deng et al. 1991)
      i. Once between homologous X chromosomes at the first meiosis
      ii. Twice between sister chromatids in both X chromosomes in the secondary oocytes at the second meiosis
   b. Followed by the fertilization by a sperm contributing the fifth chromosome X
3. Formation of four Barr bodies
   a. Lyon hypothesis
      i. Inactivation of all X chromosomes but one
      ii. Accounts for the viability of the X chromosome aneuploidies
   b. Inactivation of four X chromosomes resulting in four Barr bodies
4. Effect of supernumerary X chromosomes: a direct relationship between the number of supernumerary X chromosomes and phenotypic abnormalities and mental retardation, with each additional chromosome increasing the severity
   a. Affects somatic development most significantly
      i. Skeletal abnormalities
      ii. Cardiovascular abnormalities
   b. Delays sexual development
   c. Affects cognitive development
      i. Severe mental retardation
      ii. Language delay (both expressive and receptive language)
      iii. Behavioral problems

Clinical Features

1. Growth and development
   a. Prenatal growth retardation
   b. Small birth weight
   c. Low postnatal weight
   d. Failure to thrive
   e. Hypotonia
   f. Short stature
   g. Delayed psychomotor retardation
   h. Mental retardation
2. Craniofacial features
   a. Microcephaly
   b. Flattened occiput
   c. Epicanthus
   d. Upslanting palpebral fissures
   e. Ocular hypertelorism
   f. Uncoordinated eye movements

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   g. Flat broad nose
   h. Cleft palate
   i. Low-set ears
   j. Malformed teeth
3. Skeletal abnormalities
   a. Short neck
   b. Lax joints
   c. Multiple dislocations
      i. Shoulders
      ii. Elbows
      iii. Hips
   d. Radioulnar synostosis
   e. Spinal abnormalities
   f. Clinodactyly of the fifth fingers
   g. Lower leg abnormalities
      i. Genu valgum
      ii. Talipes
      iii. Metatarsus varus
   h. Delayed bone age
4. Congenital heart defects
   a. Ventricular septal defect
   b. Patent ductus arteriosus
5. Abnormal lobulation of the lungs
6. Renal hypoplasia
7. Sexual development
   a. Delayed puberty
   b. Incomplete secondary sexual development
   c. Small uterus
   d. Hypoplastic/absent ovaries
      i. Composed mainly of stroma and atrophic follicles
      ii. Absence of ova
      iii. Unilateral absence of an ovary reported
   e. Reduced fertility
8. Normal external genitalia
9. Dermatoglyphics
   a. Finger-dermal-ridge hypoplasia and a low total ridge count, consistent with the inverse proportion between the number of X chromosomes and the total ridge count (exceptions exist)
   b. Transverse palmar creases

Diagnostic Investigations

1. Chromosome analysis
   a. 49,XXXXX karyotype
   b. Fluorescence in situ hybridization (FISH), using DNA probe for α-satellite sequence in chromosome X (DXZ1), reveals five signals representing the presence of XXXXX.
2. Radiography
   a. Dislocations of the elbows and/or hips
   b. Radioulnar synostosis
   c. Clinodactyly

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: not reported due to severe mental retardation
2. Prenatal diagnosis
   a. Ultrasonography: bilateral radioulnar synostosis
   b. Amniocentesis and CVS
      i. Chromosome analysis
      ii. FISH using DNA probe (DXZ1) applied to uncultured amniocytes
3. Management
   a. Physical/occupational therapy
   b. Speech therapy

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Fig. 1 The first reported case of 49,XXXXX at infancy (**a**) and adulthood (**b**) with four Barr bodies (**c**), two drumsticks in a polymorphonuclear leukocyte (**d**), and a karyotype of 49,XXXXX (**e**)

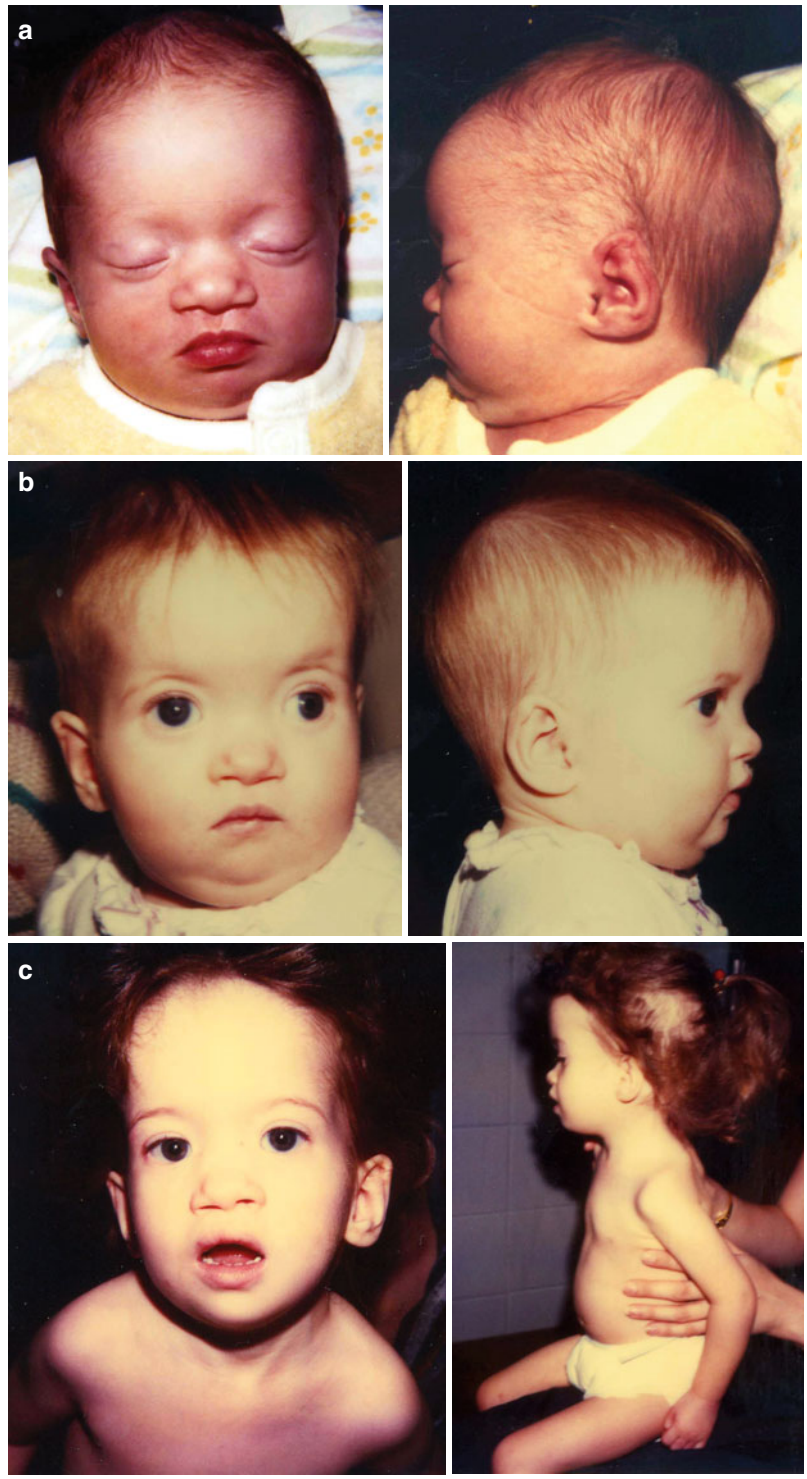

Fig. 2 A girl with 49,XXXXX syndrome at birth (**a**), 6 months (**b**), and 2 years and 4 months (**c**)

XXXXY Syndrome

49,XXXXY syndrome was first described by Fraccaro and Lindsten in 1960. The incidence is estimated to be approximately 1 in 85,000 newborn males (Pallister 1982).

Synonyms and Related Disorders

49,XXXXY syndrome

Genetics/Basic Defects

1. Etiology: three extra X chromosomes are responsible for the 49,XXXXY syndrome.
2. Mechanism
   a. All four X chromosomes are of maternal in origin.
   b. Resulting from successive nondisjunctions in maternal meiosis I and II, fertilized by a normal Y sperm (Deng et al. 1991)
   c. Inactivation of three out of four X chromosomes results in three Barr bodies (Lyon hypothesis).
3. Effect of supernumerary X chromosomes: a direct relationship between the number of supernumerary X chromosomes and phenotypic abnormalities and mental retardation, with each additional chromosome increasing the severity
   a. Somatic development most significantly affected
      i. Skeletal abnormalities
      ii. Cardiovascular abnormalities
   b. Gonadal development in males: particularly susceptible to extra genetic material
      i. Addition of a single X chromosome to a 46, XY karyotype resulting in seminiferous tubal dysgenesis rendering infertile such males with Klinefelter syndrome
      ii. Additional extra X chromosomes in polysomy X males such as 48,XXXY and 49,XXXXY can result in not only infertility but also hypoplastic and malformed genitalia.
   c. Affects cognitive development
      i. Severe mental retardation
      ii. Language delay (both expressive and receptive language)
      iii. Behavioral problems

Clinical Features

1. "Classic triad"
   a. Mental retardation
   b. Radioulnar synostosis
   c. Hypogonadism
2. Growth and development
   a. Growth retardation
   b. Severe speech impairment
   c. Varying degree of mental retardation
3. Craniofacial features
   a. Microcephaly
   b. A full, round face
   c. Ocular hypertelorism
   d. Upslanted palpebral fissures
   e. Epicanthus
   f. Broad nasal bridge
   g. Micrognathia
   h. Prognathism
   i. High-arched or cleft palate
   j. Irregular teeth implantation
   k. Malformed ears
4. Webbed and short neck

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5. Congenital heart defects
   a. Patent ductus arteriosus
   b. Atrial septal defect
   c. Pulmonic stenosis
   d. Tetralogy of Fallot
6. Skeletal abnormalities
   a. Short stature
   b. Proximal radioulnar synostosis
   c. Proximal tibiofibular synostosis (Nishimura et al. 2008)
   d. Vertebral anomalies
   e. Clinodactyly of the fifth fingers
   f. Coxa valga
   g. Genu valgum
   h. Pes planus
7. Genital abnormalities
   a. Hypoplastic male genitalia
   b. Micropenis
   c. Hypospadias
   d. Small testes
   e. Hypogonadism
   f. Infertility
8. Dermatoglyphics
   a. Decrease in total finger ridge count
   b. Transverse palmar creases
9. Psychological profile
   a. Timid and shy
   b. Emotional disturbances with low frustration level
   c. Strong reaction to minor changes
   d. Adaptive function higher than cognitive function
10. The phenotypic presentation of the boys with 49, XXXXY (Gropman et al. 2010)
    a. Shares some characteristics with 47, XXY
    b. Other unique and distinctive features
       i. Previously unappreciated intact nonverbal skills are evident in conjunction with moderate to severe developmental dyspraxia.
       ii. Variability in clinical and cognitive functioning may reflect skewed X inactivation, mosaicism, or other factors that warrant further investigation

Diagnostic Investigations

1. Chromosome analysis showing 49,XXXXY
2. Radiography
   a. Elbows
      i. Proximal radioulnar dysostosis
      ii. Radioulnar dislocation without synostosis
      iii. Elongated upper radius
      iv. Wide, club-shaped proximal ulna
   b. Wrists and hands
      i. Elongated distal ulna
      ii. "Pseudoepiphyses"
      iii. Clinodactyly of the fifth fingers
      iv. Brachymesophalangia V
      v. Retarded bone age
      vi. Corner defect in capitate
      vii. Poor modeling of the fifth metacarpals
   c. Pelvis and hips
      i. Coxa valga
      ii. Narrow iliac wings
   d. Knees
      i. Shallow intercondylar fossa
      ii. Genu valgum
   e. Ankles and feet
      i. Gap between the first and second toes
      ii. Short wide distal phalanx of the great toes
   f. Skull
      i. Sclerotic cranial sutures
      ii. Thick cranial vault
      iii. Ocular hypertelorism
      iv. J-shaped sella
      v. Prognathism
   g. Spine
      i. Scoliosis
      ii. Thoracic kyphosis
      iii. Square vertebral bodies
   h. Sternum
      i. Thick
      ii. Abnormal segmentation
3. Echocardiography for congenital heart defects
4. MRI of the brain (Hoffman et al. 2008)
   a. Varying degree of brain volume loss
   b. Abnormalities in white matter
5. Histology of testicular biopsies: dysgenesis of testicular germ cells and tubules leading to fibrosis

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: no offspring due to infertility of the condition

2. Prenatal diagnosis
   a. Ultrasonographic markers
      i. Polyhydramnios
      ii. Cystic hygroma
      iii. Clubfoot
      iv. Micropenis
   b. Amniocentesis and CVS
      i. Chromosome analysis
      ii. FISH using DNA probe (DXZ1) applied to uncultured amniocytes
3. Management
   a. Early intervention and stimulation programs
      i. Speech/language therapy
      ii. Physical/occupational therapy
   b. Testosterone replacement therapy

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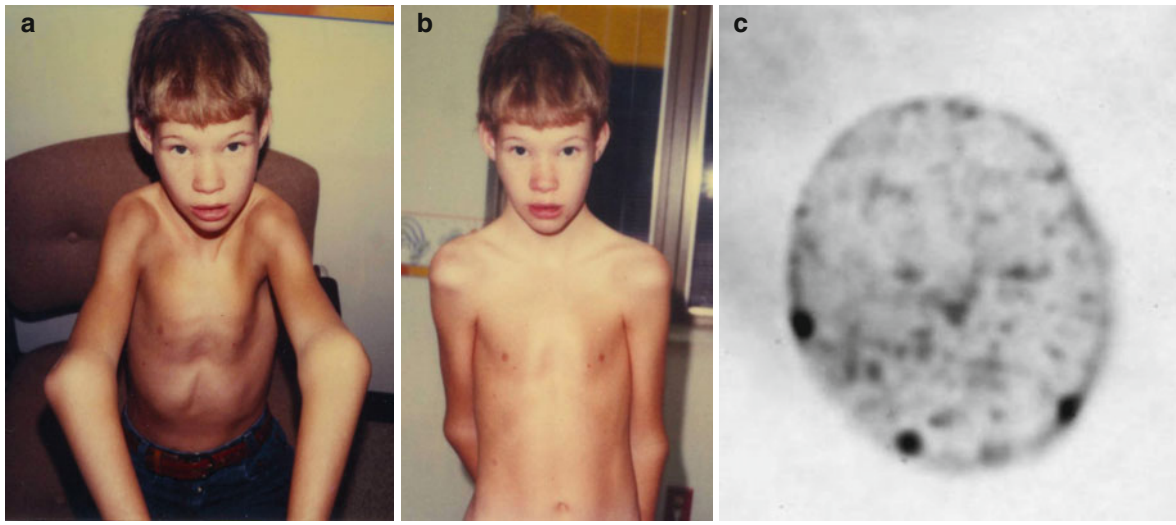

Fig.1 (**a**–**c**) An older boy with 49,XXXXY showing bilateral dislocation of the elbows, radioulnar synostosis, and three Barr bodies (buccal smear)

Fig. 2 (**a**, **b**) A younger boy with 49,XXXXY showing a full, round face. He also has incontinentia pigmenti achromians

XY Female

XY females are completely sex-reversed individuals who are phenotypically females with 46,XY karyotype, failure to develop secondary sex characteristics, amenorrhea, and "streak gonads."

Synonyms and Related Disorders

46,XY disorder of sex development; 46,XY sex reversal syndrome

Genetics/Basic Defects

1. Sexual differentiation (Michala and Creighton 2010): Genetic sex is determined at conception, when the ovum is fertilized by an X or Y chromosome containing spermatozoon (Ahmed and Hughes 2002).
   a. Testicular development
      i. The presence of the Y chromosome directs testicular development, through a switch gene present on its short arm, called the *SRY* gene (Sinclair et al. 1990).
      ii. This, along with other testes-determining factors (TDFs), will guide the differentiation of the undifferentiated gonad into testicular tissue (Cameron and Sinclair 1997).
      iii. Further genital differentiation is promoted by hormones that are produced by testicular tissue and that will lead to virilization.
      iv. Sertoli cells produce anti-Müllerian hormone (AMH), which triggers the regression of Müllerian structures while Leydig cells secrete testosterone, which promotes the development of Wolffian structures into the vas deferens, seminal vesicles, and epididymis (Rey and Picard 1998).
      v. Testosterone is further converted into dihydrotestosterone (DHT), a potent androgen, in the periphery, leading to the virilization of the external genitalia (Zhu et al. 1998).
   b. Ovarian development
      i. Ovarian tissue develops in the absence of TDFs and in the face of the antitesticular action of the genes *DAX1*, *Rspo1*, and *WNT4*.
      ii. Ovaries do not produce hormones during fetal life and the development of female genitalia is independent of hormone production.
      iii. The fetus is recognizable as male or female at 12 weeks and this can be identified ultrasonographically from the second trimester of pregnancy onwards (Odeh et al. 2009).
2. *SRY* gene and its mouse homologue, *Sry* (Schäffler et al. 2000)
   a. The sex-determining region on the Y chromosome
      i. Mapped to the short arm of the Y chromosome
      ii. Encodes for a testis-determining factor (TDF)
      iii. Candidate gene narrowed down to a 35-kb interval on the Y chromosome adjacent to the pseudoautosomal boundary which contains a Y chromosomal–specific sequence, named SRY (sex-determining region Y gene)
      iv. Demonstration that mice transgenic for Sry developed into sex-reversed males despite an XX karyotype provided the confirmation of SRY being the TDF that directs the undifferentiated gonad into a testis.

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b. Deletions or mutations occurring in the *SRY*
   i. Result in failure of testis development
   ii. Sex differentiation along the female pathway
3. Mechanism of male to female sex reversal (abnormalities of XY sex determination)
   a. Mutations in the SRY gene resulting in XY females with gonadal dysgenesis (vs. translocation of this gene sequence to X chromosome giving rise to XX males)
      i. Increasing variety of unique mutations within SRY gene reported in patients with gonadal dysgenesis/XY reversal. These patients are, in general, normal 46,XY females with complete gonadal dysgenesis.
      ii. SRY gene mutations noted in 15–20% of cases with complete gonadal dysgenesis
         a) Most mutations are located in the High Mobility Group (HMG) box.
         b) De novo mutations affect only one individual in a family in the majority of cases.
         c) Phenotypic variability is associated with different mutations.
      iii. About one third of the *SRY* mutations reported are inherited.
         a) No apparent explanation available to explain why an inherited SRY mutation which results in sex reversal in the offspring is associated with a normal male phenotype in the father and sometime in brothers and uncles.
         b) Paternal mosaicism for the mutant *SRY* provides an explanation for the other familial cases of XY gonadal dysgenesis.
      iv. Eighty percent of patients with sporadic or familial 46,XY gonadal dysgenesis lack a mutation or deletion of the SRY gene, indicating that other autosomal or X-linked genes have a role in sex determination.
   b. *Sox9*
      i. Another gene involved in sex determination identified by positional cloning of a chromosomal breakpoint has been identified in the XY female with campomelic dysplasia, a condition in which three quarters of XY patients show genital and gonadal malformations.
      ii. Belongs to a family of SRY-box-related (SOX) genes which encode proteins with at least 60% amino acid homology to the HMG box of the SRY protein
   c. *Atrx*
      i. The gene responsible for the ATR-X syndrome causes α-thalassemia, severe mental retardation, and multiple congenital anomalies which may include 46,XY gonadal dysgenesis and undermasculinization.
      ii. The C-terminal region of the protein has been lost in most cases where there has been gonadal dysgenesis associated with ATR-X syndrome.
   d. Deletions of variable portions of the short arm of chromosome 9 (*DMRT-1* identified as a candidate gene) result in partial or complete gonadal dysgenesis in XY females.
   e. Sex-reversing Xp duplication (Xp21) (Bardoni et al. 1994)
4. Classification of 46,XY disorders of sex development (DSD) (Hughes 2008; Mendonca et al. 2009)
   a. 46,XY DSD due to gonadal (testicular) development
      i. Gonadal agenesis
      ii. Complete or partial gonadal dysgenesis (e.g., *SRY*, *SOX9*, *SF1*, WT1, DHH)
      iii. Ovotesticular DSD
      iv. Embryonic testis regression syndrome
      v. Gonadal dysgenesis associated with syndromic phenotype
   b. Disorders of androgen syndromes
      i. Disorders of androgen synthesis
         a) LH receptor mutations
         b) Smith–Lemli–Opitz syndrome
         c) Steroidogenic acute regulatory protein mutations
         d) Cholesterol side-chain cleavage(*CYP11A1*)
         e) 3β-hydoxysteroid dehydrogenase 2 (*HSD3B2*)
         f) 17α-hydroxylase/17,20-lyase (*CYP17*)
         g) P450 oxidoreductase (*POR*)
         h) 17β-hydoxysteroid dehydrogenase(*HSD17B3*)
         i) 5α-reductase 2 (*SRD5A2*)
      ii. Disorders of androgen action
         a) Androgen insensitivity syndrome
         b) Drugs and environmental modulators
   c. Others
      i. Syndromic associations of male genital development (e.g., cloacal anomalies, Robinow, Aarskog, hand-foot-genital, popliteal pterygium)

ii. Persistent Müllerian duct syndrome
iii. Vanishing testis syndrome
iv. Congenital hypogonadotropic hypogonadism
v. Cryptorchidism (*INSL3*, *GREAT*)
vi. Environmental influences
vii. Nonclassical forms
a) Isolated hypospadias (*CXorf6*)
b) 46,XY gender identity disorders (male to female transsexualism)

Clinical Features

1. Clinical presentation of an XY female (Berkovitz 1992; Michala and Creighton 2010)
a. Primary amenorrhea with delayed puberty (Swyer syndrome)
i. 46,XY females (individuals with 46,XY complete gonadal dysgenesis)
ii. Diagnosis usually not made until puberty when the patient presents with delayed pubertal development
iii. Unambiguous female phenotype with completely female external genitalia
iv. Gonadal dysgenesis (streak gonads)
v. Well-developed Müllerian structures: Lack of secretion of anti-Müllerian hormone (AMH) results in the normal development of the uterus, fallopian tubes, and vagina
vi. Absence of testicular development
vii. Absence of Wolffian structures
viii. Absence of other somatic abnormalities
ix. Absence of secondary sexual characteristics
x. Amenorrhea
xi. High risk of developing gonadal tumors
a) Gonadoblastoma
b) Dysgerminoma
b. Primary amenorrhea with normal breast development and absent or scanty pubic and axillary hair (complete androgen insensitivity syndrome): Please see the chapter
c. Ambiguous genitalia at birth or virilization at puberty: Possible causes:
i. Mixed gonadal dysgenesis
ii. 5α-reductase deficiency
iii. 17β-hydroxysteroid dehydrogenase deficiency
iv. Partial androgen insensitivity syndrome
v. Leydig cell hypoplasia
d. Inguinal hernia: Possible causes:
i. Complete androgen insensitivity syndrome
ii. 5α-reductase deficiency
iii. 17β-hydroxysteroid dehydrogenase deficiency
iv. Partial androgen insensitivity syndrome
e. Discordant phenotype to karyotype following prenatal diagnostic testing: can be due to all conditions
f. Testing following the diagnosis of an affected sibling: can be due to all conditions
2. Differential diagnosis
a. Individuals with 46,XY partial gonadal dysgenesis (also called 46,XY mixed gonadal dysgenesis or dysgenetic male pseudohermaphroditism)
i. Majority of patients present in the newborn period for evaluation of ambiguous genitalia
ii. Partial testicular determination. The extent of masculinization of the external genitalia depends on the extent of testicular differentiation.
iii. Dysgenetic gonads
iv. Presence of Müllerian and Wolffian structures
v. Regarded as the clinical spectrum of 46,XY gonadal dysgenesis
b. Individuals with 46,XY embryonic testicular regression syndrome (also called true agonadism or gonadal agenesis)
i. A term used to describe the spectrum of genital anomalies resulting from regression of testis development from 8 to 14 weeks of gestation
ii. Regression of the fetal testes between 8 and 10 weeks of gestation
a) Complete absence of gonads
b) Rudimentary Müllerian and/or Wolffian ductal structures
c) Hypoplastic uterus
d) Female genitalia with/or without ambiguity
iii. Regression of the testes after the critical period of male differentiation (around 12–14 weeks)
a) Anorchia
b) Partial testicular regression resulting in a male phenotype as in anorchia but with small rudimentary testes

Diagnostic Investigations

1. Karyotype analysis
   a. 46,XY in phenotypic females
   b. To exclude 45,X/46,XY and other forms of mosaicism, served to exclude the more common forms of gonadal dysgenesis
2. Molecular analysis for *SRY* gene
   a. Nucleotide substitutions (missense/nonsense)
   b. Deletions
   c. Insertions
3. Ultrasonography/laparotomy
   a. Complete gonadal dysgenesis
      i. Streak gonads
      ii. Presence of Müllerian ducts
      iii. Absence of Wolffian ducts
   b. Partial gonadal dysgenesis
      i. Dysgenetic gonads
      ii. Presence of Müllerian and Wolffian structures
4. Gonadal histology
   a. Streak gonads
      i. Absence of primordial follicles
      ii. Wavy ovarian stroma intermixed with fibrous tissue
   b. Gonadal tumors observed in about 30% of cases
      i. Gonadoblastomas: usually benign
      ii. Dysgerminoma
      iii. Embryonal carcinoma: more life-threatening
5. Biochemical findings
   a. Elevated levels of FSH and LH
   b. Low levels of estradiol
   c. No elevation of androgen levels

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: recurrence risk depending on whether the inheritance is X-linked recessive, male-limited autosomal dominant, or autosomal recessive
   b. Patient's offspring: The patients are nonreproductive.
   c. To rule out the disease in siblings because of the presence of familial aggregation
2. Prenatal diagnosis: demonstration of the sexual discrepancy between fetal karyotype (XY) and ultrasonographic fetal phenotype (Bretelle et al. 2002)
   a. To exclude sample error and placental mosaicism
   b. Detailed fetal ultrasound examination to check for syndromic gender discrepancy such as:
      i. Campomelic dysplasia (skeletal malformation)
      ii. Denys–Drash syndrome
      iii. Smith–Lemli–Opitz syndrome
         a) Microcephaly
         b) Abnormal cholesterol metabolism
      iv. Alfi syndrome
         c) Craniostenosis
         d) Trigonocephaly
         e) Multiple congenital anomalies
   c. Prenatal diagnosis possible by SRY analysis for XY gonadal dysgenesis (SRY-negative XY female and SRY-positive XY female)
      i. FISH using SRY probe on metaphase chromosomes
      ii. Sequencing of entire coding region
3. Management
   a. Removal of gonads to avoid malignancy
   b. Initiate cyclic hormonal therapy with estrogen and progesterone at puberty
   c. Vaginoplasty should be performed in adolescence to prevent the risk of vaginal stenosis
   d. Psychological counseling
      i. Raise as a female
      ii. Information regarding the condition and the karyotype should be provided to the patient and her family
      iii. Increase patient's knowledge about medical and surgical history and karyotype
      iv. Counseling for sexual function
      v. Achievement of pregnancy in some patients following in vitro fertilization with a donor egg

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Fig. 1 (**a**–**c**) A patient with 46,XY female with gonadal dysgenesis at 42 years of age. Patient has short stature (4'6"), primary amenorrhea, lack of secondary sex characteristics (absent axillary hair, poor breast development), but normal female external genitalia. Laparotomy revealed absent Wolffian structures and presence of uterus and streak gonads which were excised

XYY Syndrome

In 1961, Sandberg described an XYY man. The incidence is estimated to be approximately 1 in 1,000 live male newborns and more frequent in infertile population (Martin 2008).

Genetics/Basic Defects

1. Caused by an additional Y chromosome in males (Rives et al. 2003)
2. Mechanisms of the extra Y chromosome in 47,XYY males
   a. Paternal nondisjunction at meiosis II after a normal chiasmate meiosis I (84%)
   b. Postzygotic mitotic error or nondisjunction at meiosis II after a nullichiasmate meiosis I (16%)
3. Spermatogenesis
   a. Normal spermatogenesis in majority of XYY males
      i. The supernumerary Y chromosome probably lost at the early stage of spermatogenesis
      ii. A large proportion of primary spermatocytes containing only one Y chromosome
   b. Altered spermatogenesis in a proportion of XYY males: Persistence of the supernumerary Y chromosome through meiotic prophase increases spermatocyte degeneration.
4. A higher incidence of the XYY complement in the institutions for the retarded, the mentally ill, the criminally insane, and the aggressive offender: controversial and biased

Clinical Features

1. Earlier observation of the association between the additional Y chromosome and aggressive behavior: considered to be due to selection bias and has since been challenged (Linden et al. 2002)
2. No consistent physical stigmata or medical disorders
3. Growth and development
   a. Increased growth velocity during earliest childhood
   b. Tall stature
   c. Larger tooth size
   d. At risk for mild speech/language and motor delays and learning disabilities
4. Intelligence
   a. Normal range
   b. IQ: 10–15 points lower than siblings
5. Behavioral profile
   a. Childhood temper tantrums
   b. No increased incidence of aggression
   c. Heterosexual
6. Normal reproduction
7. Normal adult adaptation
8. Low fertility

Diagnostic Investigations

1. Chromosome analysis to detect 47,XYY
2. Psychological and psychiatric evaluations when needed

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3. Studies of sperm karyotypes or FISH analysis of sperm: The majority of sperm are chromosomally normal in 47,XYY men (Martin et al. 2001).
4. EEG (Tomiero et al. 2011)
   a. Normal background activity and sleep organization
   b. Particular local spikes and sharp waves localized mostly over the vertex and/or central-temporal regions which increased during sleep

Genetic Counseling

1. Recurrence risk
   a. Patient's sib: not increased
   b. Patient's offspring: Patient generally has chromosomally normal children, despite the high theoretical risk of aneuploidy.
2. Prenatal diagnosis: fetal karyotyping from amniocytes or CVS
3. Management (Bender et al. 1984; Linden et al. 2002)
   a. The extra Y chromosome represents a risk factor for motor and language development, but the environment remains a primary force in shaping child's development.
   b. The increased frequency of prenatal detection of 47,XYY by amniocentesis necessitates the importance of making accurate information about the developmental prognosis of these individuals.
   c. Infancy and toddler: assess developmental milestones
   d. Childhood: assess school performance and provide intervention if needed
   e. Adolescence: no intervention needed
   f. Adulthood annual physical examination

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Fig. 1 A 7-year-old boy with 47,XYY syndrome showing normal phenotype

Fig. 2 A 13-year-old boy with XYY syndrome showing normal phenotype. He also has systemic carnitine deficiency and received Carnitol treatment

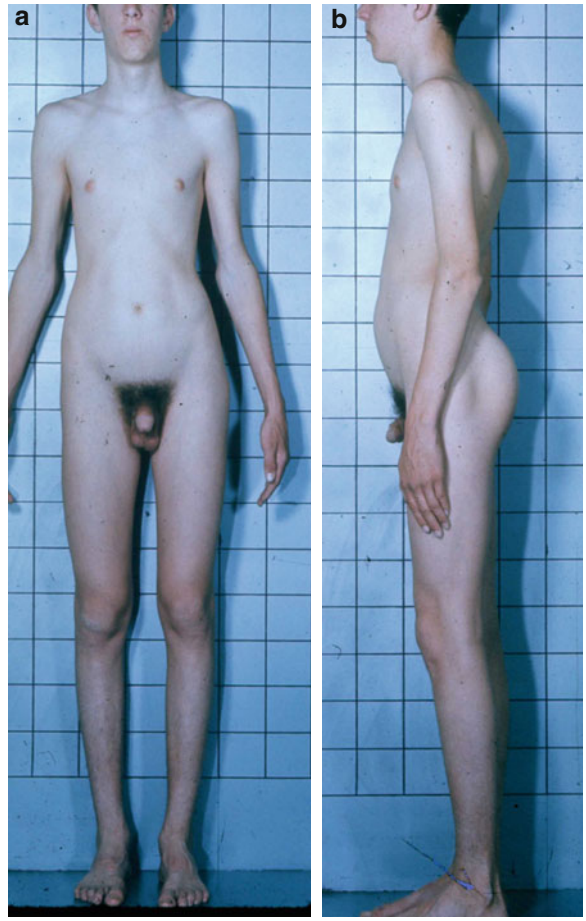

Fig. 3 (**a**, **b**) An adult with 47,XYY syndrome showing tall stature

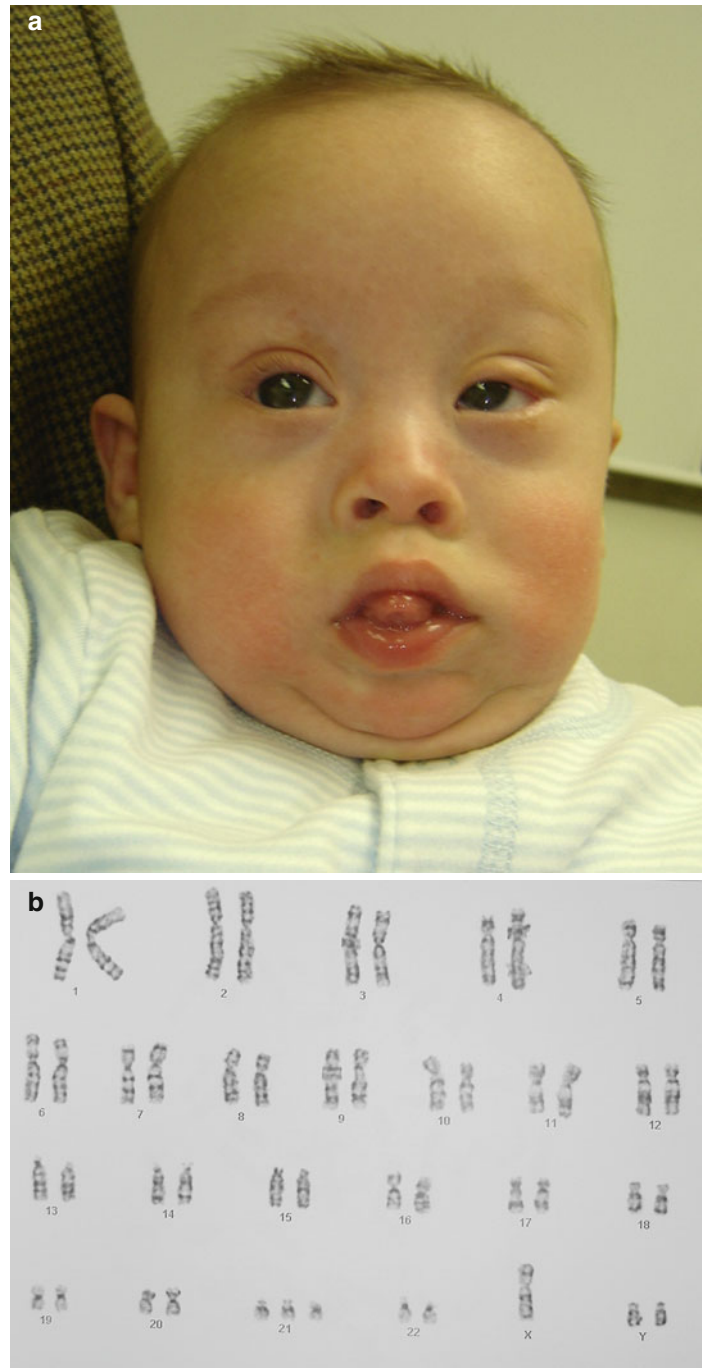

Fig. 4 (**a**, **b**) An infant with XYY and trisomy 21 (48, XYY,+21)