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To all the children.
To my own children and grandchildren,
but especially to those children everywhere whose lives have been touched by adversity.

BLACKWELL'S NEUROLOGY AND PSYCHIATRY ACCESS SERIES

Child and Adolescent Neurology

SECOND EDITION

EDITED BY

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Richmond
Virginia

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Preface

Traditional textbooks convey knowledge. It is the goal of this text in the Blackwell's Neurology & Psychiatry Access Series to convey not only essential knowledge but also the collected wisdom of its many highly regarded contributors. To achieve the goal of conveying not only knowledge but wisdom, each book in this series is built on a structural framework that was well received by critics and readers alike in David: *Pediatric Neurology for the Clinician* and the first editions of *Child and Adolescent Neurology*, *Adult Neurology*, *Child and Adolescent Psychiatry* and *Adult Psychiatry* (Mosby). Each volume is divided into three sections:

- Tools for diagnosis
- Diseases and disorders
- Common problems

Also included to facilitate a physician's use of this book are:

- Nosologic diagnosis tables
- "Pearls and Perils" boxes
- "Consider Consultation When…" boxes
- Selected annotated bibliographies
- A complete bibliography

and (new in this edition)

- Key Clinical Questions

The Nosologic Diagnosis tables are based on a discriminator model to promote clearer understanding and are superior to a criterion-based model and others that lack similar specificity. (See the Appendix for complete description of how this system was developed.)

> Whoever having undertaken to speak or write hath first laid for themselves some [basis] to their argument such as hot or cold or moist or dry or whatever else they choose, thus reducing their subject within a narrow compass.
>
> Hippocrates

As Hippocrates has suggested, structure is the key to learning. Unless there is a structure onto which knowledge can be built, confusion and disorganization are the inevitable consequences.

Classification systems induce orderliness in thinking and enhance our ability to communicate effectively. A review of the most enduring hierarchical classification systems, particularly that of Linnaeus (that is, phyla, genera, species), makes clear the value of grouping according to discriminating features, as well as the value of simplicity, expandability, and dynamism.

The goal, whatever the classification system, is to seek the most powerful discriminating features that will produce the greatest diagnostic clarity. Discriminating features should avoid crossing domains. Much of the confusion that arises in diagnosis may be the result of the clinician who unwittingly crosses the anatomic, pathologic, pathophysiologic, phenomenologic, and etiologic classification domains used in medicine (for example, the inclusion of anatomically-oriented "temporal lobe seizures" in a phenomenologically based classification system that includes complex partial seizures). Some conditions, such as brain tumors, are classified according to their histopathology and lend themselves well to this classification system. Others, such as headaches and movement disorders, are classified phenomenologically and are therefore much less easily classified. In other cases, discriminators must encompass inclusionary as well as exclusionary features. At times, we can only use a criterion-based system or construct tables to compare features.

Arbitrarily, we label as consistent features those which occur more than 75% of the time; features are considered variable when they occur less than 75% of the time. The diagnostic tables should be viewed, therefore, only as a beginning in the extremely difficult effort to make diagnosis more precise and biologically based. How well this book accomplishes the goals of identifying the most powerful discrimination features for maximum diagnostic clarity is limited by the current state of the art in child and adolescent neurology. In some areas, several features, when clustered together, serve to discriminate.

This text is designed to be pithy, not exhaustive, as there are already many available of this ilk. Each text in this series reflects appropriate stylistic differences among content editors. However, each is built upon the same structural framework, hence the value of this text to the users.

Chapter 16 on "Order and Disorders of Nervous System Development" is particularly noteworthy because of its unique treatment of this very important and timely subject matter.

As a part of this preface, I would like to acknowledge some of the people who have made key contributions to this effort. They include: Craig Percy, who initially saw the potential of

this effort; the National Institute of Neurological Disorders and Stroke (NINDS)* for its support in nosologic research; and the investigators who were involved with this NINDS project; Dr Grover Robinson, a long-time friend (who suggested the "Consider Consultation When…" boxes); Ms Laura DeYoung, Mr Stuart Taylor and all the Blackwell team who made this vision a reality. I am also particularly grateful to my associate editor colleagues, Drs John Bodensteiner, David Mandelbaum, and Barbara Olson, for their most significant contribution. Their help is reflected, I feel, in the extraordinary quality of the present effort. Lastly, I would like to thank Merle Colglazer and C.L Womack for their invaluable editorial assistance and Dr Mary Dominski for her careful review of the manuscripts for clarity and consistency.

This text is therefore in no way a singular effort and reflects the expertise of all who contributed in so many different ways and it is my hope that this is reflected in the quality of the effort. It is therefore my fondest wish that this text reside on your desk, rather than your bookshelf.

Ronald B. David, MD

*NINDS 1PO1NS20189–01A1 (Nosology, Higher Cortical Function Disorders in Children)

SECTION 1

Pediatric Neurologic Evaluation

John B. Bodensteiner, MD

CHAPTER 1

Neurologic History

Ronald B. David, MD and John B. Bodensteiner, MD

OUTLINE

Demographic data
Medical information/history
Treatment information/history
Pregnancy, birth, and development information/history
Attention/activity/behavior/habits
Skills and abilities

Some clinicians have suggested that the taking of the neurologic history is as important as, or potentially more important than, the neurologic examination itself. Other clinicians have suggested that the neurologic history identifies the nature of the disorder or disease and the neurologic examination pinpoints its location. The history itself may be a narrative recapitulation of information provided by a child's primary caregiver(s), or it may be generated in response to a questionnaire or checklist. Experienced clinicians realize that the key to making a successful diagnosis often lies in asking the right questions and listening carefully to the answers. Responses to questionnaires or checklists can be used as part of a formal structured interview. Diagnostically they can be both reliable and valid. For example, a patient may be asked the following questions with respect to headaches: (1) Are your headaches confined to one side of your head? (2) Are your headaches associated with vomiting or a desire to sleep? (3) Do you have visual symptoms, such as dancing lights or other phenomena? An affirmative response to all three questions would permit accuracy of close to 100% for the diagnosis of migraine. No other questions or laboratory investigations may be necessary. Other questions provide clinical rather than diagnostic information, useful in practicing the art as well as the science of medicine. The questions that follow are those used by many clinicians to accomplish this end. Some are also valuable in answering research questions. They are all designed to be useful in the practice of pediatric neurology. Note: This form may be reproduced for clinical use without further permission from the author or publisher.

A. Demographic data

1 Name _____

2 Child's date of birth _____ _____ / ____ _____ / _____ _____

3 Child's age _____ _____ / _____ _____

4 Child's sex

- **a** Male _____
- **b** Female _____

5 Child's race

- **a** Caucasian _____
- **b** African American _____
- **c** Latino _____
- **d** Asian _____
- **e** Other

6 Birthplace _____

7 Name of hospital _____

8 Child's siblings (please list oldest first)

	Age		Sex		Relation to this child			
Initials	Years	Months	M	F	Full	Half	Adopted	Step

9 Marital status of parents
- **a** Married _____
- **b** Single _____
- **c** Separated _____
- **d** Divorced _____

10 Relationship of caregiver to child
- **a** Natural parent _____
- **b** Adoptive parent _____
- **c** Stepparent _____
- **d** Foster parent _____
- **e** Grandparent _____
- **f** Aunt or uncle _____
- **g** Brother or sister _____
- **h** Other _____

11 Parents' educational experience

	Father	Mother
a Eighth grade or less	_____	_____
b Attended high school	_____	_____
c High school graduate	_____	_____
d Attended college	_____	_____
e Two-year degree	_____	_____
f Four-year degree	_____	_____
g Master's degree	_____	_____
h Doctorate	_____	_____

12 Handedness of parents

	Father	Mother
a Right	_____	_____
b Left	_____	_____
c Ambidextrous	_____	_____

13 Please check if the parent was or is considered to have difficulty with any of the following:

	Father	Mother
a Speech	_____	_____
b Confusion of left and right hands	_____	_____
c Overactivity, restlessness, hyperactivity	_____	_____
d Being clumsy or awkward	_____	_____
e Walking	_____	_____
f Math	_____	_____
g Spelling	_____	_____
h Reading	_____	_____
i Delayed or unintelligible language	_____	_____
j Seizures or convulsions	_____	_____
k Nerves or nervous breakdown	_____	_____
l Mental retardation	_____	_____

B. Medical information/history

1 Please check if your child has ever experienced any of the following	Yes	No
a More than two episodes of otitis media	_____	_____
b Tubes in ears (myringotomy)	_____	_____
c Visual difficulty requiring either glasses or visual training	_____	_____
d Hearing difficulty requiring the use of a hearing aid	_____	_____
e Movement problems requiring the use of special shoes, splints, braces, or a wheelchair or a specialized program of motor training	_____	_____

	Yes	No
f Failure to thrive	_____	_____
g Poisoning or drug overdose	_____	_____
h Eating unusual substances (e.g. paint, plaster)	_____	_____
i Unconscious spells, fainting	_____	_____
j Convulsions, seizures, epilepsy	_____	_____
k Bedwetting beyond the age of 5 years	_____	_____
l Soiling beyond the age of 3 years	_____	_____
m Sleeping problems	_____	_____
n Poor growth or poor weight gain	_____	_____
o Unusual reactions to baby shots	_____	_____
p Toe walking	_____	_____
q Ran or walked more awkwardly than other children	_____	_____
r Ran or walked more slowly than other children	_____	_____
s Picked last or close to last in games where children pick sides	_____	_____
t Tics or unusual movements	_____	_____
u Headaches not relieved by nonprescription pain medicine	_____	_____
v Headaches not relieved by prescription pain medicine	_____	_____
w Headaches occurring in the middle of the night or upon awakening	_____	_____
x Production of unusual odors	_____	_____
y Unusual habits	_____	_____
z Difficulty swallowing	_____	_____
aa Excessive drooling	_____	_____
bb Poor sucking or feeding as an infant	_____	_____
cc Lost once-attained skills (speech, language, or motor)	_____	_____
dd Seemed to be in a world of his own	_____	_____
ee Had difficulty with taking turns	_____	_____
ff Became upset if lined-up toys were disturbed	_____	_____
2 Has your child ever been diagnosed as		
a Hyperactive (hyperkinetic)	_____	_____
b Brain damaged	_____	_____
c Retarded	_____	_____
d Developmentally delayed or disabled	_____	_____
e Having epileptic seizures (including febrile)	_____	_____
f Motor delayed	_____	_____
g Cerebral palsied	_____	_____
h Language delayed	_____	_____
i Immature	_____	_____
j Hearing impaired or deaf	_____	_____
k Blind or partially sighted	_____	_____
l Emotionally disturbed	_____	_____
m Hypotonic	_____	_____
n Spastic	_____	_____
o Attention deficit disordered	_____	_____
p Learning disabled	_____	_____
q Autistic or demonstrating autistic-like behavior	_____	_____
3 Has your child ever		
a Had a special diet	_____	_____
b Received speech therapy	_____	_____
c Attended a preschool special education program	_____	_____
d Received counseling (family or individual)	_____	_____
e Received special education services, grades K through 12	_____	_____
f Been hospitalized	_____	_____
g Been suspended or discharged from day care, kindergarten or school	_____	_____

C Treatment information

	Yes	No
1 Has your child ever been evaluated by a		
a **(1)** Neurologist (child or general)	_____	_____
(2) Pediatrician	_____	_____
(3) Family doctor	_____	_____
(4) Psychiatrist	_____	_____
(5) Physiatrist (physical medicine or rehabilitation specialist)	_____	_____
b School psychologist	_____	_____
c Teacher	_____	_____
d Special education placement committee	_____	_____
e Child development specialist	_____	_____
f Physical or occupational therapist	_____	_____
g Speech/language pathologist	_____	_____
2 Has your child ever taken		
a Phenobarbital	_____	_____
b Dilantin (phenytoin)	_____	_____
c Mysoline (primidone)	_____	_____
d Depakene, Depakote (valproic acid)	_____	_____
e Tegretol (carbamazepine)	_____	_____
f Zarontin (ethosuximide)	_____	_____
g Valium (diazepam)	_____	_____
h Haldol (haloperidol)	_____	_____
i Klonopin or Clonopin (clonazepam)	_____	_____
j Neurontin (gabapentin)	_____	_____
k Felbatol (felbamate)	_____	_____
l Lamictal (lamotrigene)	_____	_____
m Trileptal (oxcarbazepine)	_____	_____
n Zonegran (zonisamide)	_____	_____
o Keppra (levetiracetam)	_____	_____
p Topamax (toparamate)	_____	_____
q Gabitril (tiagabine)	_____	_____
r Carbitrol (carbamazepine)	_____	_____
s Ativan (lorazepam)	_____	_____
t Mellaril (thioridazine)	_____	_____
u Dexedrine (dextroamphetamine) or Adderall (mixed amphetamine salts)	_____	_____
v Ritalin (methylphenidate)	_____	_____
w Cylert (pemoline)	_____	_____
x Asthma medication(s)	_____	_____
y Antihistamine(s)	_____	_____
z Decongestants	_____	_____
i Prozac	_____	_____
ii Zoloft	_____	_____
iii Paxil	_____	_____
iv Lexapro	_____	_____
v Celexia	_____	_____
vi Wellbutrin	_____	_____
vii Effexor	_____	_____
viii Abilify	_____	_____
ix Geodon	_____	_____
x Risperdal	_____	_____
xi Seroquel	_____	_____
xii Herbs and complementary medicine	_____	_____
xiii Zyprexia	_____	_____

3 Has your child ever had any unusual reaction to any of the medications listed above?
Please list and describe reaction

_____
_____
_____

4 Describe each of your child's emergency room visits or hospitalizations. Begin with the most recent

Age (Years/Months)			Reason
_____	_____ /	_____	_____
_____	_____ /	_____	_____
_____	_____ /	_____	_____
_____	_____ /	_____	_____

D Pregnancy, birth, and development information/history

1 How many pregnancies did child's mother have?

		Yes	No
2	Did you (she) have any		
a	Miscarriages	_____	_____
b	Abortions	_____	_____
c	Tubal pregnancies	_____	_____
d	Stillbirths	_____	_____
3	Were any medicines prescribed during your (her) pregnancy with this child, such as		
a	Pills for nausea	_____	_____
b	Antibiotics	_____	_____
c	Water pills	_____	_____
d	Pain pills	_____	_____
e	Thyroid medicine	_____	_____
f	Medicine to prevent miscarriage	_____	_____
g	Medicine to suppress appetite	_____	_____
h	Sedatives	_____	_____
i	Tranquilizers	_____	_____
j	Sleeping pills	_____	_____
k	Blood pressure pills	_____	_____
l	Other (name if known _____)	_____	_____
4	Were any of the following used during this child's pregnancy?		
a	Cigarettes	_____	_____
b	Alcohol (beer, wine, or hard liquor)	_____	_____
c	Coffee	_____	_____
d	Medicine that you bought at the drug store	_____	_____
5	Did you (she) have any of the following complications during this pregnancy?		
a	Significant abdominal injury	_____	_____
b	Any illness with fever and rashes	_____	_____
c	Diabetes	_____	_____
d	Operation	_____	_____
e	Emotional upset	_____	_____
f	Morning sickness	_____	_____
(1)	Requiring special attention	_____	_____
(2)	Requiring hospitalization	_____	_____
g	Rh incompatibility	_____	_____
h	Bleeding from the vagina	_____	_____
i	Staining	_____	_____
j	Anemia	_____	_____
k	Swollen ankles	_____	_____
l	Heart disease	_____	_____
m	Toxemia, eclampsia, preeclampsia	_____	_____
n	High blood pressure	_____	_____
o	Kidney disease	_____	_____
p	German measles	_____	_____
6	How much weight was gained during pregnancy?	_____ ib	
7	How long was the total period of labor?	_____ h	
8	How long was the period of hard labor?	_____ h	
9	How long was it from the time your (her) water broke until the baby was delivered?	_____ h	
10	During this pregnancy	Yes	No
a	Were you confined to bed for more than 1 day?	_____	_____
b	Was an ultrasound performed?	_____	_____

		Yes	No
c	Were there any abnormalities in the ultrasound?	_____	_____
d	Were your baby's movements before birth	_____	_____
	(1) Normal	_____	_____
	(2) Increased	_____	_____
	(3) Decreased	_____	_____
e	Was amniocentesis performed?	_____	_____
f	If so, were there any abnormalities in the amniocentesis?	_____	_____
11	Was the baby considered premature?	_____	_____
12	Was your baby overdue by more than 2 weeks?	_____	_____
13	Was there internal manipulation of your baby?	_____	_____
14	Was a Caesarean birth performed?	_____	_____
a	If performed, was it an emergency?	_____	_____
b	Was a general anesthetic used?	_____	_____
15	Was the baby head first?	_____	_____
16	Were forceps used?	_____	_____
17	Did the baby have any bruises?	_____	_____
18	Did the baby have any birthmarks?	_____	_____
19	Did the baby have breathing problems?	_____	_____
20	Was the cord wrapped around the baby's neck?	_____	_____
21	If so, was the cord wrapped more than once around your baby's neck or was there a true knot in the cord?	_____	_____
22	Did your baby cry quickly?	_____	_____
23	Was your baby's color normal?	_____	_____
24	Was your baby blue?	_____	_____
25	Was your baby yellow (jaundiced)?	_____	_____
26	Did your baby require transfusions?	_____	_____
27	Did your baby require phototherapy (lights)?	_____	_____
28	Was your baby placed in an isolette, incubator, or intensive special care unit?	_____	_____
29	Did your baby have seizures or convulsions?	_____	_____
30	Did your baby require oxygen?	_____	_____
31	Was your baby placed on a respirator (breathing machine)?	_____	_____
32	Were there concerns about your baby's heart rate?	_____	_____
33	Was the fluid stained with your baby's meconium (bowel movement)?	_____	_____
34	Were there other complications?	_____	_____
	List if known _____		
35	Did your baby have physical features which were unusual or very much unlike baby's relatives?		
36	Do you remember your baby's Apgar score?	_____	_____
a	Apgar score of 1 minute _____		
b	Apgar score of 3 minutes _____		
c	Apgar score of 5 minutes _____		
37	How long after birth did you take your baby home? ____ days		
38	During the first 2 weeks after the birth of your baby		
a	Was your baby considered to be limp?	_____	_____
b	Was your baby considered to be stiff?	_____	_____
c	Did your baby have feeding or sucking problems?	_____	_____
39	During the first year of life, did your baby		
a	Have difficulty sleeping?	_____	_____
b	Fail to grow or gain weight?	_____	_____
c	Show any unusual trembling or unusual movements of arms, legs, or head?	_____	_____

40 How old was your baby (your best guess) when he or she first

	< 6 mo	6-12 mo	12-18 mo	18-24 mo	24-36 mo	36-48 mo	48+ mo
a Sat alone	_____	_____	_____	_____	_____	_____	_____
b Crawled	_____	_____	_____	_____	_____	_____	_____
c Stood alone	_____	_____	_____	_____	_____	_____	_____
d Walked with assistance	_____	_____	_____	_____	_____	_____	_____
e Walked without assistance	_____	_____	_____	_____	_____	_____	_____
f Showed hand preference	_____	_____	_____	_____	_____	_____	_____

	< 6 mo	6-12 mo	12-18 mo	18-24 mo	24-26 mo	36-48 mo	48+ mo
g Was toilet trained–bowel							
h Was toilet trained–urine							
i Began to vocalize (babble)							
j Began to use words							
k Began to talk in sentences							

	Left	Right	Both
41 Which hand does your child prefer?			

42 Does your child	Yes	No
a Cry excessively?		
b Rarely or never attempt to communicate?		
c Use mainly gestures to communicate?		
d Have a hearing problem?		
e Turn head to distinguish from where a sound is coming?		
43 General language skills: Does your child		
a Have difficulty learning new vocabulary words?		
b Omit words from sentences (i.e. do his sentences sound telegraphic)?		
c Speak in short, incomplete sentences?		
d Have trouble with verbs, such as is, am, was, and were?		
e Have difficulty following directions?		
f Have difficulty understanding long sentences?		
g Have difficulty responding appropriately to questions?		
h Have problems asking questions beginning with who, what, where, and why?		
i Have trouble using present and past tense verbs correctly?		
j Show little or no progress in speech and language in the last 6 to 12 months?		
k Omit sounds from words?		
l Do you feel your child's speech is more difficult to understand than it should be in view of his or her age?		
m Does it seem that your child uses t, d, k or g in place of most other consonants when speaking?		
44 Receptive language skills: Does your child		
a Understand "where is mother?"		
b Point to one body part on request?		
c Follow two-step commands two times out of three?		
d Know six body parts?		
e Understand the concept of "one"?		
f Point to spoon and ball and show how a cup is used?		
g Recognize day and night?		
h Know three out of four prepositions (on, under, in front, behind, etc.)?		
i Understand the concept of "three"?		
j Identify right and left on self?		
45 Expressive language skills: Does your child		
a Know two to four single words?		
b Use two-word sentences?		
c Refer to self by own name?		
d Use plurals?		
e Converse in sentences?		
f Give full name?		
g Comprehend "tired," "cold," and "hungry"?		
h Name opposite analogies two times out of three (up/down, mother/father, in/out)?		
i Comprehend senses (taste, feel, smell, see, hear)?		
j Define words correctly six out of nine times (ball, desk, house, banana, curtain, ceiling, bush, sidewalk)?		

		Yes	No
46	Other language skills:		
	Does your child		
a	Have difficulty finding the correct words in conversation?	_____	_____
b	Have difficulty in getting the correct word out to use in conversation?	_____	_____
c	Put words in the wrong order?	_____	_____
d	Confuse words that have similar sounds?	_____	_____
e	Have difficulty pronouncing words or sounds?	_____	_____
f	Hesitate or stop before he or she completes sentences?	_____	_____
g	Stutter or stammer?	_____	_____
h	Respond inconsistently to sound and speech?	_____	_____
i	Understand what is said to him or her?	_____	_____
j	Label objects (house, tree, car, ball)?	_____	_____
k	Label actions (walk, run, sleep, ride, jump, read, write)?	_____	_____
l	Understand stories read to him or her?	_____	_____
m	Tell about events happening during the day?	_____	_____
n	Comment on what he or she is doing?	_____	_____
o	Relay a short message?	_____	_____
47	Is your child		
a	Understood by parents and family?	_____	_____
b	Understood by other adults?	_____	_____
c	Understood by other children?	_____	_____
d	Teased by children about his or her voice?	_____	_____
e	Teased by children about his or her speech?	_____	_____
48	Social skill development and idiosyncratic behaviors:	_____	_____
a	Does your child		
(1)	Exhibit affection spontaneously?	_____	_____
(2)	Like to be held or played with as much as other children?	_____	_____
(3)	Share or take turns with other children readily?	_____	_____
(4)	Tend to be bossy or attempt to dominate other children?	_____	_____
(5)	When compared with other children, show decreased eye contact?	_____	_____
(6)	When with a group of children his or her age, stand outside or apart frequently?	_____	_____
(7)	Appear to be in a world of his or her own?	_____	_____
(8)	Walk on his or her tiptoes?	_____	_____
(9)	Flap his hands or arms when excited or stressed?	_____	_____
(10)	Exhibit other repetitive movements when excited or stressed?	_____	_____
50	Basic educational skills:		
a	Can your child		
(1)	Count from 1 to 10?	_____	_____
	Count from 10 to 20?	_____	_____
(2)	Count 1 to 10 objects?	_____	_____
	Count 10 to 20 objects?	_____	_____
(3)	Identify the numbers 1 to 10?	_____	_____
	Identify the numbers 10 to 20?	_____	_____
(4)	Recognize his or her name in print?	_____	_____
(5)	Name letters in his or her name?	_____	_____
(6)	Identify other letters in the alphabet?	_____	_____
(7)	Print his or her first name correctly?	_____	_____
(8)	Point to basic colors (red, green, blue, yellow, black, white)?	_____	_____
(9)	Understand the concept of money?	_____	_____
(10)	Identify coins (penny, nickel, dime, quarter)?	_____	_____
(11)	Print the numbers 1 to 10?	_____	_____
(12)	Print all the letters of the alphabet?	_____	_____
(13)	Include at least six body parts (head, arms, body, legs, eyes, ears, nose, fingers, hair) when drawing a person?	_____	_____
(14)	Understand the concept of "same or different"?	_____	_____
(15)	Repeat a short sentence?	_____	_____

	Yes	No
(16) Recognize similar letters?	_____	_____
Recognize similar words?	_____	_____
Recognize similar numbers?	_____	_____
b Does your child have problems in		
(1) Reading		
Word identification?	_____	_____
Comprehension?	_____	_____
Phonics?	_____	_____
(2) Spelling		
Oral?	_____	_____
Written?	_____	_____
(3) Writing		
Legibility?	_____	_____
Slow speed?	_____	_____
Sentence construction?	_____	_____
Basic grammar?	_____	_____
(4) Math		
Memory of basic facts (addition, subtraction, multiplication, division)?	_____	_____
Operations (addition, subtraction, multiplication, division)?	_____	_____
Word problems?	_____	_____
(5) Organization		
Completing classroom assignments?	_____	_____
Completing and turning in homework?	_____	_____
Planning study time or morning routine?	_____	_____
(6) Reasoning and problem solving (personal or in school)?	_____	_____
(7) Science, social studies, humanities, foreign languages?	_____	_____

E Attention/activity/behavior/habits

1	Does your child		
a	Sit still for a fascinating activity, such as television or being read to		
(1)	For under 5 minutes?	_____	_____
(2)	For 5 to 10 minutes?	_____	_____
(3)	For 10 to 15 minutes?	_____	_____
(4)	For more than 15 minutes	_____	_____
b	Sit and listen to a story when being read to individually?	_____	_____
c	Sit and listen to a story as a part of a group?	_____	_____
d	Seem attentive?	_____	_____
e	Seem to daydream?	_____	_____
f	Seem to be easily distracted?	_____	_____
g	Go quickly from one task to another?	_____	_____
h	Perform better in a calm, nondistracting setting?	_____	_____
i	Hear, but not appear to listen?	_____	_____
j	Appear overly frightened or anxious about new experiences?	_____	_____
k	Avoid written work, such as printing or coloring?	_____	_____
l	Produce sloppy work, even though he or she tries hard?	_____	_____
m	Desire friends, but frequently makes them angry?	_____	_____
n	Insist on being in charge or he or she will not play?	_____	_____
o	Have verbal fights with children?	_____	_____
p	Have physical fights with children?	_____	_____
q	Have a violent temper?	_____	_____
r	Have temper tantrums?	_____	_____
s	Steal?	_____	_____
t	Swear or use vulgar language?	_____	_____
u	Act verbally abusive to parents?	_____	_____
v	Act verbally abusive to other adults?	_____	_____
w	Act physically abusive to parents?	_____	_____
x	Act physically abusive to other adults?	_____	_____

		Yes	No
y	Cheat in order to be the winner?	_____	_____
z	Lose his or her temper quickly?	_____	_____
aa	Allow his or her feelings to be hurt easily?	_____	_____
bb	Engage in		
(1)	Head banging?	_____	_____
(2)	Bed rocking?	_____	_____
(3)	Hand flapping?	_____	_____
(4)	Walking on tiptoes?	_____	_____
cc	Frequently place his or her hands over ears to block out sound?	_____	_____
dd	Show a lack of interest in people?	_____	_____
ee	Speak in a mechanical, machine-like voice?	_____	_____
ff	Speak in a whisper?	_____	_____
gg	Seem preoccupied with strange creatures or monsters?	_____	_____
hh	Avoid affection?	_____	_____
ii	Avoid eye contact or looking at people?	_____	_____
jj	Frequently appear to be in his or her own world?	_____	_____
kk	When observed with a group of children, seem to be apart or alone frequently?	_____	_____
ll	Seem impulsive?	_____	_____
mm	Seem explosive?	_____	_____
nn	Change moods quickly?	_____	_____
oo	Have difficulty in appreciating danger?	_____	_____
pp	Seem easily frustrated?	_____	_____
qq	Have trouble waiting his or her turn?	_____	_____
rr	Seem extremely talkative?	_____	_____
ss	Show shame or remorse?	_____	_____
2	What type of school does your child attend? public _____ private_____		
3	At what age did your child begin preschool or day care?	_____	
4	At what age did your child begin kindergarten?	_____	
5	What grade does your child attend now?	_____	

		Yes	No
6	If in a regular grade (class), does your child receive special help?	_____	_____
7	Has your child ever been absent from school for 2 weeks or longer at one time?	_____	_____
8	Has your child had frequent short absences from school, resulting in absences of more than 30 days in the school year?	_____	_____
9	Has your child ever been suspended from school?	_____	_____
10	Has your child ever been retained by either your decision or the school's?	_____	_____
11	Was your child ever elected to an honor society?	_____	_____

F Skills or abilities

1	Sports		
a	Baseball or softball	_____	_____
b	Tennis	_____	_____
c	Swimming	_____	_____
d	Football	_____	_____
e	Soccer	_____	_____
f	Basketball	_____	_____
g	Computer or video games	_____	_____
h	Other	_____	_____
2	Music		
a	Singing	_____	_____
b	Dancing (including ballet)	_____	_____
c	Instruments	_____	_____
	Specify	_____	_____
3	Art		
a	Drawing	_____	_____
b	Copying	_____	_____
c	Other	_____	_____

		Yes	No
4	Academic		
	a Reading	_____	_____
	b Creative writing	_____	_____
	c Math	_____	_____
	d Computer literate	_____	_____
	e Typing (keyboarding)	_____	_____
5	Is your child a member of a		
	a Club	_____	_____
	b Other student organization	_____	_____
	Specify _____ _____		
	_____ _____		
6	Has your child ever been elected to an office?	_____	_____

7 In what skill or ability area(s) does your child seem to excel over most children his or her age?

_____

_____

PEARLS & PERILS

- The diagnosis can often be determined or inferred from one or two key questions
- Willingness to comply with treatment can be probed by use of key questions.
- Willingness to accept diagnosis can be probed through key questions.

CHAPTER 2

The Neurologic Examination of the Preterm and Fullterm Neonate and of the Infant

Patricia H. Ellison, MD and Donna K. Daily, MD

OUTLINE

What should be part of the neurologic examination?
Who should do the neurologic examination?
What is the prognosis for neurologic abnormality?
Appendix: neonatal and infant neurologic examination

In a medical world of high technology, in particular the ready availability of neonatal head ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), does the neurologic examination of babies still contribute to the diagnosis and treatment of neurologic disorders? Does it have other attributes, such as reassurance to the parents and clinicians? Can it be used as a measure of improvement from either systemic or neurologic disorder or used to identify the need for early intervention planning and services?

As clinicians who have reviewed hundreds of medical charts, the authors have noted considerable diversity in the numbers and types of items recorded by physicians as part of the neonatal neurologic examination. However, in general, the report is modest, with progress notes often consisting of brief phrases, such as "alert, moves all extremities." The most detailed examinations are often those of the physical or occupational therapist or those of a developmental pediatrician or pediatric neurologist, if consulted. The neurologic abnormality is often first noted after a clinical event, such as a seizure, or an abnormal imaging study indicating cerebral hemorrhage, or after the observation of significant lack of response, such as depression following birth or failure to suck well.

Single item abnormalities, such as a facial palsy or brachial plexus injury, appear to be noted fairly soon, if not in the delivery room, then in the initial newborn examination. Other neurologic abnormalities, such as decreased alertness or even fairly diffuse hypotonia, may not be identified in the brief newborn hospitalization which is common presently. That places an increased obligation on the physician for the physical and neurologic examination of the infant at 2 weeks.

What should be part of the neurologic examination?

Fortunately, there has been a series of clinicians who have keenly observed newborns and infants and who have created a large pool of items which could be used for neurologic examinations. Most of these clinicians have described and recommended a far larger number of items than can be done owing to limitations of time for the clinician, or tolerance, especially by sick newborns. The first consideration is to find some method of limiting the number of items. Secondly, the examination needs to be reliable, using the definitions developed by scientists for clinical measurement. In short, the examination method should have a mathematical cohesiveness of reliability, should be highly correlated when used from one time of examination to another and should be highly correlated when used from one examiner to another. To this end we have developed instruments of measurement of the neurologic examination for three age groups: the PremieNeuro for gestational ages 23–37 weeks; the NeoNeuro & Up for the gestational ages 38 weeks to age 4 months; and the Infanib for infants ages 4–18 months. The details of the methodology have been described previously. These three examinations assess aspects at the different ages, each of which has a number of items sufficient to assure validity (Table 2.1).

In addition, some other basic neurologic information needs to be gathered. Serial head circumferences seem so basic that they would not need to be mentioned in a learned chapter. Yet they have been missing in charts under review from the initial newborn evaluation; serial evaluations have been missing in newborns already identified with brain abnormality, and in

FEATURES

Table 2.1 Neurologic Examinations of the Newborn and Infant – Comparative Characteristics

	PremieNeuro	NeoNeuro & Up	Infanib
Age group to be tested	23–37 weeks gestational and/or post conception age	38 weeks gestation to 56 weeks post conception age	4–18 months of age
Diagnostic category for total score	Abnormal, questionable, normal	Severely abnormal, moderately abnormal, mildly abnormal, normal	Abnormal, transient, normal
Factors (elements which comprise the total score)	Neurologic, movement, responsiveness	Hypertonus, primitive reflexes, limb tone, neck support, reflexes and tremor, alertness, fussiness	Spasticity, vestibular function, head and trunk, French angles, legs
Number of items	16 (<28 weeks/on respirator) 24 (≥28 weeks/off respirator)	32	20
Includes behavioral measures	2 items	8 items	0 items

infants with a chief complaint that could refer to the brain. A second problem is that different services are often performed at different locations and by different clinicians, with poor communication of measurements of head circumference from one clinician to another. Always get the head circumference!

The definition of a head circumference which is abnormal should be straightforward. Any head circumference two standard deviations from the mean is abnormal (macrocephaly = 98th percentile or above; microcephaly = 2nd percentile or below). In addition, inappropriately enlarging heads need attention. Both accelerations and decelerations of growth should trigger concern. Obtain an imaging study with any measurement at the 98th percentile or above. In infants less than 6 months of age, an ultrasound will define the size of the ventricles. In most hospitals computed tomography is readily available, quick, and much more infant-friendly than in the past.

Who should do the neurologic examination?

It is obvious on chart reviews that neurologic examinations are being done by clinicians and therapists with different types of training. The documentation of the neurologic examination as performed by other health care professionals such as nurses, occupational and physical therapists can complement that of the treating physician.

Scored assessment instruments

I. The PremieNeuro scoring sheet

The PremieNeuro is a neurologic examination of preterm infants between the ages of 23 and 37 weeks gestational age. It consists of 24 items divided into three factors (Neurological, Movement, Responsiveness), each with eight items. If the infant is very immature or on the ventilator, only the first 16 items are scored because they can be done with minimal disturbance of the infant. The items in Factor 1 (Neurological) address reflexive behavior, progression of muscle tone, and movement type. The items in Factor 2 (Movement) document rate per minute of avoidance behaviors and limb movement. Lastly, the items in Factor 3 (Responsiveness) address head and trunk control as well as alertness and responsiveness. The examination should be scheduled one-half to 1 hour before a feeding. Asymmetry of findings should be noted for scoring. The examination consists of techniques commonly used for more mature infants but criteria for describing the very immature infant's responses differ (see photographs in NeoNeuro examination).

1. *Arm Recoil.* With the infant in supine position, take both hands and extend them alongside the trunk, hold 3 seconds and release. Note the amount of flexion at the elbow that is observed within 5 seconds.
   (a) 180° (b) 100–179° (c) 60–99° (d) <60°.
2. *Arm Traction.* With the infant in supine position, grasp the wrist slowly and pull arms to vertical. Score the amount of elbow flexion and resistance that is noted at the moment the infant is initially lifted off the surface.
   (a) ≥180° (b) 160–179° (c) 120–159° (d) 100–119° (e) <100°.
3. *Palmar Grasp.* With the infant in supine position, insert index finger into hand and gently press palmar surface. Grade according to strength of finger flexion.
   (a) absent (b) weak flexion (c) medium flexion (d) strong flexion spread to forearm (e) very strong – lifts off bed.
4. *Plantar Grasp.* With the infant in supine position, give pressure to the ball of the infant's foot. Grade according to strength of toe flexion.
   (a) absent (b) weak (c) medium (d) strong (e) very strong.
5. *Scarf Sign.* Hold the infant's arm near the elbow and move the arm across the infant's chest until resistance is met. Observe the angle formed by the upper arm and a line parallel to the trunk.
   (a) >85° (b) 60–85° (c) 45–60° (d) 15–45° (e) 0–15°.

6 *Popliteal Angle.* With both hips abducted, approximate knees and thighs to abdomen; extend legs by gentle pressure with index finger behind each ankle at the same time until resistance is met. When scoring this test, measure the angle of extension such that 180° equals a fully extended knee.
(a) ≥180° (b) 150–180° (c) 130–150° (d) 110–130° (e) 90–110° (f) <90°.

7 *Heel to Ear.* With the infant's feet held together, grasp both thighs and flex hips with knees extended until resistance is met. Measure the angle between the infant's trunk and legs.
(a) <10° (b) 10–40° (c) 40–60° (d) 60–90° (e) 90–100° (f) ≥100°.

8 *Movement Type.* Observe predominant type of movement: sluggish, uncoordinated, jerky, athetoid, stretching, smooth, alternating, both spontaneous and elicited seen throughout the examination.
(a) mostly sluggish (b) mostly stretching or smooth (c) smooth alternating (d) markedly asymmetrical (e) mostly tremulous.

9 *Tremors.* Record the number of episodes of tremors (trembling, shaking) observed in any part of the body, including face, and extremities.

10 *Thrashing.* Record episodes of overshooting, flailing movements, which could involve head and trunk, whole body, or single extremity.

11 *Facial Grimace.* Record number of facial movements (frowns, grimaces, quizzical) seen during the examination.

12 *Startle.* Observe the infant for a sudden flexor response of the arms in response to a loud noise, bright light or if one is elicited spontaneously.

13 *Yawn.* Record the number of yawns observed during the examination.

14 *Color Change.* Observe the infant for any noticeable color change that is observed during the examination, including mottling, duskiness, pallor, or increased redness anywhere on the body.

15 *Arm Movements.* Record the number of spontaneous arm movements observed during the examination.

16 *Leg Movements.* Record the number of spontaneous leg movements observed during the examination.

17 *Arm Flexion.* With the infant in the supine position, grasp both wrists and by applying gently traction, elevate the shoulders about 45°. Note the flexion response at the elbows. (Done simultaneously with No. 18).
(a) >170° (b) 140–170° (c) 110–140° (d) 70–110° (e) <70°.

18 *Head Lag.* Grasp both wrists and by applying gentle traction, elevate the shoulders about 45°. Observe the amount of head lag.

19 *Held Sit.* Hold the infant in an upright position with examiner's hands used to support the infant's shoulders. Observe the length of time the head is held in an upright position.
(a) head stays forward or backward (b) head up <3 seconds (c) head up 3–10 seconds (d) head up >10 seconds

20 *Posterior Neck.* Place the infant in supported sitting. Allow head to fall forward as you hold the shoulders, wait 15 seconds. Grade according to ability to lift head and maintain it upright.
(a) no attempt to raise head (b) tries but cannot raise head (c) head upright by 30 seconds, drops head (d) head upright by 30 seconds, maintained (e) examiner cannot extend head.

21 *Anterior Neck.* Place the infant in supported sitting. Allow head to drop backward as you hold the shoulders, wait 15 seconds. Grade according to ability to lift head and maintain it upright.
(a) no attempt to raise head (b) tries but cannot raise head (c) head upright by 30 seconds, drops head (d) head upright by 30 seconds, maintained (e) examiner cannot flex head.

22 *Alert.* Estimate the amount of time the infant is in the quiet, alert state, i.e. alert, with a bright look, minimal motor activity, regular respirations.
(a) 0–4 sec. (b) 5–10 sec. (c) 11–30 sec. (d) 31–60 sec. (e) > 60 sec.

23 *Ventral Suspension.* Place one hand under infant's abdomen in prone and suspend horizontally. Observe curvature of back, flexion of limbs, and relationship of head to trunk.

24 *Responsiveness.* Note the infant's awareness level throughout the examination, a subjective and qualitative assessment of the infant's response to movement, touching, handling, noise, hunger, etc.
(a) not very responsive (b) average (c) very responsive.

Using the PremieNeuro scoring sheet

The PremieNeuro scoring sheet (Fig. 2.1) lists the test items and their descriptions on the left side of the examination sheet. Each item should be evaluated and the appropriate description letter circled at that time. On the right-hand side of the page is the scoring for gestational ages 23–37 weeks. When scoring items 1–7, remember to record a score for both the right and left extremities. When an asymmetry is present, score the lower value if there is a one-letter difference. When the asymmetry is greater than or equal to two levels, score the letter indicated in the central column and its corresponding value for the corrected gestational age. Enter the points that correspond to the letter circled in the scoring columns at the far right. For items 9–16, determine rate based on number of observations divided by total time taken to complete the examination. Each column is summed to yield a factor score. Factor scores are then summed to yield a total score. Scoring ranges for three categories (normal, questionable, and abnormal) are indicated for neonates <28 weeks/on a respirator and ≥28 weeks/off a respirator. Patient information is recorded at the bottom of the page.

PREMIE NEURO

A Neurological Examination for Preterm Infants

	Item	Description				
FACTOR 1 - NEUROLOGICAL	1. ARM RECOIL	a) ≥180°	b) 100-179°	c) 60-99°	d) <60°	
	2. ARM TRACTION	a) ≥180°	b) 160-179°	c) 120-159°	d) 100-119°	e) <100°
	3. PALMAR GRASP	a) absent	b) weak flexion	c) medium flexion	d) strong flexion spread to forearm	e) very strong lifts off bed
	4. PLANTAR GRASP	a) absent	b) weak	c) medium	d) strong	e) very strong
	5. SCARF SIGN	a) >85°	b) 60° to 85°	c) 45° to 60°	d) 15° to 45°	e) 0° to 15°
	6. POPLITEAL ANGLE	a) ≥180°	b) 150° to 180°	c) 130° to 150°	d) 110° to 130°	e) 90° to 110° f) <90°
	7. HEEL TO EAR	a) <10°	b) 10° to 40°	c) 40° to 60°	d) 60° to 90°	e) 90° to 100° f) ≥100°
	8. MOVEMENT TYPE	a) mostly sluggish uncoordinated, jerky or athetoid	b) mostly stretching or smooth, some random, athetoid or jerky	c) smooth alternating movements	d) markedly asymmetrical	e) mostly tremulous
FACTOR 2 - MOVEMENT	9. TREMORS	MINUTES ____ ____	NO. _____	RATE/MINUTE ____.____ ____		
	10. THRASHING		_____	____.____ ____		
	11. FACIAL GRIMACE		_____	____.____ ____		
	12. STARTLE		_____	____.____ ____		
	13. YAWN		_____	____.____ ____		
	14. COLOR CHANGE		_____	____.____ ____		
	15. ARM MOVEMENTS		_____	____.____ ____		
	16. LEG MOVEMENTS		_____	____.____ ____		
FACTOR 3 - RESPONSIVENESS	17. ARM FLEXION	a) >170°	b) 140-170°	c) 110-140°	d) 70-110°	e) <70°
	18. HEAD LAG	a)	b)	c)	d)	e)
	19. HELD SIT	a) head stays forward or backward	b) head up <3 seconds	c) head up 3-10 seconds	d) head up >10 seconds	
	20. POSTERIOR NECK	a) no attempt to raise head	b) tries but cannot raise head	c) head upright by 30 seconds, drops head	d) head upright by 30 seconds, maintained	e) examiner cannot extend head
	21. ANTERIOR NECK	a) no attempt to raise head	b) tries but cannot raise head	c) head upright by 30 seconds, drops head	d) head upright by 30 seconds, maintained	e) examiner cannot flex head
	22. ALERT	a) 0-4 sec	b) 5-10 sec	c) 11-30 sec	d) 31-60 sec	e) >60 sec
	23. VENTRAL SUSPENSION	a)	b)	c)	d)	e)
	24. RESPONSIVENESS	a) not very responsive	b) average	c) very responsive		

Hosp. No. _____ **Sex:** ☐ F ☐ M

Name _____ **Gestational age at birth** _____

Date of birth _____ **Gestational age at exam** _____

Date of exam _____ **Birth weight** _____

Fig. 2.1 Premie Neuro scoring sheet. (*Continued overleaf.*)

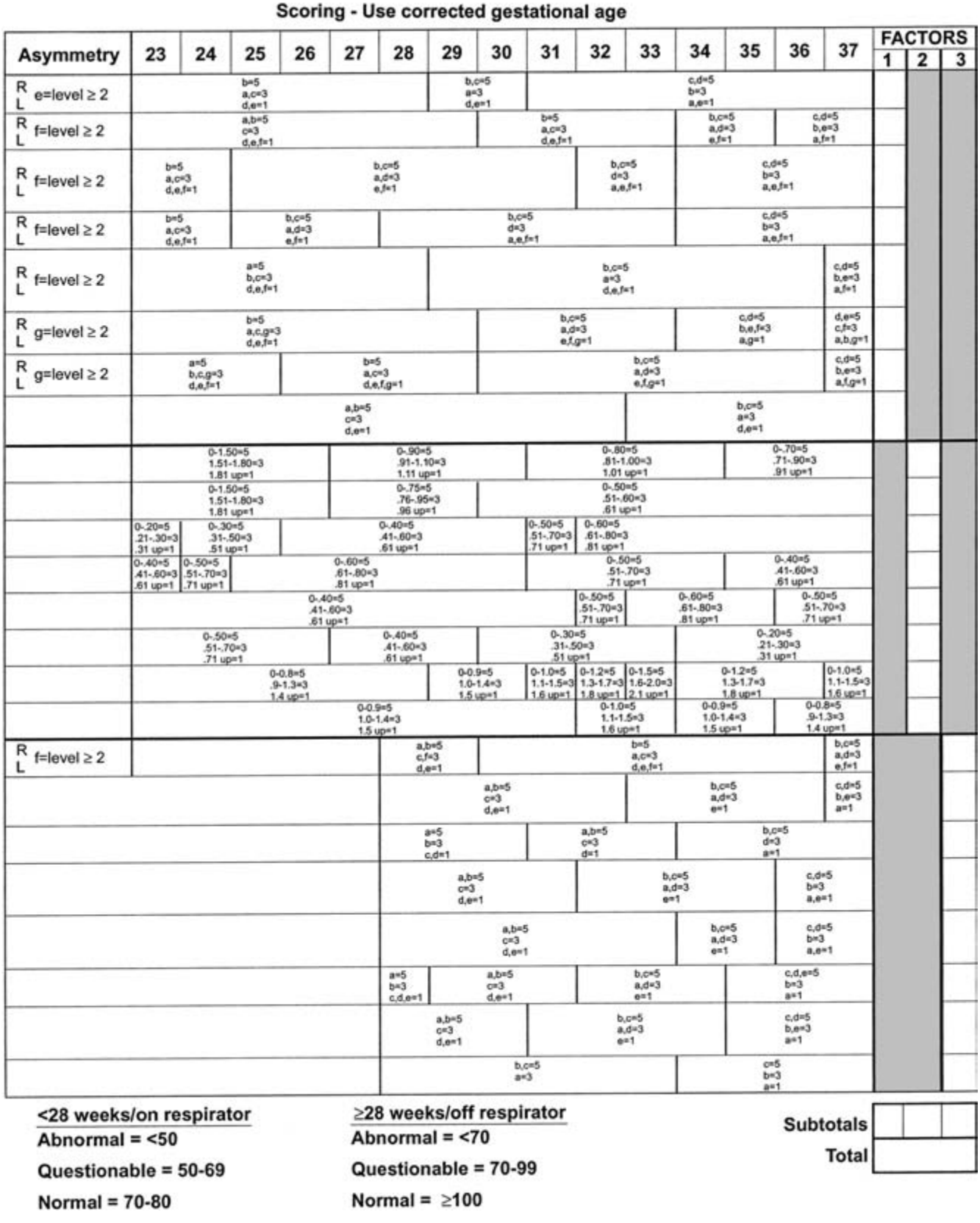


Fig. 2.1 (*Continued*)

II. NeoNeuro & Up scoring sheet

Items 1–4. These four questions are asked of the main caretaker by the examiner. They make a nice introduction to the baby and immediately give the examiner helpful information about apathy/irritability.

1 Caretaker must awaken to feed infant:
(a) rarely; (b) sometimes; (c) often.

2 Number of feedings between 6 PM and 6 AM:
(a) none (b) 1 (c) 2 (d) 3 (e) 4 (f) 5 (g) 6 or more.

3 Ease of caring for:
(a) too easy (b) easy (c) not so easy (d) difficult.

4 Cries how long before consoled?
(a) 1–3 min (b) 4–7 min (c) 8–12 min (d) 13–18 min (e) 19–24 min (f) 25 min or more.

5 *Posture.* Observe the predominant posture at rest. Make separate note of extension, semiflexion, flexion, or strong flexion for arms and for legs. Also note recurrent asymmetry. The normal position for a full-term neonate is one of semiflexion or flexion of both arms and legs (Fig. 2.2).

6 *Abnormal Posturing.* Observe throughout the examination for decorticate, decerebrate, or opisthotonic posturing. In Fig. 2.3a, there is flexion of the arms and extension of the legs (decorticate). There is also some neck retraction. In Fig. 2.3b, there is extension of the arms and extension of the legs (decerebrate). In Fig. 2.3c, the neonate assumes an opisthotonic posture. Note also extension of the arms and the clenched hands.

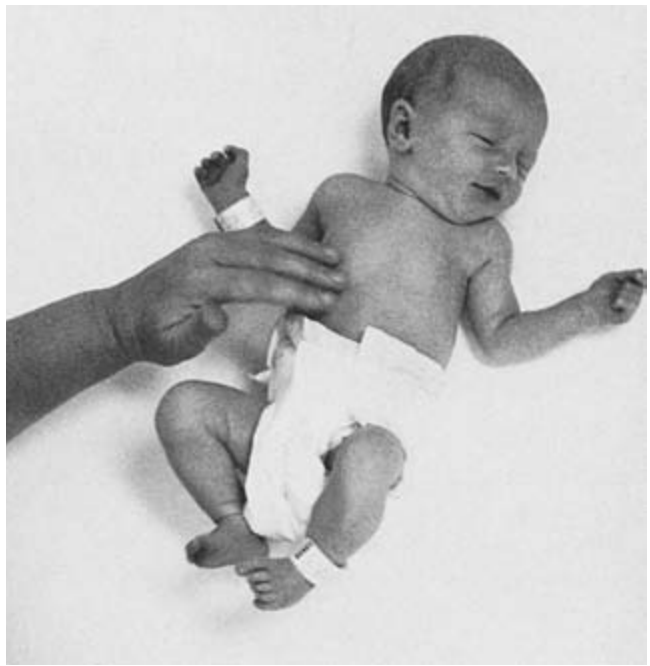


Fig. 2.2

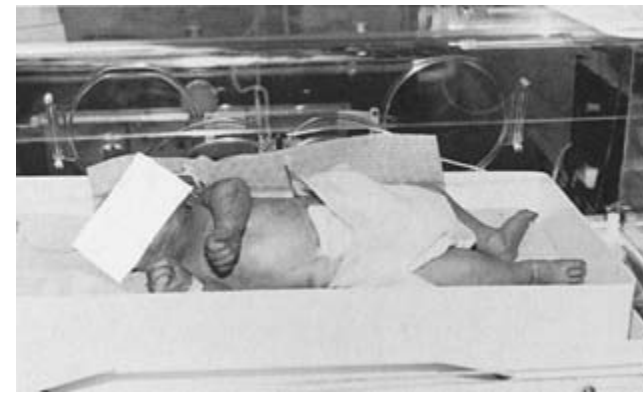


Fig. 2.3a

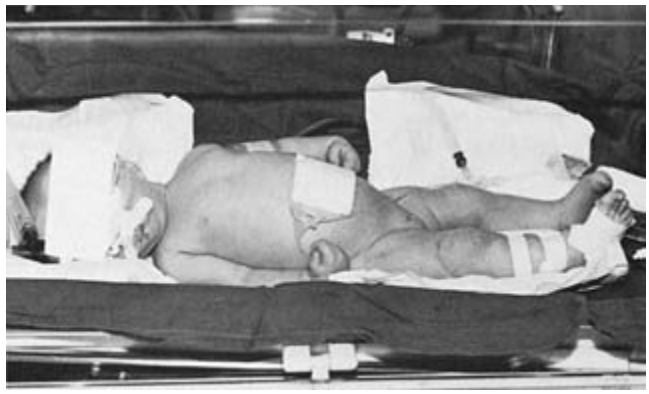


Fig. 2.3b

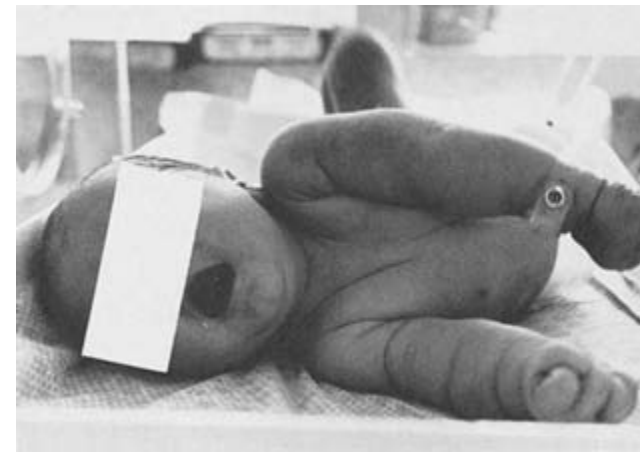


Fig. 2.3c

7 *Hands Open/Closed.* Observe whether the hands are clenched, clenched with stress, closed, sometimes closed, open. In Fig. 2.4a, the hands of a normal newborn are shown. In Fig. 2.4b, the hands are persistently clenched. Note also the opisthotonic posturing.
8 *Palmar Grasp.* Place a finger across the palm from the little finger side of the hand. Observe the degree of flexion of the fingers and arm. The normal degree of flexion for a newborn is shown in Fig. 2.5.
9 *Plantar Grasp.* Press a thumb or finger against the balls of the feet and observe the degree of plantar flexion of the toes. The normal degree of flexion for a newborn is shown in Fig. 2.6.

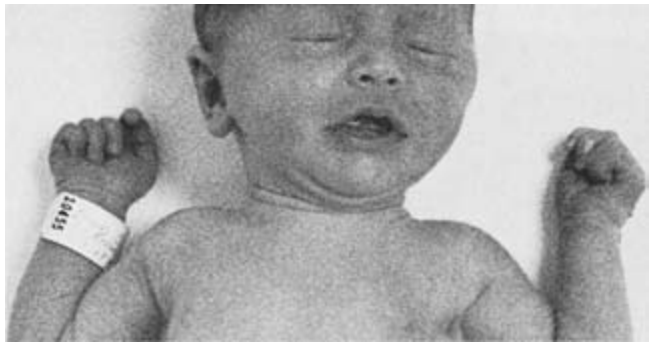


Fig. 2.4a

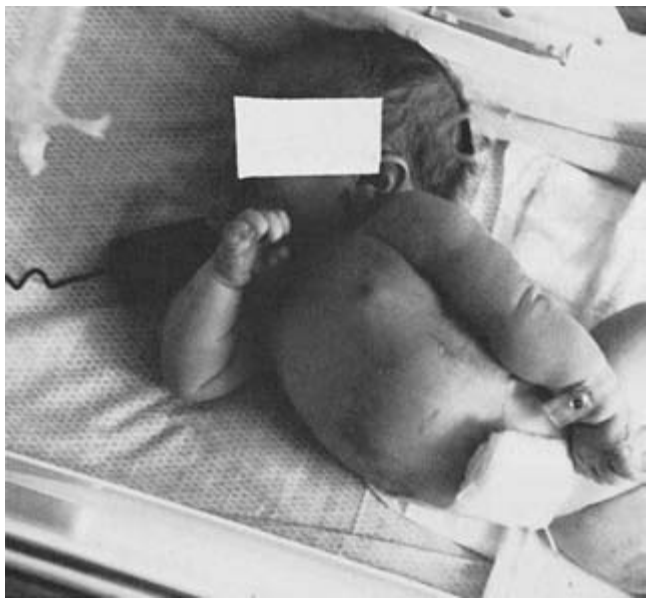


Fig. 2.4b

Fig. 2.5

Fig. 2.6

10 *Asymmetric Tonic Neck Reflex.* Turn the head slowly to one side, and hold it. Observe for a fencing position: extension of the arm near the face and flexion of the opposite arm. Repeat on the other side. Observe whether this response is absent or present. If present, observe for ability of the infant to overcome the position and for persistence of the position. The position for a normal newborn is shown in Fig. 2.7.

11 *Scarf Sign.* Grasp the upper arm near the elbow and move the arm across the chest. Observe the angle formed by the upper arm and a line parallel to the body. In Fig. 2.8a, the angle is shown for a normal neonate. In Fig. 2.8b, the infant demonstrates the excessive excursion of hypotonia or of prematurity.

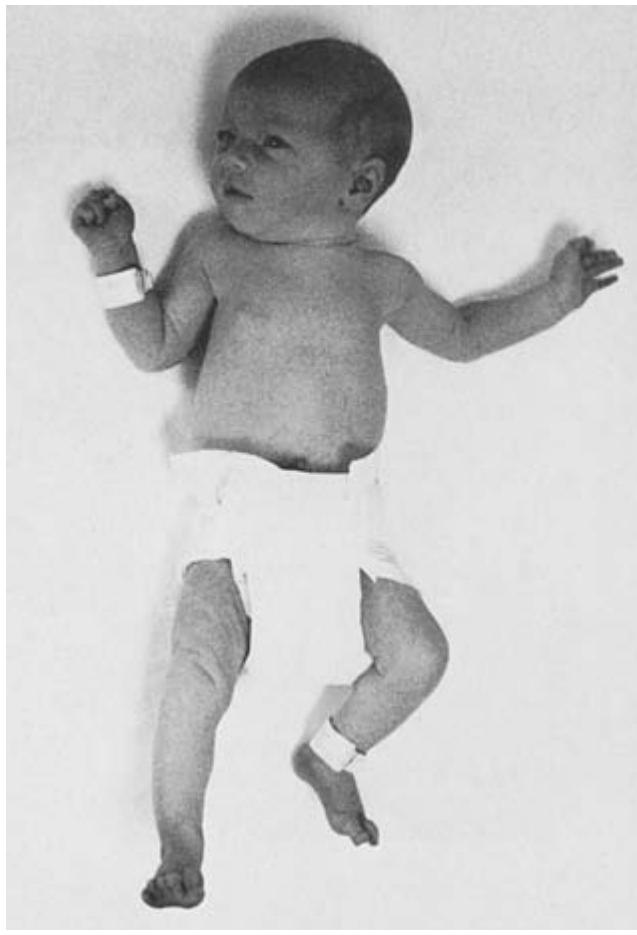


Fig. 2.7

Fig. 2.8a

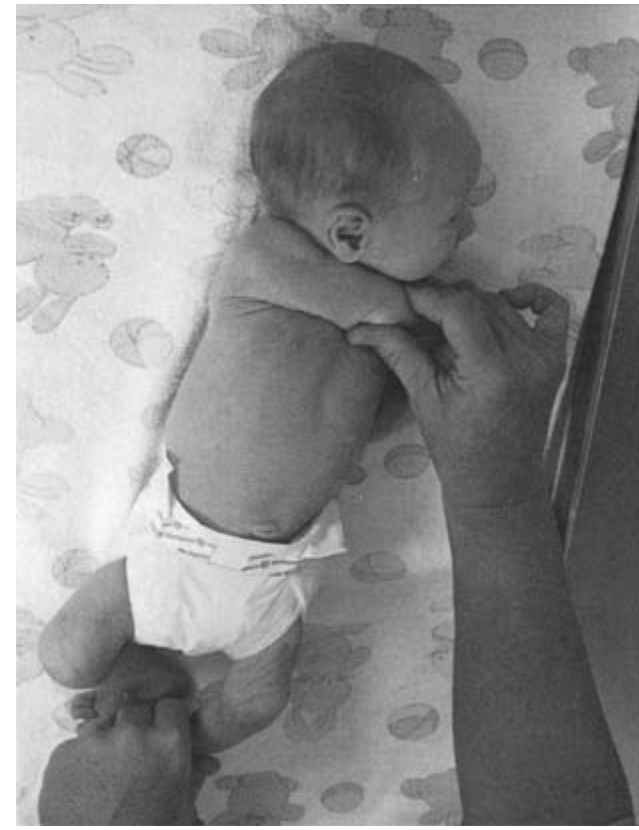


Fig. 2.8b

12 *Popliteal Angle.* Grasp the legs near the knee. Extend the lower leg by gentle pressure. Observe the angle formed by the neonate's upper leg and lower leg with the back of the knee as the fulcrum. In Fig. 2.9a, the normal popliteal angle is shown. In Fig. 2.9b, the excessively wide angle of hypotonia or prematurity is demonstrated.

13 *Heal to Ear.* Grasp the legs near the ankles. Draw the feet as close to the head as they will go, keeping the buttocks on the table. Observe the angle between the infant's trunk and legs with the hips as the fulcrum. In Fig. 2.10a, the normal newborn angle is shown. In Fig. 2.10b, the neonate's toes may be brought near the nose more readily than is normal for age, again indicating hypotonia or as seen when infant is premature.

14 *Knee Reflex.* Relax the leg by slight flexion at the knee. Tap the patellar area with a finger or with a small reflex hammer.

15 *Ankle Clonus.* Rapidly press the distal side of the foot while maintaining the leg slightly flexed. Observe for a response of quick, jerking movements of the foot.

16/ *Pull to Sit.* Use traction on both wrists to pull the
17 infant slowly to the sitting position. Score the head lag and arm flexion separately. In Fig. 2.11, the delayed head

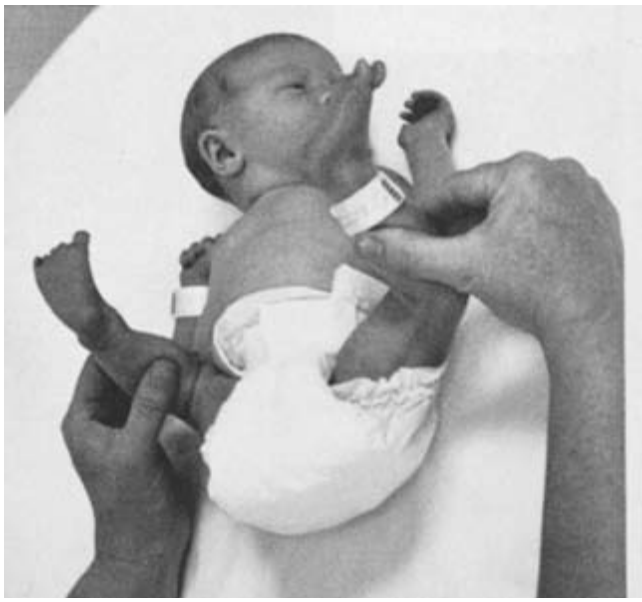


Fig. 2.9a

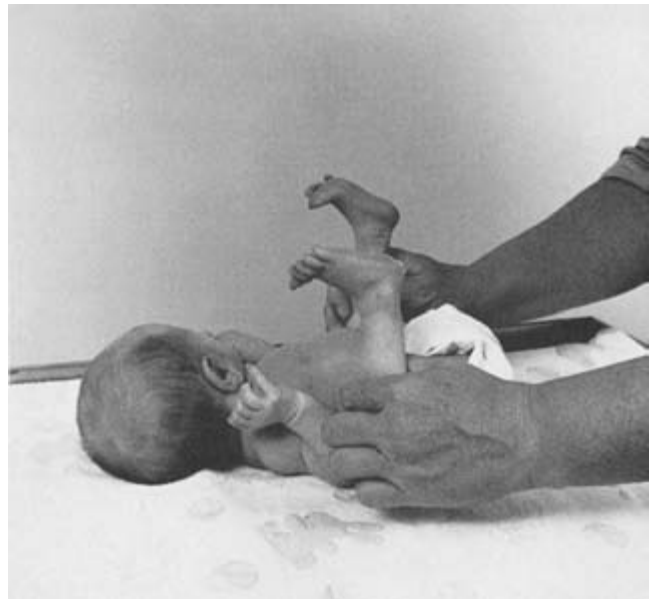


Fig. 2.9b

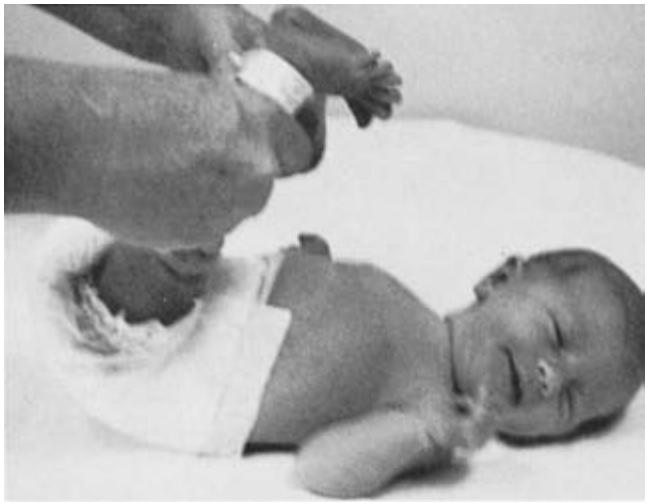


Fig. 2.10a

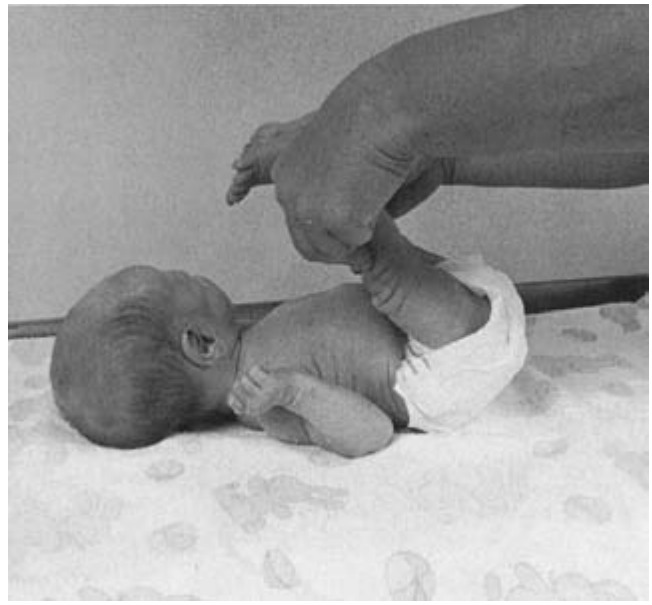


Fig. 2.10b

lag and lack of arm flexion associated with hypotonia are demonstrated.

18 *Held Sit.* Hold the infant in an upright position with the examiner's hands used to support the infant's shoulders. Observe the length of time the head is held in an upright position. See item 19 for support at the shoulders; note that in 19, the head has been allowed to fall forward.

19 *Posterior Neck.* Support the infant at the shoulders, as in item 18. Allow the head to fall forward, and wait 30 seconds. Note attempts to raise the head and ability to maintain the head in an upright position. See Fig. 2.12

20 *Anterior Neck.* Support the infant at the shoulders, as in item 19. Allow the head to fall backward, and wait 30 seconds. Note attempts to raise the head and maintain the head in an upright position. See Fig. 2.13.

21 *Auditory* (to rattle or to mother's voice). Support the infant's head in midline position, permitting head to rotate. The infant may be placed supine on the table. The mother's voice is a powerful stimulus for young infants. Ask her to call the infant's name from a meter away, to either side. Grade the response.

22 *Visual* (to black-and-white bull's eye). Support the infant's head in the midline supine position. Present the bull's-eye in the midline about 12 inches from the face. Move it laterally in either direction, then vertically, and finally in an arc.

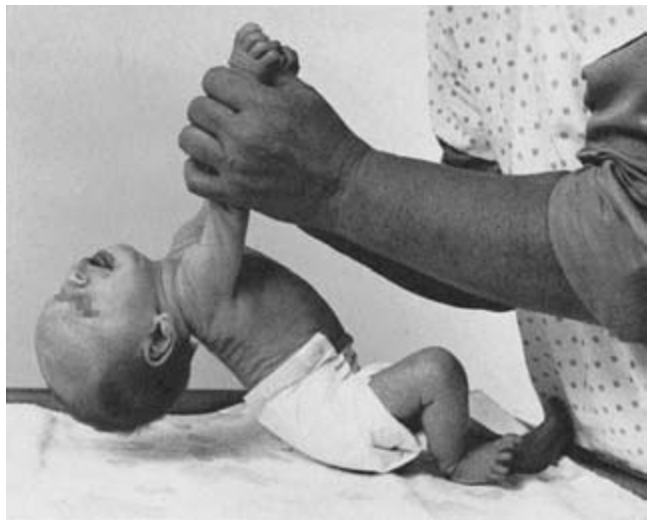


Fig. 2.11

Fig. 2.12

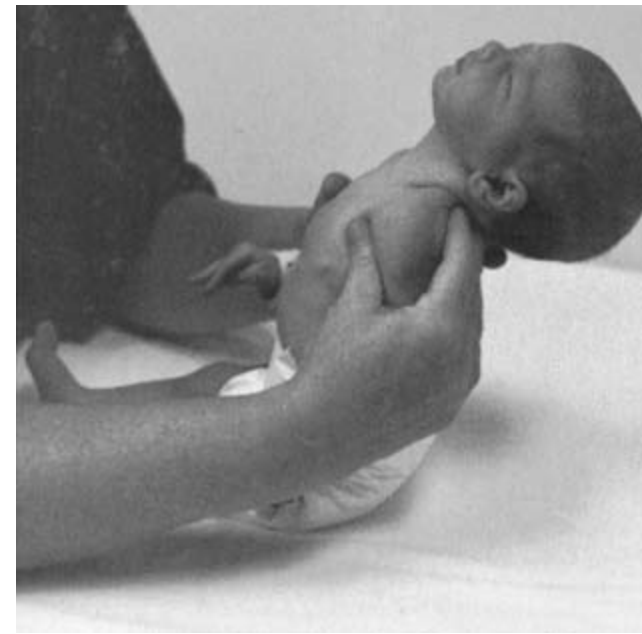


Fig. 2.13

23 *Alert.* The examiner talks or makes noises to the infant to obtain his or her attention and counts the seconds before the gaze is averted.

24 *Ventral Suspension.* Place one hand under the infant's abdomen in the prone position and suspend the infant horizontally. Observe the curvature of the back, the position of the head in relation to the trunk, and the flexion of the arms and legs. In Fig. 2.14a, normal neonatal ventral suspension is shown. In Fig. 2.14b, the drooping quality of hypotonia is demonstrated.

25 *All Fours and Prone.* Place infant in prone position, and observe head turning, head and arms positioning. It helps to talk to the infant to encourage the best performance. The normal infant in Fig. 2.15a at age 2 months holds her head up 90°; she extends on the left arm and rests on the right arm. In Fig. 2.15b, this 2-month-old infant, who is otherwise normal, has difficulty holding up his head. Note: This is seen frequently now because infants are positioned to sleep on their backs or sides. As an isolated finding, it does not indicate neurologic abnormality.

Fig. 2.14a

Fig. 2.14b

Fig. 2.15a

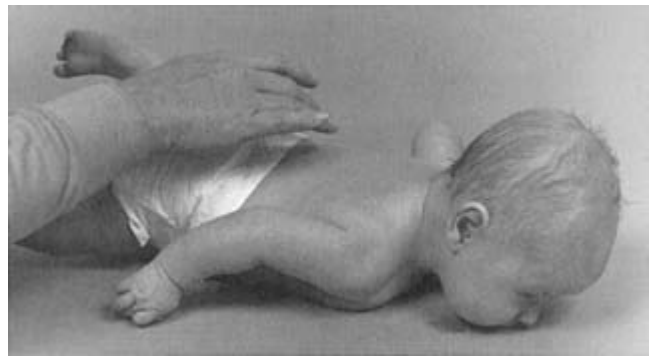


Fig. 2.15b

26 *Moro Reflex.* Support the neonate's head with one hand and the back in the midline with the other hand. Suddenly, drop the neonate 4–8 inches and observe the response of the hands and arms. In Fig. 2.16a, the neonate demonstrates a normal response. In Fig. 2.16b, the neonate has a spontaneous exaggerated Moro reflex. Each time the neonate changes position, the Moro response is elicited.

27 *Suck.* Place index finger in the mouth with finger pad toward the palate. Assess strength and rhythm of suck.

28 *Tremor.* Observe the frequency of tremor throughout the examination. Observe also the state of the neonate at the time of tremor.

29 *Responsiveness.* The examiner talks or makes noises to the infant in an attempt to elicit a response.

30 *Vocalization.* The examiner talks or makes noises to the infant, then pauses awaiting some response from the infant.

31 *Attends to Examiner.* The examiner assesses the amount of stimulation needed to attract the infant's attention.

32 *Attends during Exam.* The examiner notes the attentiveness of the infant to the examiner throughout the examination.

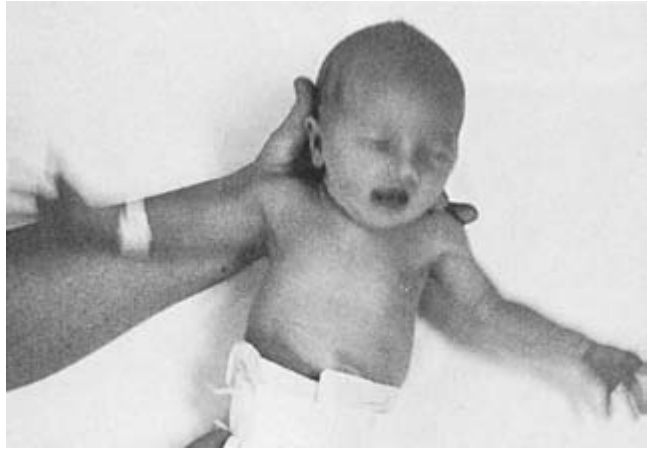


Fig. 2.16a

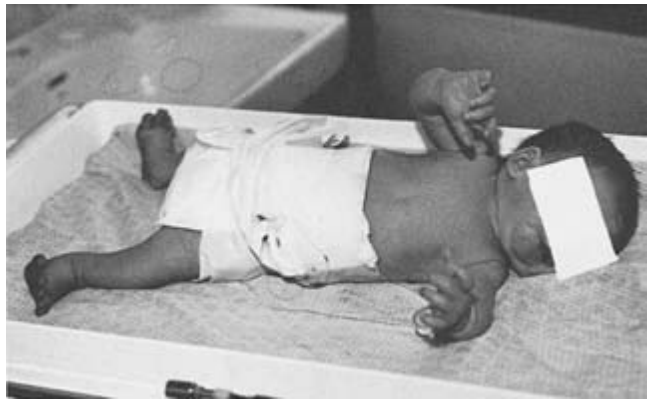


Fig. 2.16b

Using the NeoNeuro & Up scoring sheet

The NeoNeuro & Up scoring sheet (Fig. 2.17) comprises two facing pages. The left-hand side of each page is used for the description of each item. The items are listed in an order that is logical from a clinical viewpoint. Each one should be evaluated and circled at the time of examination.

To the right of the description for each item lies the scoring for 38 weeks to age 4 months corrected gestational age. The points for each item are then entered in the scoring columns at the far right. Each column is summed to yield a factor score. Factor scores are then summed to yield a total score. Two time periods are given: 0 through 48 hours and 48 hours to age 4 months.

Scoring ranges for four categories of normality and abnormality are indicated for each of the two time periods. The categories are normal, mildly abnormal, moderately abnormal, and severely abnormal.

Considerable thought has been given to further description of early infancy, other than factor scores and levels of abnormality. Our data indicated that a variety of types of abnormal newborns appeared in the moderately and severely abnormal ranges. These types are more numerous than the three types described by Prechtl and Dijkstra (1960): hemisyndrome, apathetic, and hyperexcitable. There were two basic types of mildly abnormal newborns with extension of these characteristics into early infancy: (1) irritability or apathy (irritability was more frequent) and (2) less-than-normal head control, some hypotonia of arms (scarf sign), some delay in held sit, posterior neck, anterior neck. Because this is frequent, the author has lightened these requirements from previous work. This should increase the predictive validity of the assessment method.

III. Infanib scoring sheet – measurements of tone and posture

1 *Hands Open/Closed.* Observe the infant's hands for constant return to a clenched hand or a tightly closed hand which would be noted with any of the stress maneuvers. These may be induced by the examiner, as in the tonic labyrinthine supine maneuver, or induced spontaneously by the infant, as with even a slight turning of the head. At age 5 months, the normal infant in Fig. 2.18a holds his hands open. At age 2 months, the infant with transient neuromotor abnormalities in Fig. 2.18b holds his hands clenched with even the slightest stimulation. At age 3½ months, the abnormal infant in Fig. 2.18c also clenches his hands with any stimulation, either examiner- or self-induced.

French Angles. The French angles form a part of the measure of gestational age by assessment when both physical and neurologic items are combined. The progressions are described from extreme immaturity to full term. Reversed progressions occur from full term to approximately 9–10 months in infancy. The scarf sign, heel to

NEO NEURO & UP

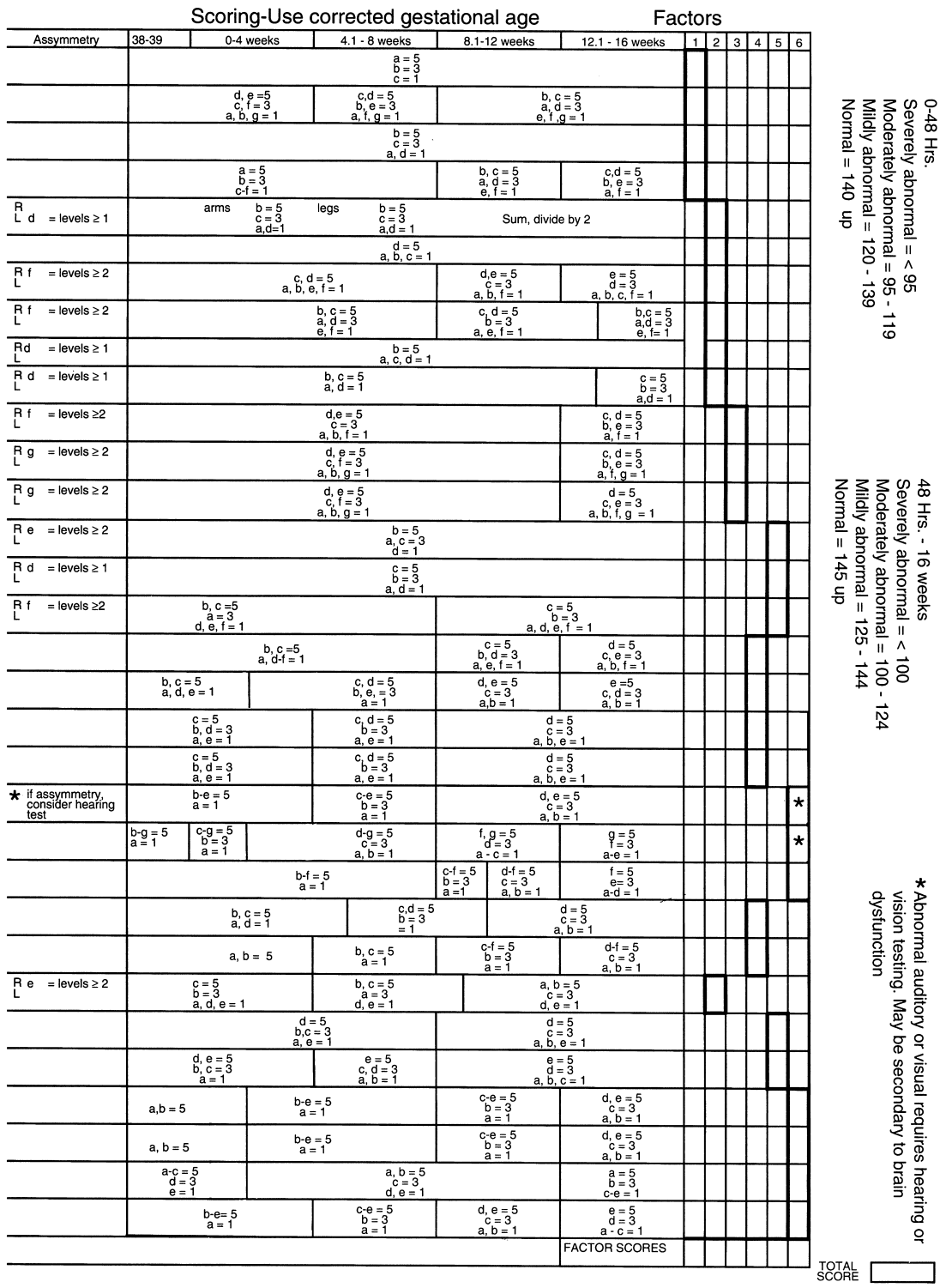
ASK CARETAKER

Name _____ Date _____ Date of birth _____ Gestational age at birth _____ Corrected gestational age _____ Sex _____

Item	Description						
1. CARETAKER MUST AWAKEN TO FEED	a) rarely	b) sometimes	c) often				
2. NUMBER OF FEEDINGS BETWEEN 6 PM - 6 AM	a) none	b) 1	c) 2	d) 3	e) 4	f) 5	g) 6 or more
3. EASY OF CARING FOR	a) too easy	b) easy	c) not so easy	d) difficult			
4. HOW LONG CRIES BEFORE CONSOLED?	a) 1-3 min	b) 4-7 min	c) 8-12 min	d) 13-18min	e) 19-24 min	f) 25 or more min	
5. POSTURE	Upper limbs Lower limbs	a) extended a) extended	b) semi-flexed or flexed b) semi-flexed or flexed		c) strongly flexed c) strongly flexed		
6. POSTURING	a) decorticate	b) decerebrate	c) opisthotonic	d) none of these			
7. HANDS OPEN/CLOSED	a) clenched	b) clenched with stress maneuver	c) closed	d) sometimes closed	e) open		
8. PALMAR GRASP	a) absent	b) weak flexion	c) medium flexion	d) strong flexion spread to	e) very strong lifts off bed		
9. PLANTAR GRASP	a) absent or weak	b) medium to strong	c) very strong				
10. ASYMMETRICAL TONIC NECK REFLEX	a) persistent or spontaneous	b) present, not persistent	c) absent				
11. SCARF SIGN	a) > 85°	b) 60° to 85°	c) 45° to 60°	d) 15° to 45°	e) 0° to 15°		
12. POPLITEAL ANGLE	a) >180°	b) 150° to 180°	c) 130° to 150°	d) 110° to 130°	e) 90° to 110°	f) < 90°	
13. HEEL TO EAR	a) < 10°	b) 10° to 40°	c) 40° to 60°	d) 60° to 90°	e) 90° to 100°	f) ≥ 1OO°	
14. KNEE REFLEX	a) absent	b) 1 + to 2 +	c) brisk	d) very brisk			
15. ANKLE CLONUS	a) > 2 beats	b) 1-2 beats	c) absent				
16. PULL TO SIT	Arm Flexion - angle at elbow	a) > 170°	b) 140° to 170°	c) 110° to 140°	d) 70° to 110°	e) < 70°	
17.	Head Lag	a)	b)	c)	d)	e)	f)
18. HELD SIT	a) head stays forward or backward	b) head up < 3 sec	c) head up 3-10 sec	d) head up > 10 sec	e) bends from L3		
19. POSTERIOR NECK	a) no attempt to raise head	b) tries but cannot raise head	c) head upright by 30 sec, drops head	d) head upright by 30 sec, maintained	e) examiner cannot extend head		
20. ANTERIOR NECK	a) no attempt to raise head	b) tries but cannot raise head	c) head upright by 30 sec, drops head	d) head upright by 30 sec, maintained	e) examiner cannot flex head		
21. AUDITORY	a) no reaction or startle	b) brightens or stills	c) shifts eyes	d) shifts and turns	e) prolonged head turning		
22. VISUAL	a) no focus or following	b) focuses	c) follows 30° horizontally	d) follows 30°-60° horizontally	e) also follows vertically	f) follows past midline	g) follows full circle
23. ALERT	a) 0-4 sec.	b) 5-10 sec	c) 11-30 sec	d) 31-60 sec	e) > 60 sec.	f) regards hand or object in hand	
24. VENTRAL SUSPENSION	a)	b)	c)	d)			
25. ALL FOURS/PRONE	a) no head turning	b) turns head side to side	c) lifts head 45° drops	d) lifts head 45° holds	e) head up 90° drops	f) head up 90° holds	
26. MORO	a) absent or minimal	b) partial	c) full	d) exaggerated - immediate brisk response			
27. SUCK	a) no attempt	b) weak	c) strong irregular	d) strong regular	e) jaw clenched		
28. TREMOR	a) all states	b) only in states 5, 6	c) also in state 4	d) only in sleep or after mono	e) none		
29. RESPONSIIVENESS	a) no smile	b) smiles to self	c) smiles responsively	d) gets excited anticipation of food	e) breathes heavily gets excited		
30. VOCALIZATION	a) none	b) small noises	c) talks back some way	d) chuckles	e) squeals, laughs outloud		
31. ATTENDS TO EXAMINER	a) no stimulus needed	b) with mild stimuli	c) moderate stimuli	d) really have to stimulate	e) does not attend		
32. ATTENDS DURING EXAM	a) does not attend	b) with stimulus only	c) some	d) recurrently	e) most of exam		

NEO NEURO & UP

Fig. 2.17 Neo Neuro & Up scoring sheet.


Scoring-Use corrected gestational age
Factors
Assymmetry
38-39
0-4 weeks
4.1 - 8 weeks
8.1-12 weeks
12.1 - 16 weeks
1
2
3
4
5
6
R L d = levels ≥ 1
arms b = 5 c = 3 a,d=1
legs b = 5 c = 3 a,d = 1
Sum, divide by 2
R f L = levels ≥ 2
R f L = levels ≥ 2
R d L = levels ≥ 1
R d L = levels ≥ 1
R f L = levels ≥2
R g L = levels ≥ 2
R g L = levels ≥ 2
R e L = levels ≥ 2
R d L = levels ≥ 1
R f L = levels ≥2
R e L = levels ≥ 2
* if assymmetry, consider hearing test
FACTOR SCORES
TOTAL SCORE
0-48 Hrs.
Severely abnormal = < 95
Moderately abnormal = 95 - 119
Mildly abnormal = 120 - 139
Normal = 140 up
48 Hrs. - 16 weeks
Severely abnormal = < 100
Moderately abnormal = 100 - 124
Mildly abnormal = 125 - 144
Normal = 145 up
* Abnormal auditory or visual requires hearing or vision testing. May be secondary to brain dysfunction

ear, popliteal angle, and leg abduction look similar in the preterm neonate who has a gestational age of 28 weeks and in the 9- to 10-month-old infant. Significant deviations are indicative of hypotonia or hypertonia.

2 *Scarf Sign.* Hold the infant's arm near the elbow and move the arm across the infant's chest until resistance is met, as indicated in Fig. 2.19c. (In the other figures the maneuver is performed less well technically but the angle is seen more clearly.) Observe the angle between a vertical line dropped from the insertion of the arm and the upper arm.

A scarf sign with larger excursion than normal is an excellent indicator of hypotonia of the upper body, a very common finding in infants with other indicators of neurologic abnormality. Early hypertonia is uncommon. Progression from hypotonia to hypertonia in the upper body occurs in those infants with spastic tetraparesis and dyskinesia.

In the first series, the normal progression is shown from Fig. 2.19a, 0–3; to Fig. 2.19b, 4–6; to Fig. 2.19c, 7–9; and Fig. 2.19d, 10–12 months. Note the increasing ease with which the shoulder (and trapezius muscle) extends and the arm is moved across the chest. In the second series (Figs 2.19e–2.19h), the progression is reversed. Initially (0–3 months), the arm is extended too easily, indicating hypotonia. At each subsequent step (4–6, 7–9, and 10–12 months), the shoulder extends less easily, indicating a progression from hypotonia to hypertonia.

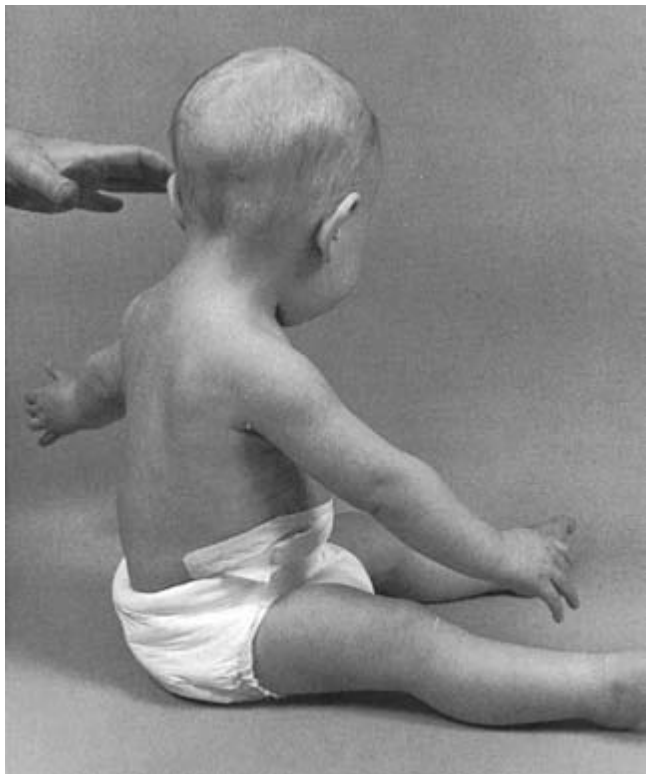


Fig. 2.18a

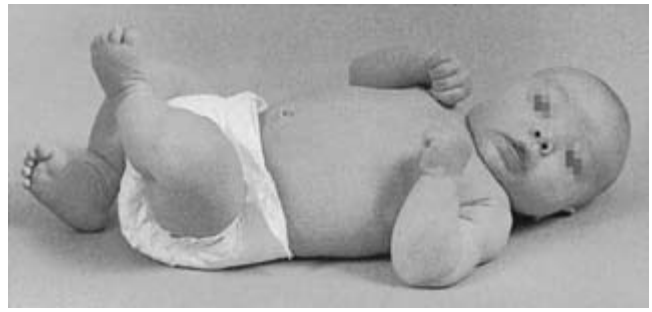


Fig. 2.18b

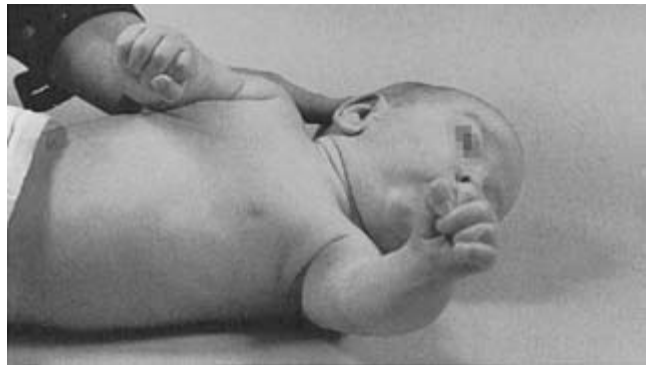


Fig. 2.18c

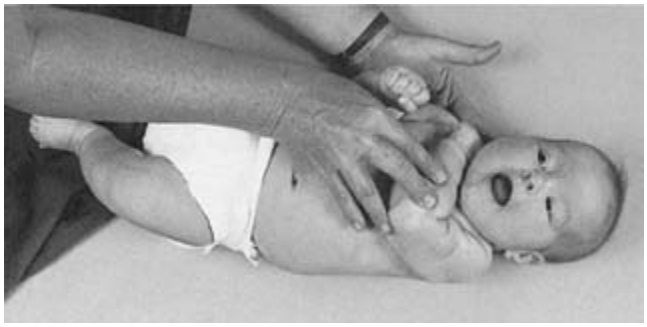


Fig. 2.19a

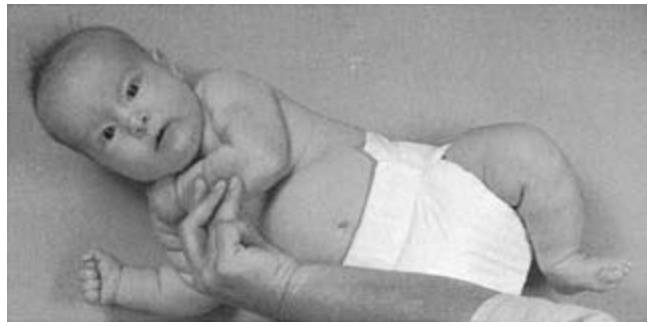


Fig. 2.19b

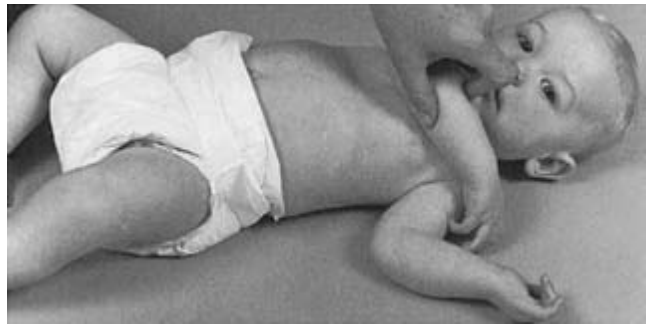


Fig. 2.19c

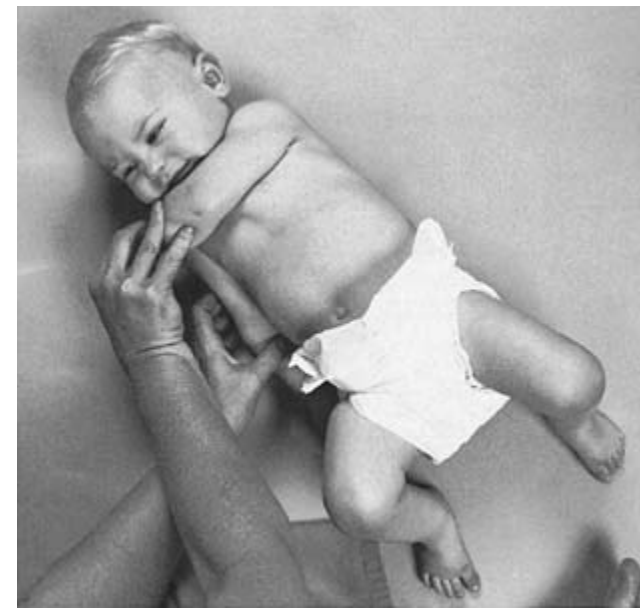


Fig. 2.19d

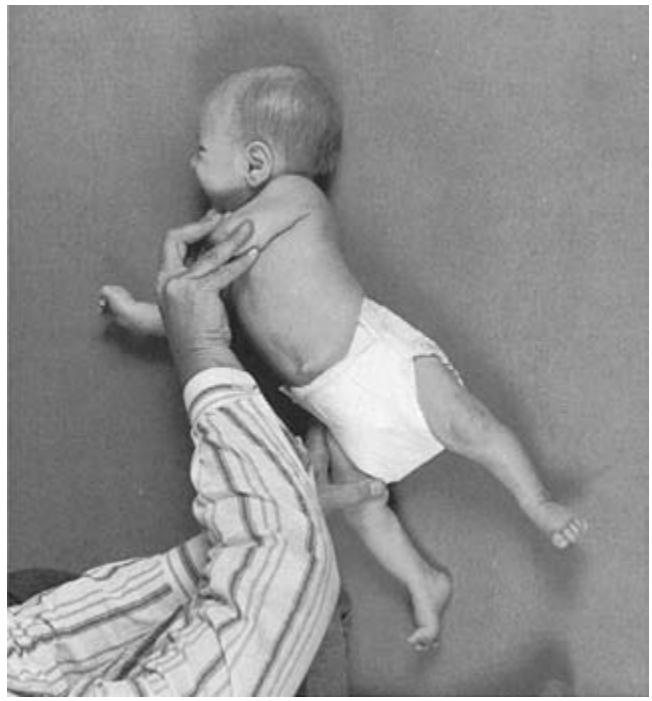


Fig. 2.19e

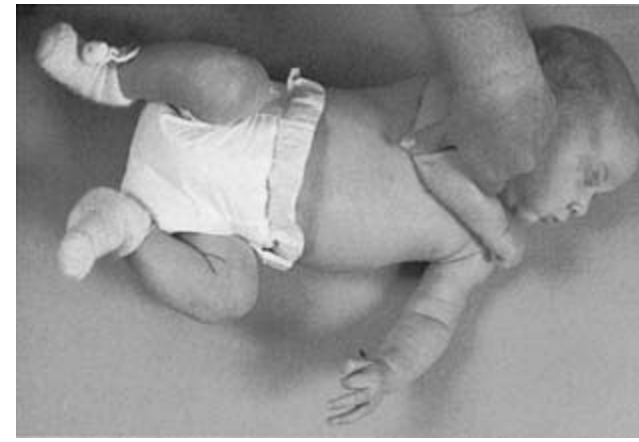


Fig. 2.19f

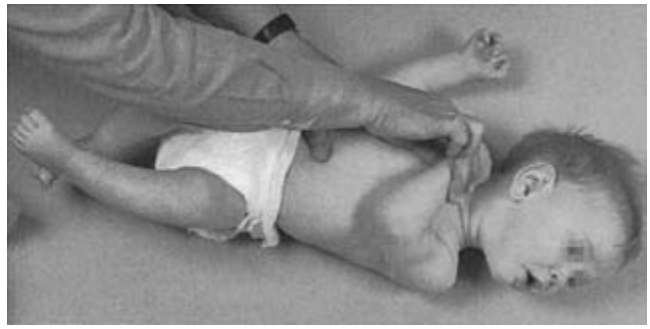


Fig. 2.19g

Fig. 2.19h

3 *Heel to Ear.* Grasp the legs at the knees so that the legs are extended and the position of the buttocks is well controlled. As much as possible, the buttocks should remain on or near the examining table (specifically this is not a measure of the flexibility of the spine; it is a measure of the flexibility of the hips). Measure the angle between the infant's trunk and legs.

This is one of the best early indicators of hypertonia of the lower body. Infants with spastic diplegia or spastic tetraparesis and dyskinesia generally show change first in the flexibility of the hips or knees (see item 4). A developmental milestone that represents this progression is the item "plays with feet," used in the Gesell Screening Inventory at age 28 weeks.

In the first series (Figs 2.20a–d), the normal infant shows the normal progression from 0–3, to 4–6, to 7–9, to 10–12 months. In the second series (Figs 2.20e–h), the abnormal infant fails to decrease the heel-to-ear angle after 0–3 months. He departs increasingly from the normal progression as each interval passes (4–6 months, 7–9 months, 10–12 months). In addition, he assumes an asymmetric tonic neck posture and keeps his hands closed (Fig. 2.20f).

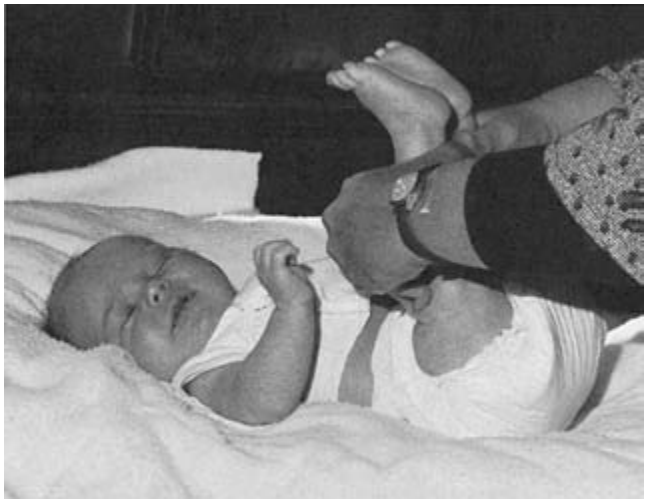


Fig. 2.20a

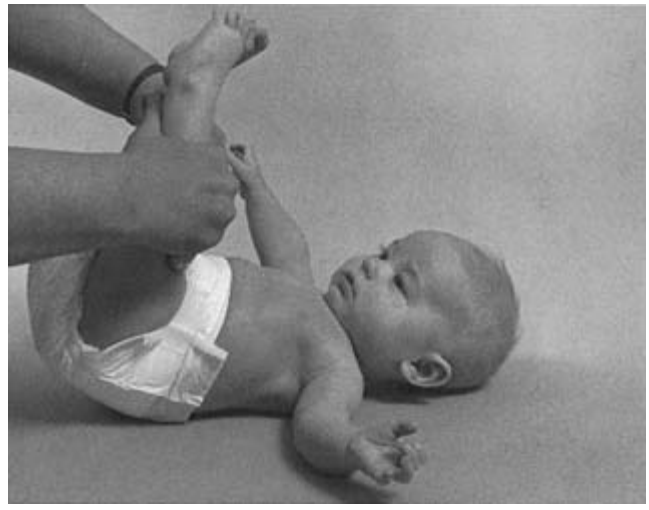


Fig. 2.20b

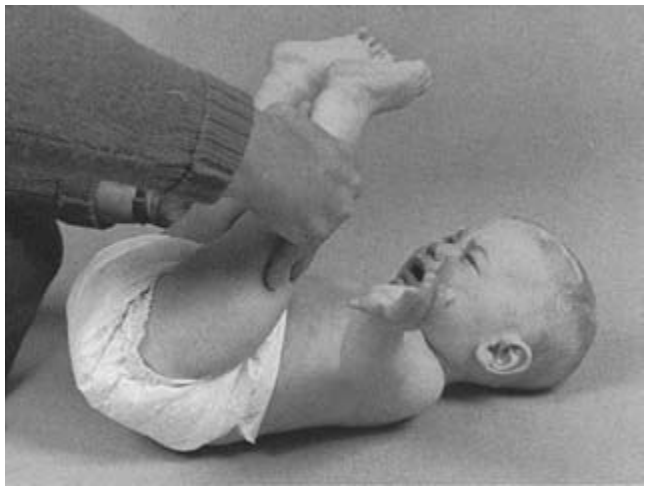


Fig. 2.20c

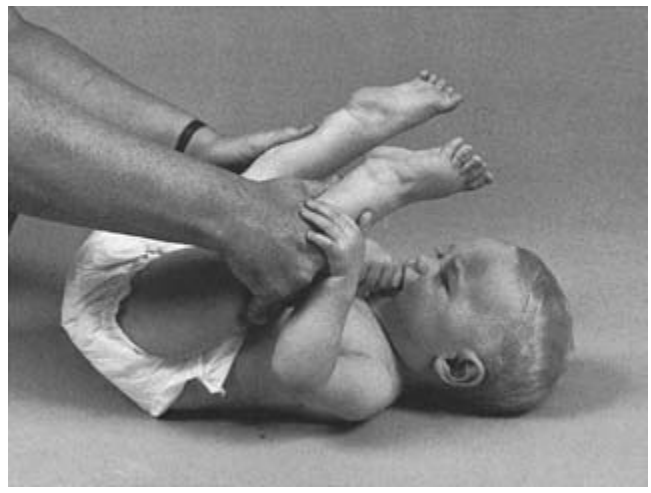


Fig. 2.20d

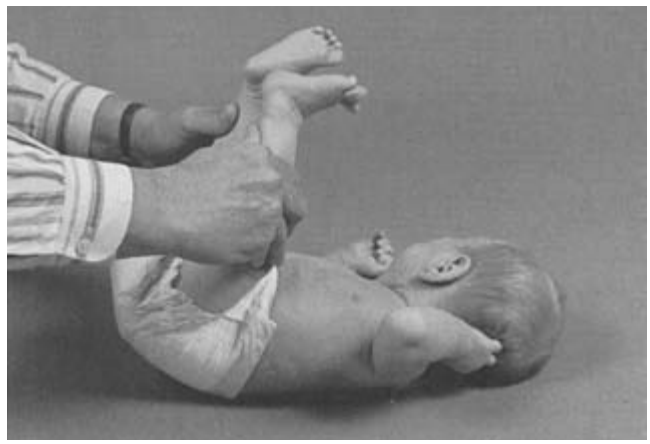


Fig. 2.20e

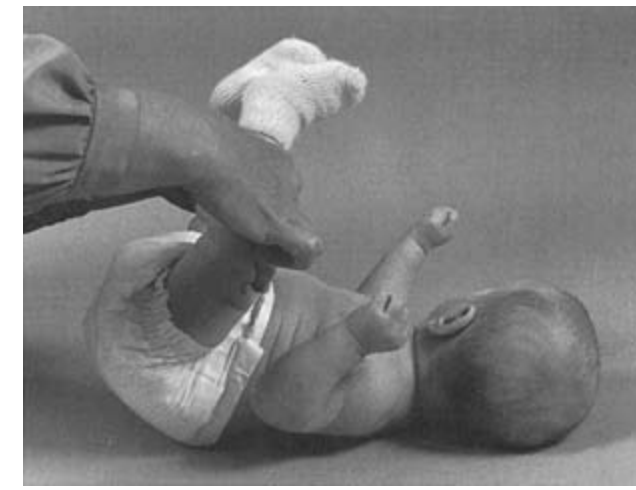


Fig. 2.20f

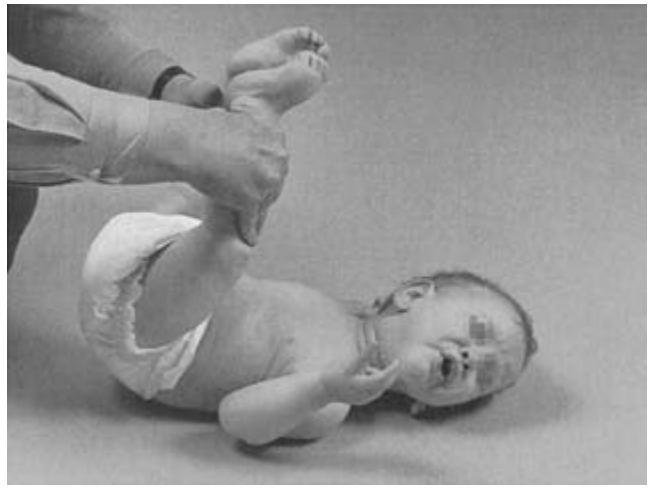


Fig. 2.20g

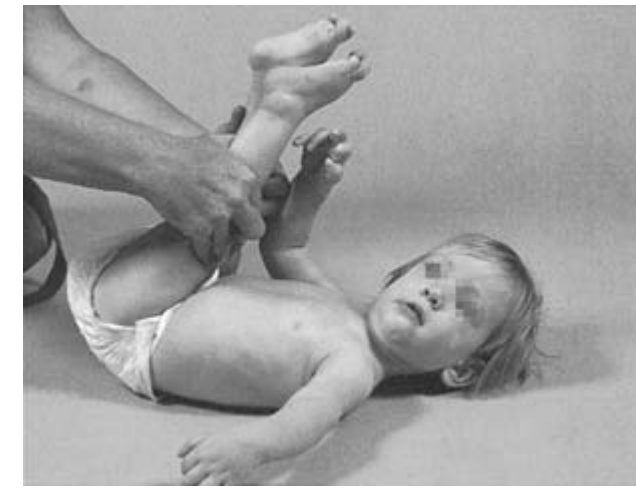


Fig. 2.20h

4 *Popliteal Angle.* Hold the legs near the knee, flex the leg at the hip, and abduct the legs, extending the lower leg until resistance is met. With the back of the knee as the fulcrum, measure the angle between the upper and lower parts of the leg. As indicated in item 3, popliteal angle is another excellent indicator of hypertonia in the lower body. Failure of the angle to increase throughout early and middle infancy often indicates spastic tetraparesis and dyskinesia, spastic diplegia, and asymmetrically, spastic hemiparesis.

In the first series (Figs 2.21a–d), the infant shows the normal progression from 0–3, to 4–6, to 7–9, to 10–12 months. In the second series (Figs 2.21e–h), the popliteal angle is initially hypotonic, but then becomes hypertonic.

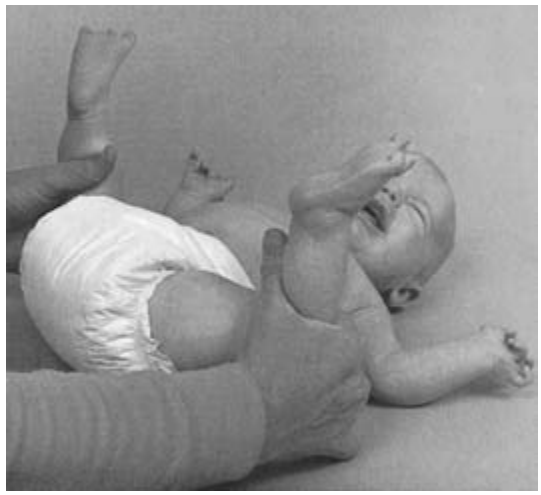


Fig. 2.21a

Fig. 2.21b

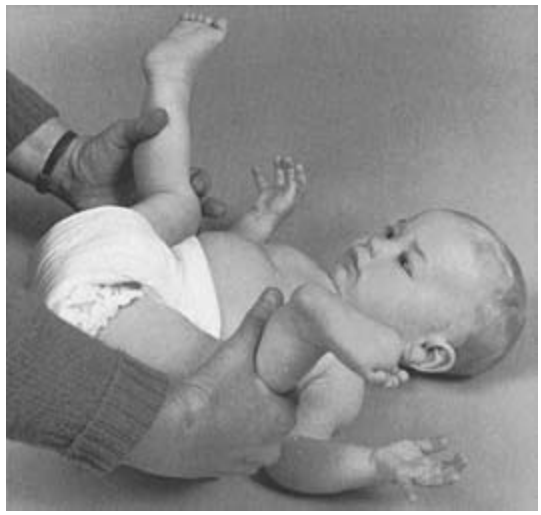


Fig. 2.21c

Fig. 2.21d

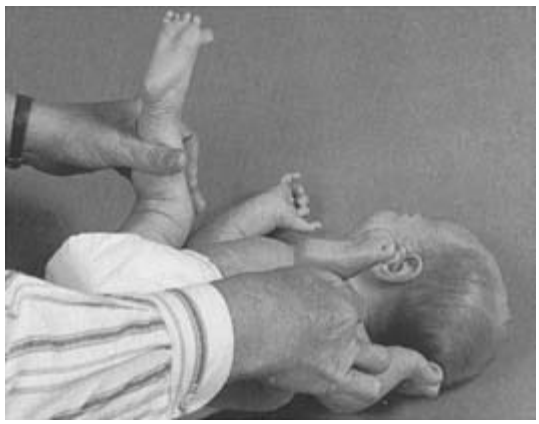


Fig. 2.21e

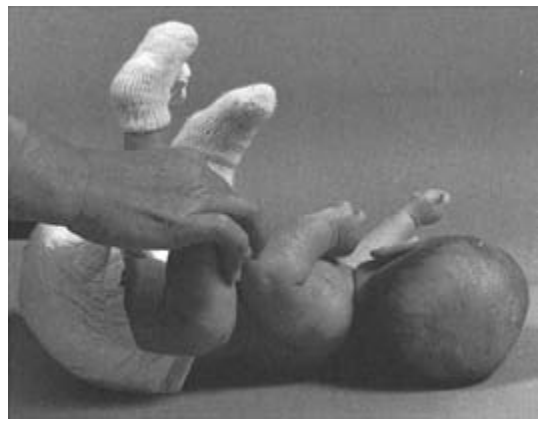


Fig. 2.21f

Fig. 2.21g

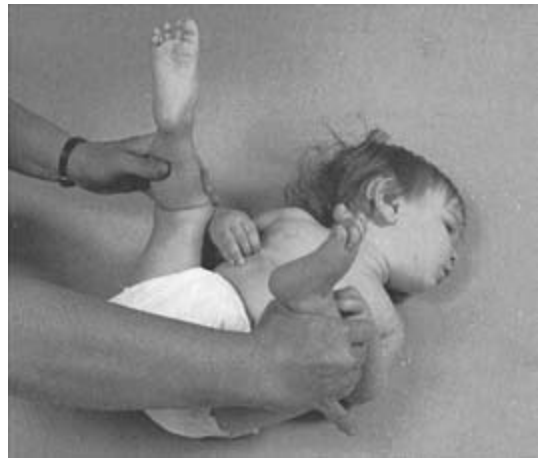


Fig. 2.21h

5 *Leg Abduction.* Hold the legs at the knee such that they are extended; abduct the legs. With the crotch as a fulcrum, measure the angle between the legs. This item is generally less sensitive than heel to ear or popliteal angle as an early indicator of hypertonia. It is an excellent indicator of hypotonia, but there are many other excellent indicators of hypotonia.

In the first series, the normal infant demonstrates the normal progression from 0–3 (Fig. 2.22a), to 4–6 (Fig. 2.22b), to 7–9 (Fig. 2.22c), to 10–12 (Fig. 2.22d). In the second series, the abnormal infant has no increase in the angle at 4–6 months (Fig. 2.22e) or at any other age range (Figs 2.22g, h).

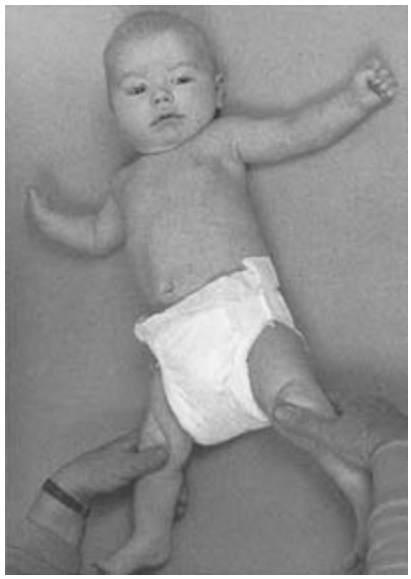


Fig. 2.22a

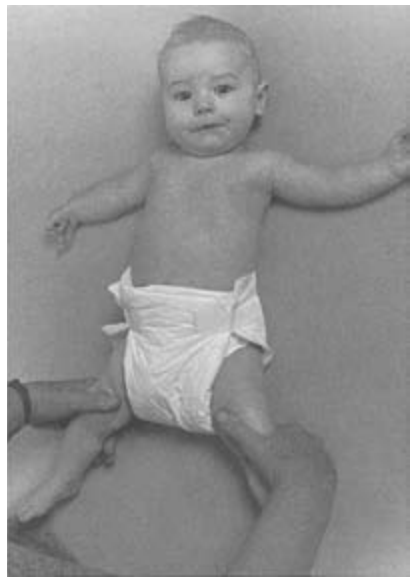


Fig. 2.22b

Fig. 2.22c

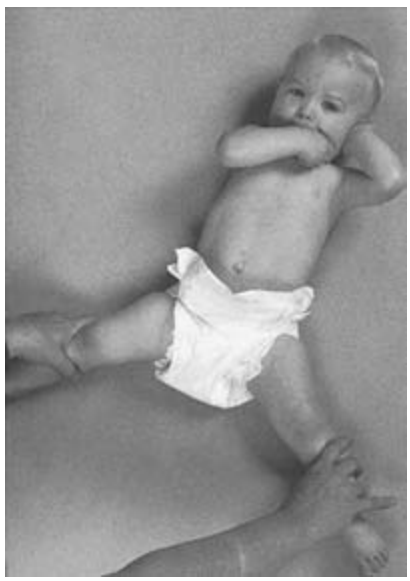


Fig. 2.22d

Fig. 2.22e

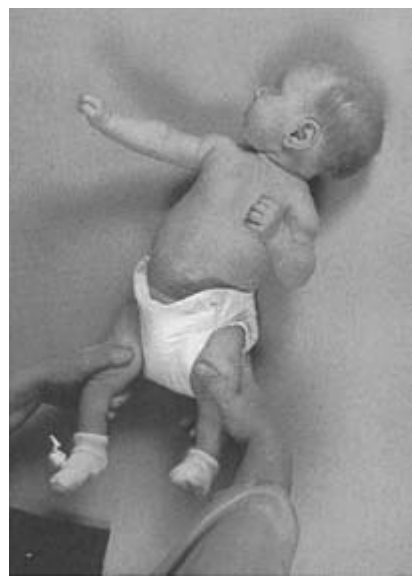


Fig. 2.22f

Fig. 2.22g

Fig. 2.22h

Fig. 2.23a

Fig. 2.23b

6 *Dorsiflexion of the Foot.* Flex the foot, pushing it against the leg until resistance is met. With the ankle as a fulcrum, measure the angle between the foot and the leg.

The feet are generally the last to show hypertonia, except in situations of very early severe hypertonicity, in which they may be in an extended position that is very difficult to change. More frequently, the feet are hypotonic until middle or late infancy, even in infants with spastic tetraparesis and dyskinesia.

At age 2 months, the normal infant (Fig. 2.23a) has a normal angle of dorsiflexion of the foot. At 4 months, the abnormal infant (Fig. 2.23b) has an increased angle of dorsiflexion of the foot.

7 *Foot Grasp.* Place the thumb or finger firmly in the footpad and observe for curling of the infant's toes toward the bottom of the foot.

Foot grasp is a primitive reflex; specifically it is an item that is normal in the neonate but disappears in the course of infancy. For many of the primitive reflexes, the range of time that is considered normal for disappearance is long. It can also be exaggerated in its manifestation in early infancy; these exaggerations are abnormal. After the age at which the item should no longer be present, it can be graded to represent levels of normality and abnormality (no grasp, barely grasps, grasp).

At 1 month of age, the normal infant (Fig. 2.24a) has a prominent but not exaggerated foot grasp. At 3 months, the abnormal infant (Fig. 2.24b) has an exaggerated foot grasp.

8 *Tonic Labyrinthine Supine.* Stimulate the intrascapular area with the hand. Observation is made of shoulder retraction and extension or flexion of arms, legs, or trunk. This item is also a primitive reflex.

At one month of age, the normal infant (Fig. 2.25a) demonstrates little response to this maneuver. The infant in (Fig. 2.25b) has a dramatic response with extension of both arms and legs; this response was graded as abnormal. The abnormal infant (Fig. 2.25c) has flexion of both arms and legs at 2 months; this response was also graded as abnormal.

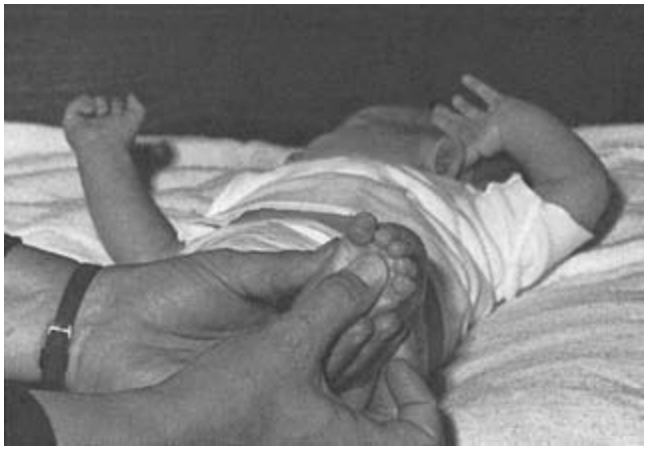


Fig. 2.24a

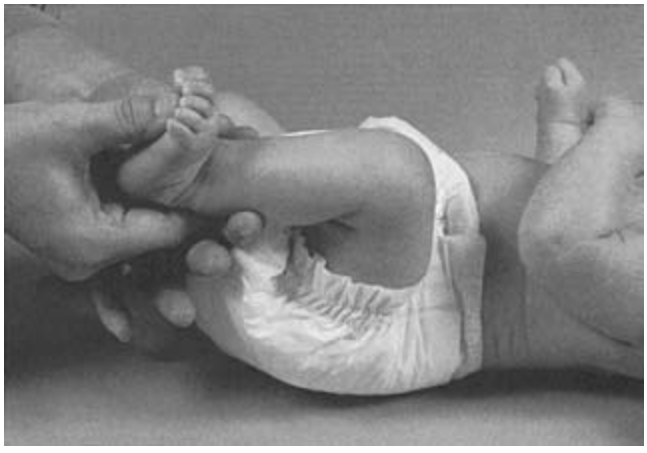


Fig. 2.24b

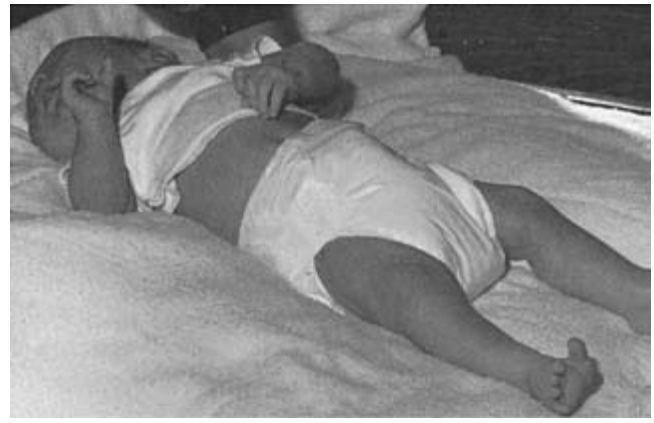


Fig. 2.25a

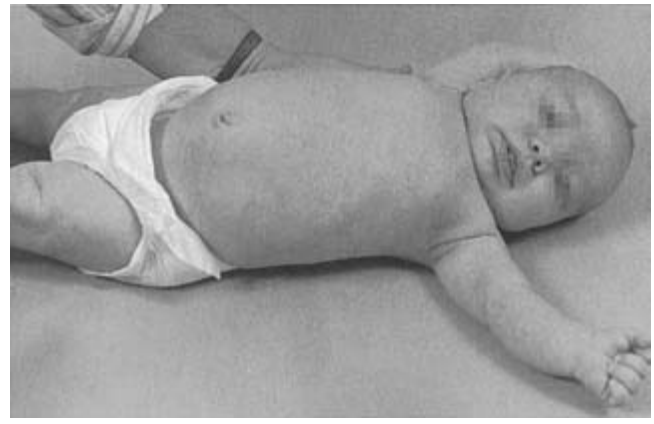


Fig. 2.25b

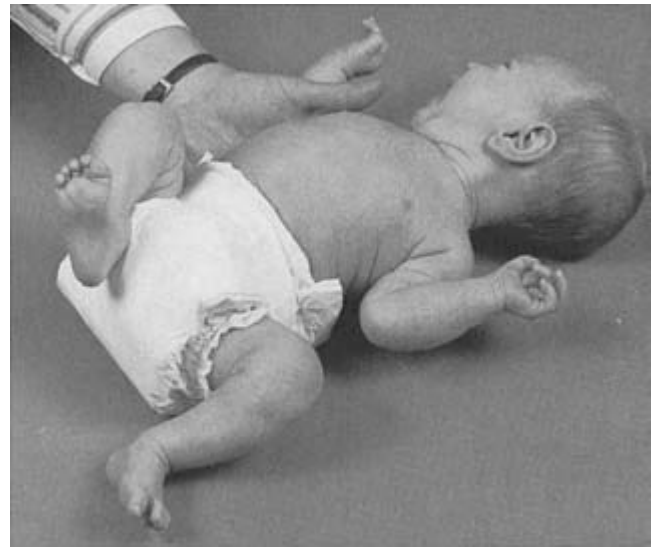


Fig. 2.25c

9 *Asymmetric Tonic Neck Reflex.* Turn the infant's head from side to side, observing the assumption of a fencing position, the extension of the arm faced, the flexion of the arm behind the head, and the extension of the leg faced. Also note the persistence of the posture: whether the infant assumes the posture and then moves out of it, in contrast to persisting in the posture. Persistence is abnormal at any age and is the manifestation of exaggeration of the reflex.

At age 1 month, the normal infant (Fig. 2.26a) manifests an asymmetric tonic neck reflex, which he then overcomes. The abnormal infant (Fig. 2.26b) at 5 months has a strong, persistent asymmetric tonic neck reflex. (It may be noted in many of the pictures of this infant that he goes into an asymmetric tonic neck reflex with many neurologic maneuvers, as well as spontaneously and repetitively when he is supine.)

10 *Pull to Sitting.* Grasp the infant's hands and pull the infant to a sitting position. As seen in the figures, a small sandbag may be used as a weight to maintain the position of the buttocks. Observe first the position of the head: extended, straight up, or flexed. Second, observe the position of the arms: extended or flexed. If there is a discrepancy in the two observations, the scoring is based on the position of the head.

The most common abnormal finding is that of delay in head control or hypotonia of the neck and upper trunk. Hypertonia is noted much less frequently. The manifestation is precocious head control with extension of the head. This is demonstrated by the infant in Fig. 2.27a at age 2 months. His head control is "superior" to that expected for his age, an indication of the hypertonicity of his neck muscles. The normal infant (Fig. 2.27b) at 2 months has normal head control. The abnormal infant (Fig. 2.27c) at 7 months persists in poor head control, which he has had since his neonatal neurologic examination.

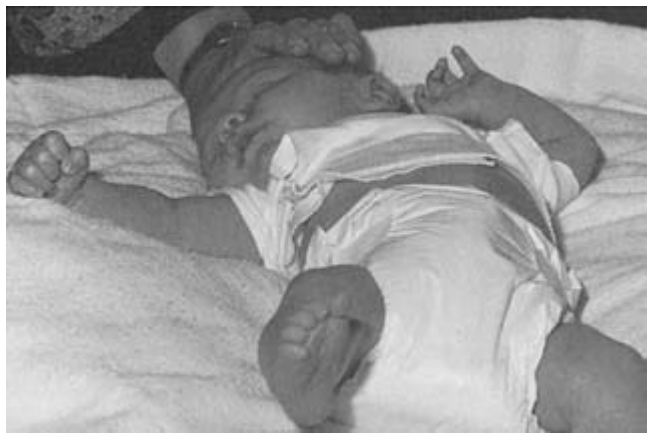


Fig. 2.26a

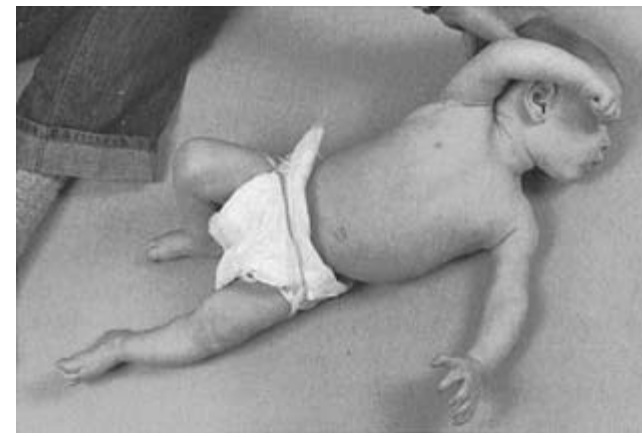


Fig. 2.26b

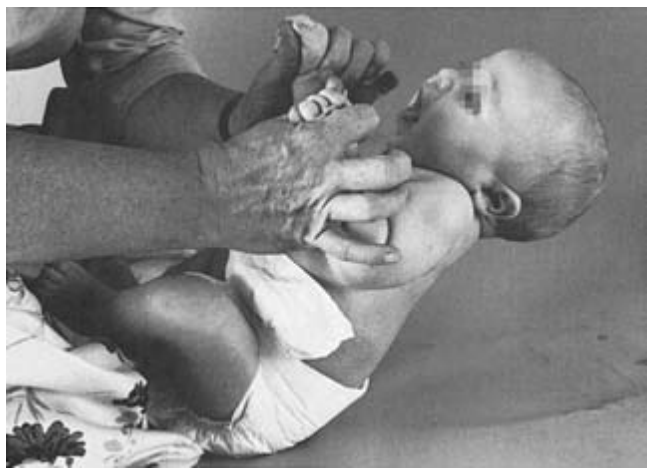


Fig. 2.27a

Fig. 2.27b

Fig. 2.27c

Fig. 2.28a

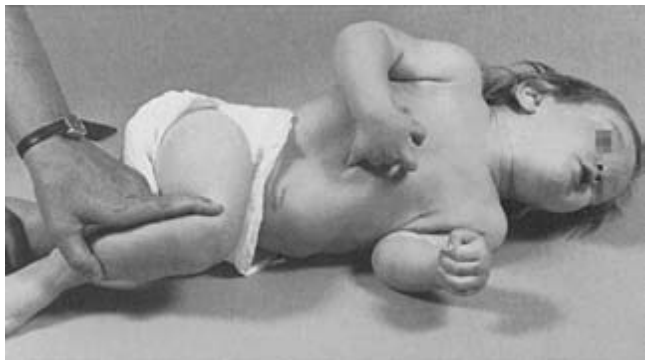


Fig. 2.28b

11 *Body Derotative.* Hold the infant by the lower legs, then rotate the legs to initiate rolling from supine to prone. Observe the infant's continuation of the maneuver. An infant with neurologic impairment may not be able to accomplish this or may do so slowly or awkwardly. To check for noncompliance, ask the parent if spontaneous rolling from supine to prone occurs at home. Full credit is given for a reported supine-to-prone roll.

At age 4 months, the normal (Fig. 2.28a) infant readily raises the upper arm and participates in the maneuver. The abnormal infant (Fig. 2.28b) flexes his arms, extends his trunk and head, and cannot complete the maneuver.

12 *Body Rotative.* The infant spontaneously rolls from supine to prone, then pulls to standing position. In normal infants, the maneuver is often accomplished spontaneously in the course of the examination. The normal infant's ease with the maneuver is seen in (Fig. 2.29a) and (Fig. 2.29b). The abnormal infant (Fig. 2.29c) accomplishes the maneuver, but he is slower and has a logrolling style: his upper and lower body are rolled as a unit.

13 *All Fours.* Move the infant to the prone position. The rating of this item is based on observation of head position, arm position, and leg position. The major component is head position. The examiner is seeking optimal performance; encouragement of the infant is not only permitted but preferable.

The normal infant (Fig. 2.30a) at age 5 months holds his head up 90° and extends his arms. The abnormal infant (Fig. 2.30b) at 4 months does not lift his head at all, even with much encouragement. His mother reported that he held his head up briefly at home.

14 *Tonic Labyrinthine Prone.* Move the infant to the prone position. Flex the infant's head, and observe shoulder retraction and flexion of arms, hips, or legs under the trunk. The infant's body may be stabilized by placement of the examiner's hand under the abdomen. This is another primitive reflex, thus exaggeration is an abnormal response in early infancy. At 7 months, the abnormal infant has a prompt and vigorous response to head flexion (Fig. 2.31).

15 *Sitting.* The examiner holds or places the infant in a sitting position and notes the point at which bending occurs (L-3, L-5). It may not be possible to get the infant into a sitting position if there is repetitive extensor posturing. Other items (such as tonic labyrinthine prone, tonic

Fig. 2.29a

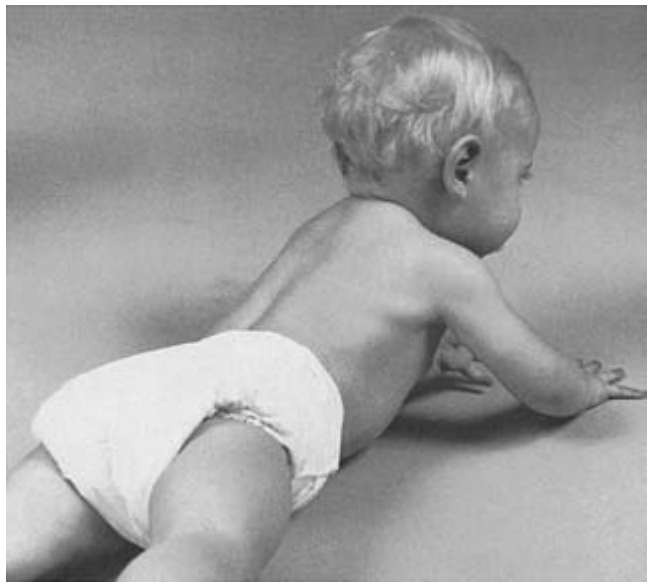


Fig. 2.29b

Fig. 2.29c

labyrinthine supine, and asymmetric tonic neck reflex) should also be abnormal with extensor posturing of this degree. More frequently, abnormality is manifested by poor trunk control with a delay in the progression of sitting positions.

At age 4 months, the normal infant (Fig. 2.32a) bends forward from L-3. At the same age, the infant in (Fig. 2.32b) bends forward from L-5 and holds his head in an extended position. This precocious sitting

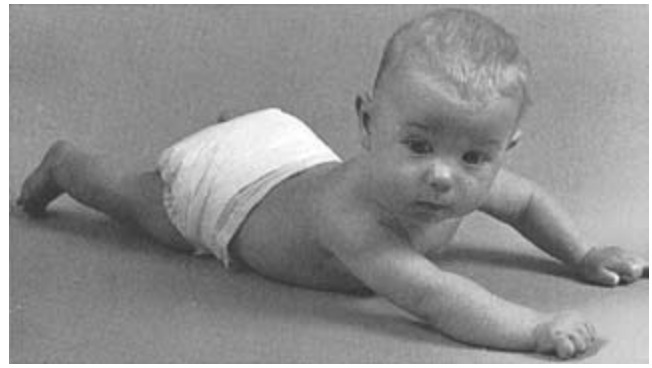


Fig. 2.30a

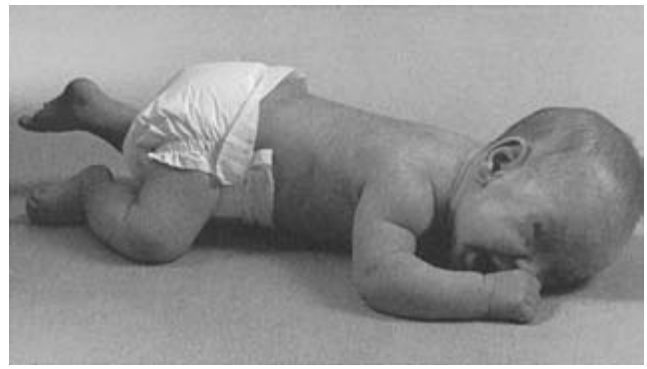


Fig. 2.30b

Fig. 2.31

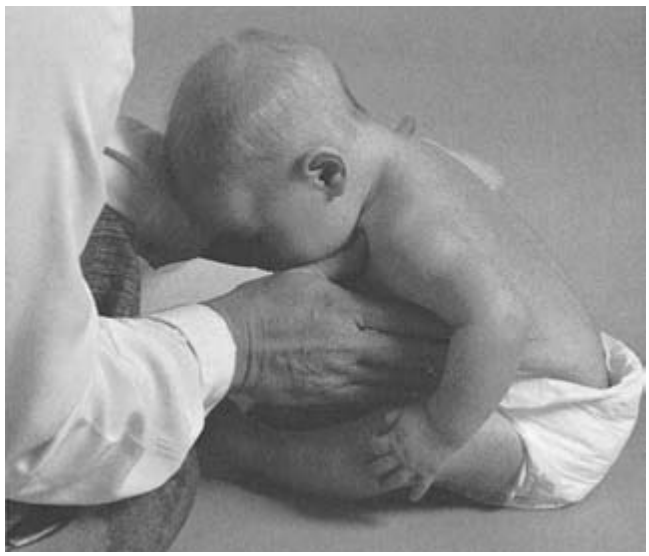


Fig. 2.32a

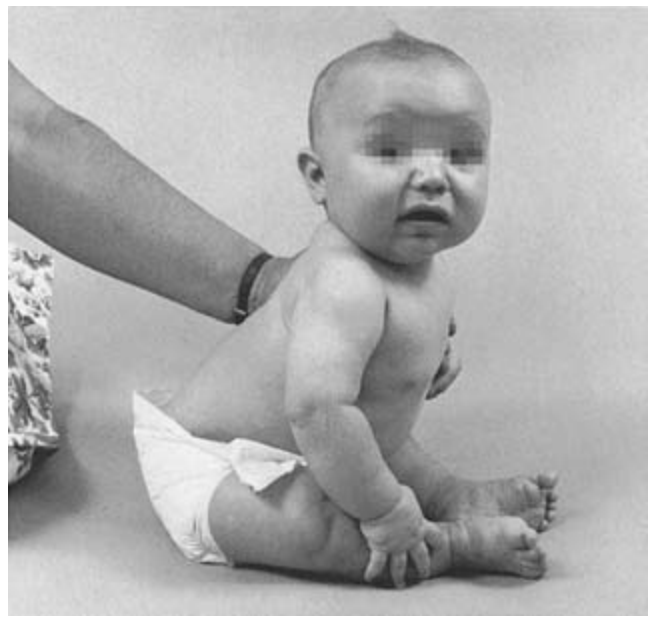


Fig. 2.32b

Fig. 2.32c

position is abnormal, indicating excessive extension. At age 6 months, the abnormal infant (Fig. 2.32c) bends forward from L-3, indicating a delay in trunk control.

16 *Sideways Parachute.* Hold the infant in a sitting position, then tip the infant gently but firmly to each side and observe for the extension of the infant's hand to "prevent" falling or provide support. The parachute items, including sideways, forward, and backward parachutes, probably provide a measure of the maturation of vestibular function. Sideways and forward parachute maneuvers are also useful in the identification of hemiparesis. A hemiparetic infant demonstrates less thrust with the impaired arm.

At 8 months of age, the normal infant (Fig. 2.33a) readily thrusts his arm and head out in support. At the same age, the abnormal infant (Fig. 2.33b) makes no effort to support himself with his arm and hand.

17 *Backward Parachute.* Gently but firmly thrust the infant backward, holding the infant at the trunk so that he or she will not lose balance and fall. Observe the posturing of the infant's arms. Some infants may turn to one side, appearing to use one arm more than the other. Because of this, the backward parachute maneuver is less useful in distinguishing asymmetry.

At 9 months of age, the normal infant (Fig. 2.34a) thrusts both arms toward the back. The abnormal infant (Fig. 2.34b) makes no effort to do so.

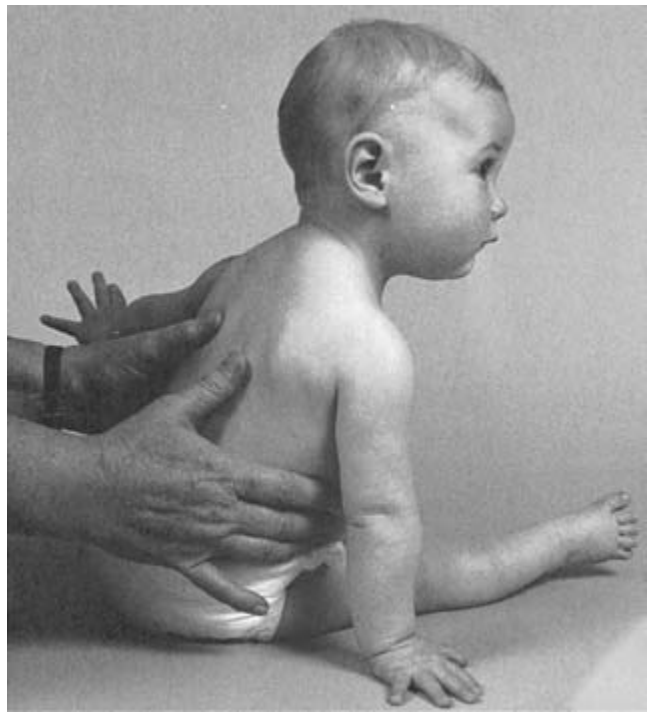


Fig. 2.33a

Fig. 2.33b

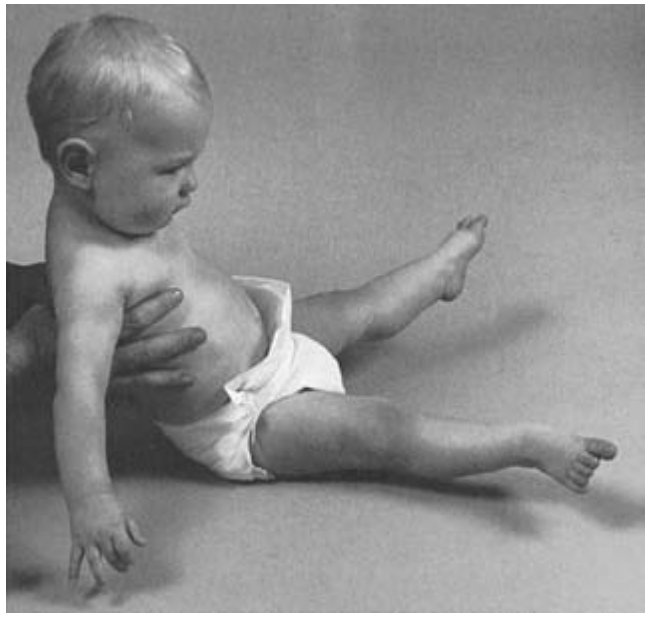


Fig. 2.34a

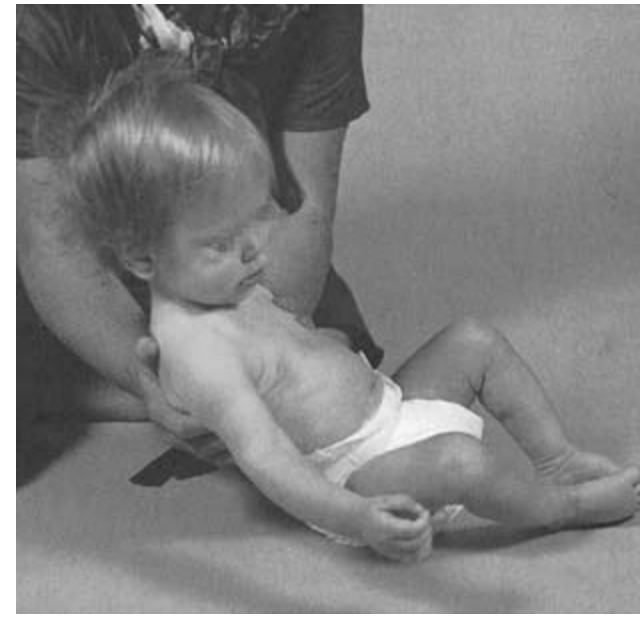


Fig. 2.34b

18 *Standing (Weight-bearing).* Place the infant in a standing position, and observe the position of the infant's body. Most newborns assume a standing position because of primitive reflexes. This tendency is lost variably but is almost always gone by age 2 months. Then the infant makes no attempt to weight-bear, or is at best unable to weight-bear.

Early weight-bearing, at approximately 2–5 months, should be associated with buckling at the knee. Specifically, the infant stands with legs straight, then bends or flexes the knees briefly and resumes a more straight-legged stance. Persistent standing without buckling often indicates hypertonia. Thus, it is scored as abnormal. Unequal weight-bearing is less clear-cut; the infant may

shift weight from one leg to another or stand such that the weight appears to be borne by one leg more than the other.

At 10 months, the normal infant (Fig. 2.35a) is sufficiently relaxed in a standing position that he appears casual and at ease. The abnormal infant (Fig. 2.35b) cannot maintain his trunk well and exhibits extensor posturing in a standing position (feet extended and head thrust back).

19 *Positive Support Reaction.* Observe the position of the infant's feet as the infant is placed in a standing position. The item is described and scored here a bit differently from usual, in order to focus attention on the feet. The item belongs with other items that describe the legs and feet: dorsiflexion of the foot, foot grasp, and weight-bearing. The abnormal infant fails to drop the heel flat to the floor (Fig. 2.36).

20 *Suspended Position: Forward Parachute.* Hold the infant at the trunk, and propel the infant forward toward a surface, such as a table, thrusting the infant's head downward. Observe the infant's thrusting of arms forward for protection or support. As noted in item 16, this item is also an excellent indicator of asymmetry as manifested by unilateral arm thrust.

At age 7 months, the normal infant (Fig. 2.37a) thrusts his arms and hands forward. At the same age, the abnormal infant (Fig. 2.37b) makes no effort to do this.

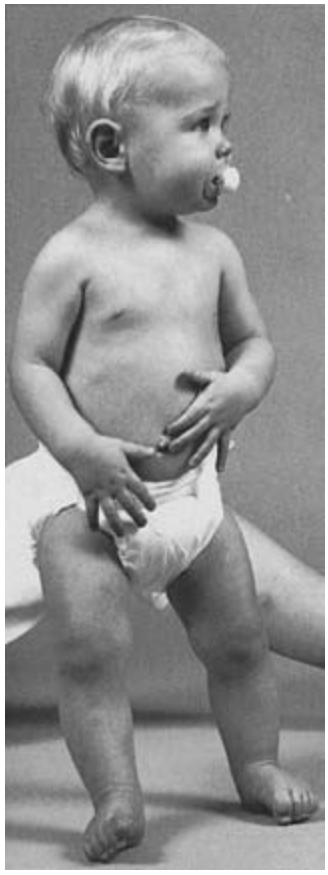


Fig. 2.35a

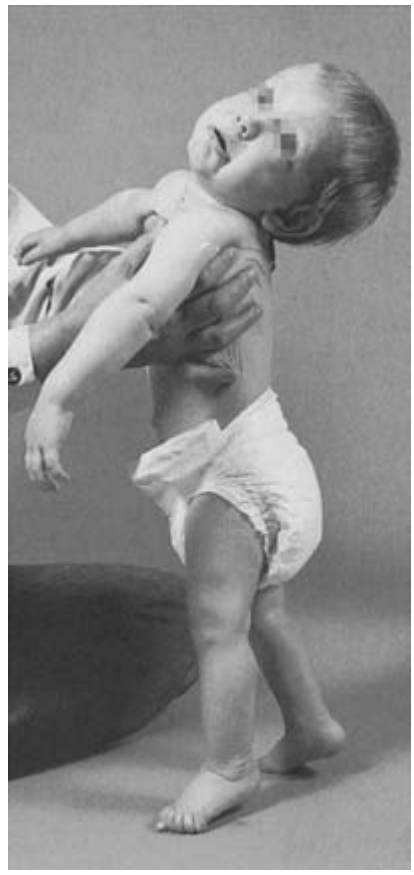


Fig. 2.35b

Fig. 2.36

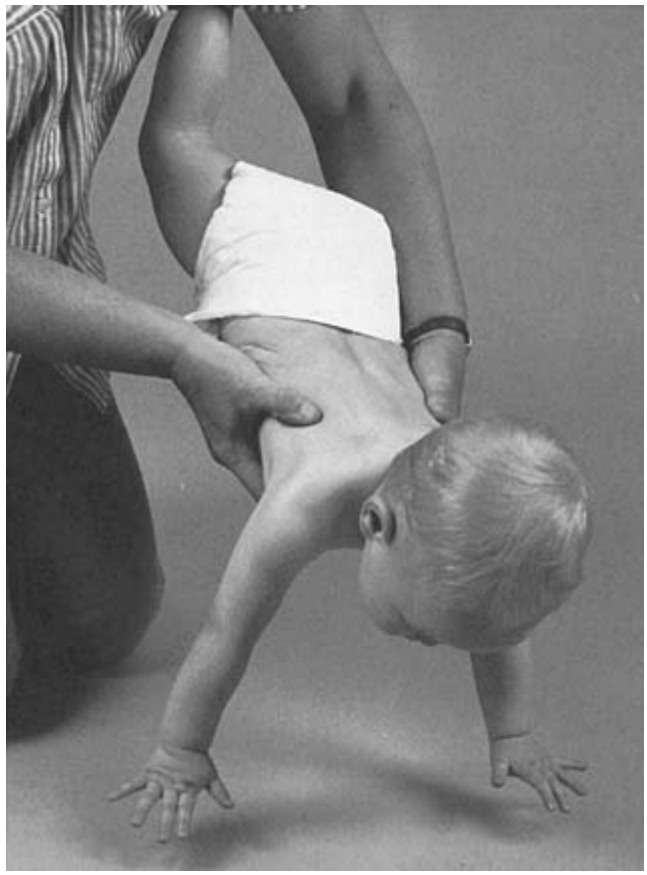


Fig. 2.37a

Fig. 2.37b

Using the Infanib Scoring Sheet

The items on the Infanib (Fig. 2.38) are listed in a logical order, progressing from supine to prone to sitting to standing to suspension. The age at which the item appears is listed at the far left. For each item, the examiner circles the description that most closely approximates the infant being examined. An item is not scored unless it is appropriate for the infant's corrected gestational age (thus, 0 points are given for items below the infant's corrected gestational age). The age at which a major change occurs appears in the second column at the left.

The examiner uses the second page of the scoring sheet to ascertain the score per item. The age of the infant (corrected gestational age) is indicated at the top. Each item is scored by its relation to the infant's age. In general, items that are normal are scored 5, items that are mildly abnormal are scored 3, and items that are markedly abnormal are scored 1. For items that progress with age, a delay of one stage is scored 3 and a delay of two stages is scored 1. For the French angles items, the deviation may be in either direction, permitting a description of hypotonia (delay) or hypertonia (precocious). As noted previously, hands closed and open, foot grasp, tonic labyrinthine supine, asymmetric tonic neck reflex, and tonic labyrinthine prone are scored in the early months as abnormal only if the response is exaggerated. Early acquisition of a skill may be abnormal. For example, infants between 2½ and 5 months who do not buckle at the knee within 60 seconds receive a score of 1 (abnormal). Similarly young infants who bring their heads forward too well on pull to sit are scored as abnormal. All asymmetric positions are also given a score of 1. This approach assists in a diagnosis of hemiparesis.

The scores for each item should be placed in the allotted spaces on the first page of the scoring sheet. Each column is summed to obtain a factor score. This helps the examiner think about the items in groups. The factor scores are then summed to obtain a total score.

The degree of normality and abnormality based on the total score is ascertained from the chart on the second page of the scoring sheet for the three age divisions: less than 4 months (it is preferable to use the NeoNeuro & Up for ages less than 4 months), 4–8 months, and 8 months or more. For those infants whose scores fall in the range of abnormal, a category of abnormality is selected by the examiner.

In most of our work with infants, we have used a limited choice of categories for designation of neurologic abnormality: spastic tetraparesis/dyskinesia, spastic hemiparesis, spastic diplegia, and moderate to severe hypotonia. The

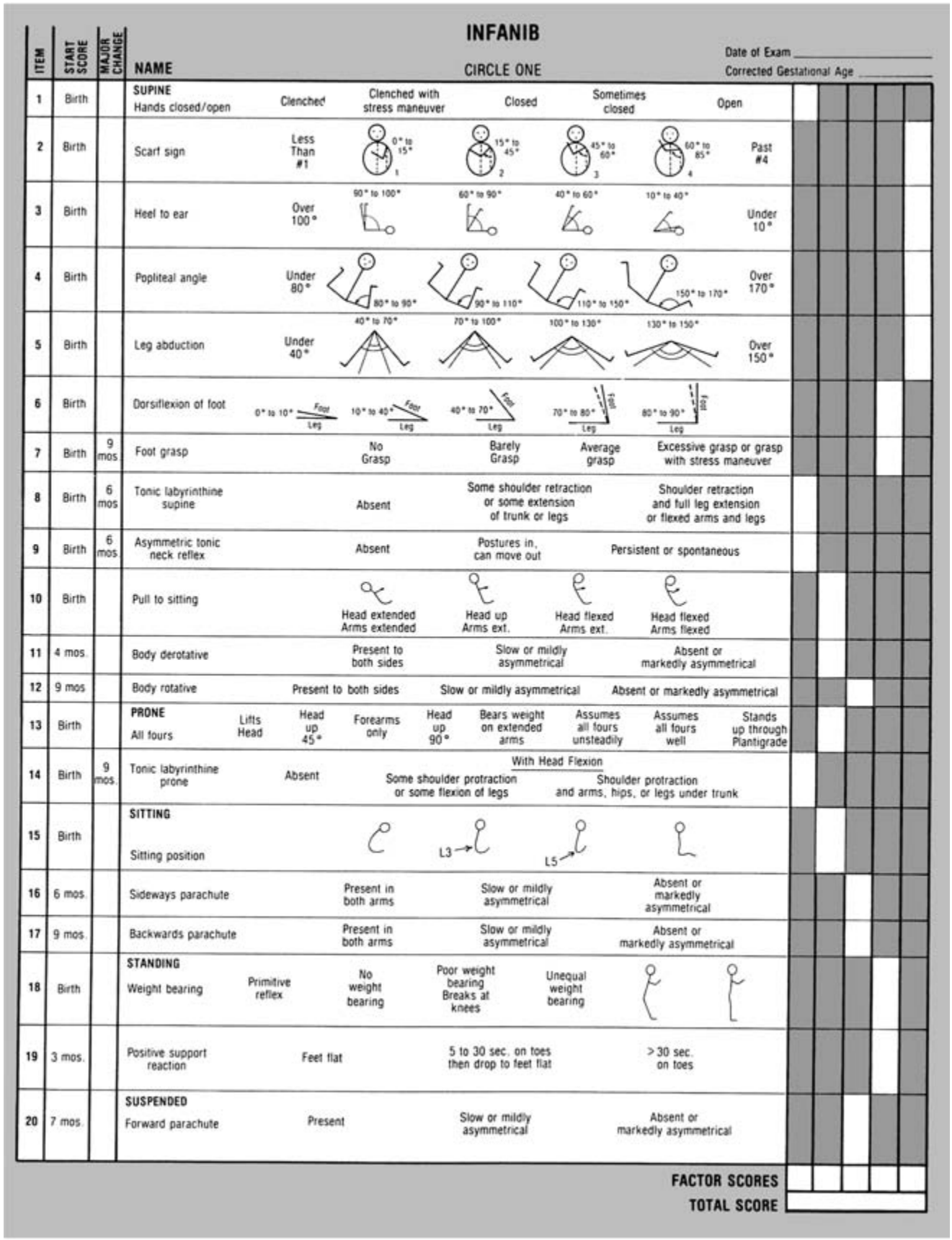


Fig. 2.38 Infanib Scoring Sheet.

INFANIB, page 2

Overall: Normal = 5, Mildly abnormal = 3, Markedly abnormal = 1

Corrected gestational age — SCORING

ITEM	0-.9	1-1.9	2-2.9	3-3.9	4-4.9	5-5.9	6-6.9	7-7.9	8-8.9	9-18 months	Comments
1.	Closed		Some times closed	Open			At any age, clenched or clenched with stress maneuver = 1				matches age = 5 One stage delay = 3 Two stage delay = 1 One closed, one open = 1
2.	 0 - 15° 1			 15 - 45° 2			 45 - 60° 3			 60 - 85° 4	5 = Picture matches age 3 = One stage away ← or → 1 = Two stages away ← or →
3.	100 - 90°			90 - 60°			60 - 40°			40 - 10°	
4.	80 - 90°			90 - 110°			110 - 150°			150 - 170°	As above except definite asymmetry = 1
5.	40 - 70°			70 - 100°			100 - 130°			130 - 150°	As for # 2 & 3
6.	0-10° = 1 40-80° = 5 10-40° = 3 80-90° = 3			0-10° = 1		10 - 40° = 3		40 - 70° = 5	70 - 80° = 3	80 - 90° = 1	Definite asymmetry = 1
7.	Excessive grasp or grasp with stress maneuver = 1, Other = 5								Absent = 5	Barely Grasp = 3 / Grasp = 1	Definite asymmetry = 1
8.	Shoulder retraction and full leg extension or flexed arms and legs = 1, Other = 5								Absent = 5	Some = 3 / Full = 1	
9.	Persistent or spontaneous = 1, Other = 5						Absent = 5	Postures in Can move out = 3		Persistent = 1	
10.							Full = 5 Partial head lag or not using arms = 3 Complete head lag and not using arms = 1				Picture matches age = 5 One stage delay = 3 Two stage delay = 1 0-4 months head flexion and arm flexion = 1
11.				Present to both sides = 5			Slow or mildly asymmetrical = 3			Absent or markedly asymmetrical = 1	
12.										Present = 5 Slow or mildly asymmetrical = 3 Absent or markedly asymmetrical = 1	
13.	Lifts Head		Head up 45°	Forearms only	Head up 90°	Bears weight on extended forearms	All fours unsteadily		All fours well	Plantigrade	Picture matches age = 5 One stage delay = 3 Two stage delay = 1
14.	Shoulder protraction, arms, hips or legs under trunk = 1, other = 5								Absent = 5	Some = 3 / Full = 1	
15.				 L3		 L5					Picture matches age = 5 One stage delay = 3 Two stage delay = 1 0-5 months L5 break and head extension = 1
16.							Present in both arms = 5		Slow or mildly asymmetrical = 3	Absent or markedly asymmetrical = 1	
17.										As Above	
18.	Primitive Reflex	No Weight-bearing		Poor weight bearing Breaks at knee			Unequal weight bearing				Picture matches age = 5 One stage delay = 3 Two stage delay = 1
											Persistent weight-bearing (> 60 sec) at 2.5 - 5 months = 1
19.				Maintains weight feet flat = 5			5 - 30 sec. on toes then drop to feet flat = 3			> 30 sec on toes = 1	
20.								Present = 5	Slow or mildly asymmetrical = 3	Absent or markedly asym. = 1	

Degree of normality/abnormality based on total score

Less than 4 months	4 to 8 months	8 months or more
Abnormal ≤ 48	Abnormal ≤ 54	Abnormal ≤ 68
Transient 49 - 65	Transient 55-71	Transient 69-82
Normal ≥ 66	Normal ≥ 72	Normal ≥ 83

Category of abnormality

If abnormal, choose a category

☐ Spastic Tetraparesis/Dyskinesia ☐ Spastic Hemiparesis ☐ Spastic Diplegia ☐ Hypotonia

mild hypotonias are included in transient neuromotor abnormalities. These categories evolved with experience and in working with other clinicians. When more categories of abnormality were used, clinicians often disagreed. Thus, the slightly broader categories were used when the research required that each category be graded for purposes of data analysis or for description of the progression of the category through infancy (Ellison *et al*. 1983). The types of abnormality and their outcome have been discussed in detail in other work (Ellison 1984a,b). Any examiner who evaluates and scores an infant should have knowledge of these progressions before discussing the infant with the parents.

PEARLS & PERILS

- Use of the reflex hammer is less reliable than evaluation of tone and posture.
- Young (0–3 months) hypotonic infants may become spastic.
- Older (6–12 months) hypotonic infants tend to become less hypotonic.
- Always obtain serial head circumference measurements.
- Do not name a neurologic condition on the basis of one or two signs; most conditions comprise a constellation of signs. Some exceptions include facial nerve palsy or brachial plexus injury.
- Address parental anxiety as their concerns are usually well founded.

What is the prognosis for neurologic abnormality?

Prematures

Clinical researchers have varied in their approaches to the identification of those prematures at risk for later neurologic dysfunction. Some have shown that the progression to a normal neurologic examination at 40 weeks gestation establishes strong indication of neurologic normality.

Others used ultrasound findings to define significant neurologic injury including one or more of the following: Grade 4 IVH, PVL at term, or ventriculomegaly at term (Ment LR *et al*. 2003).

We have used statistical techniques of path coefficients to tease out the contributions of various neonatal sickness to later neurological dysfunction. (Ellison & Foster 1992.)

Neonates

Full-term newborns that are normal neurologically are, in general, normal at follow-up. This was noted in the studies of Prechtl, in which 8% of the normal neonates had neurologic aberrations at 2–4 years (Prechtl & Dijkstra 1960), and by Amiel-Tison (1976; Amiel-Tison & Grenier 1986). Abnormal neonates, on the other hand, are much more difficult to classify in regard to prediction: citing Prechtl, 68% of the abnormal neonates had neurologic aberrations at 2–4 years. (Prechtl's "neurologic abnormality of the neonate" and "neurologic aberrations at 2–4 years" are both broad-spectrum categories.)

In our experience, neonatal factor scores may have very low relationships with each other. Even with total scores in the severely abnormal range, certain factor scores were normal for some neonates. Neonates who scored in the moderately or severely abnormal categories had different combinations of low factor scores. Neonates with mildly abnormal total scores had lower scores for irritability or the head-on-neck support factors. Clinicians should be able to determine through further research which combinations tend to improve and which do not. We should also be able to determine which combinations respond to which intervention therapies. In short, the use of the sub-scores should help us in untangling some of the unsolved problems.

Infants

Considerable information is already available about the progression of neurologic normality and abnormality from infancy through the early school years. Again, infants who are normal tend to remain so, unless there is an intervening event such as meningitis, seizures, or head injury.

Infants who are abnormal often look worse or score worse in the course of infancy. Many of them will improve in their neurologic function between infancy and early school years; they may even "outgrow" cerebral palsy. In the National Collaborative Perinatal Project, 16% of infants with a diagnosis of moderate or severe quadriplegia did not carry a diagnosis of cerebral palsy at age 7 years; 72% of infants with mild spastic diplegia outgrew their cerebral palsy, and 50% of infants with moderate to severe spastic diplegia outgrew it. Only 48% of infants with mild hemiparesis and 13% of those with moderate to severe hemiparesis outgrew it by age 7 years (Nelson & Ellenberg 1982).

Hypotonia, the most common category of abnormality for infants initially treated in the neonatal intensive care unit, tends to improve. We prefer to consider mild hypotonia as part of transient neuromotor abnormalities. In a series of 999 infants from the neonatal intensive care unit, 21% demonstrated transient neuromotor abnormalities in infancy (Ellison *et al*. 1982). Of these minor abnormalities, 79% had disappeared by 15 months. Infants with moderate to severe hypotonia also tend to outgrow it, more quickly if their other developmental skills (adaptive and personal-social) are normal.

Transient neuromotor abnormalities

By infancy, much of the neurologic abnormality noted in the neonatal intensive care unit has disappeared, at varying ages in infancy depending on the assessment items used by the examiner. What remains is a reasonable marker that "something" happened to the brain. In the National Collaborative Perinatal Project, children who were given a label of "suspected" cerebral palsy at 1 year and who did not have cerebral palsy at age 7 years had a significantly increased frequency of mental retardation, refractive errors, hyperactivity, and immature behavior (Nelson & Ellenberg 1982). Drillien found significantly lower scores in reading and spelling achievement, speech, and motor tasks in those children from a sample of 261 low birth-weight infants who had transient neurologic abnormalities (Drillien *et al*. 1980). In our work, these children had an increased frequency of combinations of problems at age 7 years: cognitive deficits, motor dysfunction, learning disabilities, and behavioral problems (Ellison *et al*. 1985b). In all of these studies, the majority of children with transient neurologic abnormalities were normal at preschool or early school years.

Appendix: neonatal and infant neurologic examination

The examination has been divided into four subsections: I, General description; II, Cranial nerves; III, Special situations: altered mental status and spinal lesions; and IV, Data from PremieNeuro, NeoNeuro & Up, and Infanib scoring sheets (Fig. 2.39).

I General description

Most experienced examiners are continually assessing the baby from the initial encounter, constantly forming and reforming a "gestalt" of the neurologic condition.

Head

The size of the head is recorded, preferably at every evaluation. The initial newborn head circumference may be misleading because of molding during the birth process. Severe molding with marked overlap of the sutures should be noted and recorded. Such a neonate may be mistakenly labeled as microcephalic. We prefer a definition of microcephaly of greater than two standard deviations below the mean (approximately the 2nd percentile). Even two standard deviations is not highly predictive of mental retardation. Three standard deviations below the mean (the 0.6 percentile) is the better predictor of brain dysfunction.

A decrease of percentiles to the second percentile in the first 6 months or later may indicate severe damage to the brain through a process such as hypoxia-ischemia. Excessively rapid growth may indicate hydrocephalus, subdural hematoma effusion, tumor, or rapid brain growth.

The shape of the skull is noted with particular attention to unusual configurations. Most of the craniosynostoses can be diagnosed by inspection.

Infants who sleep or constantly rest their heads in the same position often get unusual head shapes, especially plagiocephaly. Frequently overlooked is the rather remarkable skull configuration secondary to trauma and secondary fibrosis of the sternocleidomastoid muscle (torticollis).

The size of the anterior and posterior fontanelles is noted and recorded as is any bulging, fullness, or tension. The size of the anterior fontanelle for those infants with either larger or smaller head circumference should be recorded.

For newborns, the size and location of any caputi are recorded, either cephalohematoma (restricted to one section of the skull) or caput succedaneum (crossing a suture line).

Eyes

Conjugate deviation and repetitive nystagmus are especially good indicators of seizures. Wandering eye movements and sustained nystagmus may indicate any of several abnormalities: coma, malformation, or decreased visual acuity. Other noteworthy findings may include abnormal pupil shape, various malformations of the anterior eye (e.g. coloboma) "setting sun" sign, and conjunctival hemorrhage. Special attention must be directed to acquired signs such as nystagmus (otherwise lesions such as optic glioma, hypothalamic tumors, or metabolic disorders will be missed).

The most common eye abnormality of infancy is strabismus. Strabismus *per se* does not equal brain dysfunction, but infants with a history of brain insults have an increased frequency of strabismus and are at increased risk of amblyopia.

Skin

Every inch of the skin is inspected for café-au-lait spots, depigmented spots, hemiangiomas, and nevi. Particularly in

KEY CLINICAL QUESTIONS

- What are the early signs of cerebral palsy?
  (The constellation of delayed head control, hypotonia of arms, and limited popliteal angle or heel-to-ear angle is an excellent indicator.)
- What is the clinical significance of increased tone in the preterm infant?
  (Increased tone without abnormality of posture or movement may be transient in the preterm infant.)
- Will early spasticity in infants change over time?
  (Tetraparesis may increase over time; diplegia may decrease or appear less so; and monoparesis generally changes either by disappearing or progressing to hemiplegia or diplegia.)

babies with seizures, look for neurophakomatoses. Inspect every baby for ecchymoses. The size and location of all lesions must be recorded. For all ages, trauma is an important cause; other important causes include bleeding disorders and meningococcemia.

Dysmorphologic features

If the primary care physician cannot recognize basic dysmorphologic features, diagnoses of various syndromes may be delayed. Pay attention to distance between the eyes, ear shape and placement, hair whorls, hair texture, hair line, coarseness of facial features, shortness or webbing of neck, distance between nipples, presence of a gibbus formation, pectus excavatum, dermatoglyphics, number and placement of digits, webbing of fingers or toes, contracture of joints, and malformations of the limbs. Key the syndrome through one of the texts of dysmorphology or computer programs. Order appropriate diagnostic tests. The expertise of a dysmorphologist may be needed for genetic counseling or for further diagnostic evaluation.

Organomegaly

The size of the organs is usually assessed quickly and may give an important clue to a neurologic diagnosis (for example, hepatomegaly may suggest glycogen storage disease).

Seizures

Attention to seizures is of key importance in the neonatal period. In infancy, obvious seizures receive immediate attention by physicians. More subtle seizures – particularly the frequent, brief extension or flexion of infantile spasms – may be delayed in both diagnosis and treatment.

Apnea

The absence or presence and approximate frequency of apnea are noted.

Brachial plexus injury

This injury is usually noted in the hospital nursery. The injury is easily distinguished from hemiparesis. Brachial plexus injuries are associated with depressed reflexes and hypotonia of the arm. Hemiparesis can be associated with facial weakness and increased tone and reflexes in both arm and leg. The timing is also different: brachial plexus injury is identified early; hemiparetic lesions tend to be identified later in the first year.

Hand preference

Asymmetry of hand fisting, especially excessive clenching versus open position, is an important indicator of hemiparesis from the neonatal period through infancy. Development of handedness at less than 1 year is another indicator of hemiparesis.

II Cranial nerves

With an alert, conscious neonate or infant, the following examinations should be carried out.

A Vision and hearing

Funduscopic examination

In the neonate, look for cataracts, retinal hemorrhages, chorioretinitis, and anomalies such as optic nerve hypoplasia. For infants who are normal developmentally, the most one usually sees is a glimpse of the outline of the passing fundi. For at-risk or neurologically abnormal infants a more thorough examination is needed to find a "cherry-red spot," a phakoma, or chorioretinitis. Extra patience will often yield evidence for more obscure diagnoses.

Visual acuity

Ordinarily, visual acuity is not tested. However, one must test whether the neonate or infant sees. (The use of a black-and-white bull's-eye is strongly recommended for testing, especially in neonates and young infants.) Testing of cranial nerves III, IV, and VI helps assess vision in infants. For infants who do not respond, further testing is often necessary to separate decreased visual function from limited cognitive function.

Assessment of a visual field cut, as in a hemiparetic infant, can be performed by having the child sit on the caregiver's lap. The infant's attention is first attracted by a small toy; then the examiner brings another object from behind the head and observes the infant's head turning to that object. A dangling stethoscope or tape measure works well.

Often the determination of progressive loss of visual acuity is even more difficult. The caregiver may offer clues, for example, the observation that the baby used to pick up small items (such as Cheerios) and no longer does.

Cranial nerves III, IV, and VI

Although a human face or red yarn ball has been recommended as a stimulus for the neonate, a black-and-white bull's-eye is preferred. By 1 month of age, most neonates should track well if care is taken to test them while they are in an alert state. The bull's-eye can also be used to check the infant's ability to focus while the examiner covers one of the infant's eyes for the cover test, then removes the cover to observe for eye movement as a test for strabismus.

Cranial nerve VIII

For infants, hearing can be tested by the response to the crinkling of paper at either ear, unobserved by the infant. Another person may speak in a low voice and call the infant's name. Or the examiner may ring a bell, again unobserved by the infant. Any neonate or infant for whom there is evidence of poor response to sound deserves further evalua-

tion, including behavioral audiometry or measurement of brainstem auditory evoked response or both. As with vision, either decreased hearing or decreased mental function may contribute to decreased function.

B Facial

Cranial nerve V

Response to tactile or painful stimuli on the face may be used to assess the function of this nerve.

Cranial nerve VII

Facial movement is generally best observed through spontaneous facial expression. The examiner may choose to test further for facial asymmetry by flicking the bottom of the foot to stimulate a cry, if the infant has not already done so spontaneously.

C Bulbar function

Cranial nerves IX, X, and XI

Testing of the gag reflex is readily done with a wooden tongue blade. The infant's ability to swallow is best evaluated by report of the caregiver or nurse.

Cranial nerve XII

Fasciculations of the tongue have been observed but may be difficult to distinguish from normal movements. Unusual tongue movements such as tongue thrusting and a large, obtrusive tongue should be noted.

III Special situations

A Altered mental status

Special attention should be directed to the cranial nerves in all neonates or infants with altered mental states. This strategy can aid in localizing the site or sites of central nervous system injury. The degree of alteration should be noted.

Pupillary responses to light

Constricted pupils generally indicate brainstem dysfunction. Conversely, the dilated, poorly responsive pupil or pupils may indicate increased intracranial pressure owing to third-nerve compression.

Corneal reflexes

The examiner holds the lids apart and uses a small wisp of cotton to touch the cornea and elicit the reflex. Absence indicates brainstem dysfunction.

Doll's eyes (oculocephalic) reflex

The so-called doll's eyes reflex is the most readily elicited response indicating brainstem dysfunction. The baby's head is turned from side to side. Failure of the eyes to move so as to maintain midposition indicates brainstem dysfunction. Note that this is true only when unresponsive or comatose. Older infants when alert, will focus or fix their gaze voluntarily.

Gag reflex

In the comatose baby, the gag reflex, when absent, also reflects brainstem dysfunction.

Spontaneous respirations

Clinicians have long used the presence and vigor of spontaneous respirations as an indicator of brainstem dysfunction.

B Spinal cord

For the neonate or infant with suspected or obvious spinal cord lesion, such as, myelomeningocele, further testing is mandatory.

Sensation to touch or pinprick

When a sensory level is sought, pinprick testing is most effective. This should be done with care, as the skin of the neonate, and even of the infant, may be readily marred by pinprick. Several examiners may wish to watch a single examination rather than each performing separate trials. The testing should be done under optimal circumstances. The baby should be quiet Testing should begin distally and proceed proximally.

Sweating

The level of a cord lesion may also be detected by the observance of abnormal sweating, but this method is less precise for localization.

Stream of urination

Observation of the stream is preferable. Percussion of the bladder outline may help confirm suspicions of a neurogenic bladder. Further information about infants may be gained from questioning the mother about the stream and the length of periods for which the diaper is dry. Constant dribbling also often indicates a neurogenic bladder.

Anal wink

Testing for anal wink is done with a pin. In general, this is reserved for infants about whom there is concern about a cord lesion.

Colon function

Decreased colon innervation generally results in constipation such that the bowel becomes distended and filled with feces. Then there may be recurrent diarrhea-like stools. The combination of a history of constipation and palpation of the abdomen for firm lumps of stool generally yields the correct interpretation. Many infants with abnormal neurologic function, particularly those with poor spontaneous movements, have constipation or less-frequent stools. They

do not necessarily have poor innervation of the colon. As in most neurologic diagnoses, the constellation of findings yields the correct localization of the lesion.

CONSIDER CONSULTATION WHEN...

- An infant has an abnormal score on scored neurologic assessment methods such as those described in this chapter.
- An infant has two or more developmental evaluations which are abnormal.
- An infant has increasing head circumference with rate of growth crossing percentile norms.

I GENERAL DESCRIPTION

Head circumference

_____ Centimeters

_____ Percentile

_____ Head configuration abnormalities

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

☐ Unilateral coronal suture
☐ Acrocephaly
☐ Dolichocephaly
☐ Oxycephaly
☐ Trigonencephaly
☐ Associated hand anomalies
☐ Describe: _____
☐ *Other*: _____

_____ Anterior fontanelle abnormalities

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

☐ Bulging
☐ Concave
☐ Too large
☐ Too small

_____ Size of fontanelle (centimeters)

Other: _____

_____ Other fontanelle abnormalities

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

☐ Open posterior fontanelle
☐ Third fontanelle
☐ *Other*: _____

_____ Other skull abnormalities

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

☐ Cephalohematoma
☐ Caput succudeum
☐ Molding

_____ 1 = *Mild* 2 = *Moderate* 3 = *Severe*

☐ Overlapping sutures

_____ 1 = *Mild* 2 = *Moderate* 3 = *Severe*

☐ *Other*: _____

_____ Eye abnormalities

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

☐ Setting sun
☐ Wandering
☐ Conjugate deviation
☐ Nystagmus
☐ Strabismus
☐ Conjunctival hemorrhage
☐ *Other*: _____

_____ Skin abnormalities

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

☐ Café au lait
☐ Depigmented spots
☐ Hemangiomas
☐ Nevi
☐ Ecchymoses
☐ Other: _____

and complete the following:

Size: _____

Location: _____

_____ Dysmorphic features

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

☐ Eyes	☐ Arms
☐ Hypertelorism	☐ Legs
☐ Hypotelorism	☐ Palmar creases
☐ Skull	☐ Dermatoglyphics
☐ Neck	☐ Digits
☐ Palate	☐ Joints
☐ Chest	☐ Genitalia

☐ *Other*: _____

Fig. 2.39 An example of computer format for basic neurologic examination. *(Continued)*

and complete the following:

Describe: _____

_____

_____ Organomegaly

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

- ☐ Liver
- ☐ Kidney
- ☐ Spleen
- ☐ Heart
- ☐ *Other*: _____

and complete the following:

Describe: _____

_____

_____ Seizures

1 = *No* 2 = *Infrequent*

3 = *Repetitive* 4 = *Status epilepticus*

If *yes*, then check all that apply:

- ☐ Subtle
- ☐ Focal clonic
- ☐ Myofocal clonic
- ☐ Multifocal
- ☐ Tonic
- ☐ Myoclonic
- ☐ *Other*: _____

_____ Apnea

1 = *No* 2 = *Infrequent* 3 = *Recurrent*

_____ Brachial plexus injury 1 = *No* 2 = *Yes*

Describe: _____

_____

_____ Hand preference

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

- ☐ Right
- ☐ Left

II CRANIAL NERVES

A Vision and Hearing

_____ Fundoscopic examination abnormalities

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

- ☐ Retinal hemorrhage
- ☐ Chorioretinitis
- ☐ Optic nerve hypoplasia
- ☐ Cherry red spot
- ☐ *Other*: _____

_____ Visual acuity abnormality

1 = *No* 2 = *Yes*

Describe: _____

_____

_____ Cranial nerve III, IV, or VI abnormalities

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

- ☐ Paresis involving IV
- ☐ Paresis involving VI
- ☐ Strabismus
- ☐ *Other*: _____

_____ Pupillary abnormalities 1 = *No* 2 = *Yes*

- ☐ Not round
- ☐ Unequal
- ☐ Unreactive to light

Describe: _____

_____

_____ Hearing abnormalities 1 = *No* 2 = *Yes*

- ☐ Right
- ☐ Left

Indicate how this was determined:

- ☐ Clinical observation
- ☐ Brainstem auditory evoked response
- ☐ Behavioral audiometry
- ☐ *Other*: _____

B Facial

_____ Cranial nerve V abnormality

1 = *No* 2 = *Yes*

Describe finding: _____

_____

_____ Cranial nerve VII abnormality

1 = *No* 2 = *Yes*

If yes, then check all that apply:

- ☐ Central paresis
- ☐ Peripheral paresis
- ☐ *Other*: _____

C Bulbar function

_____ Cranial nerve IX, X, or XI abnormalities

1 = *No* 2 = *Yes*

Describe finding: _____

_____

_____ Sucking abnormality 1 = *No* 2 = *Yes*

Describe finding: _____

_____ Swallowing abnormality 1 = *No* 2 = *Yes*

Describe finding: _____

_____

_____ Cranial nerve XII abnormalities

1 = *No* 2 = *Yes*

Describe finding: _____

_____

Fig. 2.39 (*Continued*)

(Continued)

_____ Tongue abnormality 1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

- ☐ Large tongue
- ☐ Tongue atrophy
- ☐ Tongue fasciculation
- ☐ Tongue thrust
- ☐ *Other*: _____

_____ Other cranial nerve abnormalities

1 = *No* 2 = *Yes*

III SPECIAL SITUATIONS

A Altered mental status

_____ Impaired level of consciousness

1 = *No* 2 = *Yes*

- ☐ Hyperexcitable
- ☐ Stuporous
- ☐ Comatose

_____ Degree of coma 1 = *Light* 2 = *Deep*

If stupor or coma is present, then complete the following:

_____ Abnormal pupillary response to light

1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

- ☐ Dilated
- ☐ Unresponsive
- ☐ Fixed
- ☐ Midpoint
- ☐ *Other*: _____

_____ Corneal reflex

_____ Doll's eyes

_____ Gag reflex

_____ Respiration If *yes*, grade each:

_____ Heart Rate 1 = *increased* 2 = *normal*

3 = *decreased* 4 = *absent*

Other: _____

B Spinal cord

_____ Spinal cord abnormality 1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

- ☐ Abnormal pinprick response
- ☐ Abnormal sweating
- ☐ Abnormal urination stream
- ☐ Neurogenic bladder
- ☐ Anal wink absent
- ☐ Constipation
- ☐ *Other*: _____

and complete the following:

_____ Level of motor loss

_____ Level of sensory loss

Describe: _____

_____

_____ Dysraphism 1 = *No* 2 = *Yes*

If *yes*, then check all that apply:

- ☐ Open
- ☐ Closed
- ☐ Leaking cerebrospinal fluid
- ☐ Meningocele
- ☐ Encephalocele
- ☐ Myelomeningocele

_____ Level of involvement

Describe: _____

_____

IV Data from PremieNeuro, NeoNeuro & Up or Infanib Scoring Sheets

Fig. 2.39 (*Continued*)

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CHAPTER 3

The Neurologic Examination of the Young Child

Ruth D. Nass, MD

OUTLINE

The sitting examination
The standing examination
Assessment of gait and station
The prone or supine examination
Sitting assessment of the head
Eyes
Mental status

The goal of this chapter is to review the neurological and developmental/psychometric assessment of the toddler and preschool child. The reader is provided with a prototypic examination and the rationale behind it. Because no toddler or preschooler will cooperate for the entire exam, Table 3.1 provides a basic examination that, if "completed," will provide sufficient information for most purposes.

Touwen and Prechtl's 1970 monograph *The Neurological Examination of the Child with Minor Central Nervous System Dysfunction* remains a classic. Some of their general suggestions about the approach to the examination of the younger child deserve mention at the outset. As children generally dislike being undressed for examination, this should be done in stages and as necessary. Shoes and socks should be removed initially so that movements of the feet and legs can be monitored throughout. At some point the child must be completely undressed to look for skin markings diagnostic of a neurocutaneous syndrome. A Wood's lamp examination for less visible ash leaf spots should be considered, especially in the child with an autistic spectrum disorder. The child should be dressed again with some help by the parent prior to examination of the head, the final phase of the assessment. The inspection of the head, as well as that of the hands and feet, should include assessment for the minor physical anomalies listed in Table 3.2. High anomaly scores in preschoolers have been correlated with conduct problems and hyperactivity at school age (Waldrup *et al*. 1968). Head circumference should also be measured, since there is an increased frequency of head size two standard deviations above or below the mean in children with developmental disabilities. Macrocephaly should be pursued, for potentially treatable causes like hydrocephalus and for genetic causes like fragile X chromosome disorder and external hydrocephalus. Special attention should be paid to the motor function of the child with macrocephaly since such children are at increased risk for both gross and fine motor dysfunction (Lewis *et al*. 1989; Nevo *et al*. 2002).

Touwen and Prechtl (1970) are very specific about the order of the neurological examination. While the history is being taken from the parent(s), the child can be observed as he or she adjusts to the examining room and plays with toys. The sitting exam is performed first (with a young child often sitting in the parent's lap), followed in order by those parts of the exam that are performed in the standing position, those dealing with locomotion, any part of the exam requiring a prone or supine position, and finally the examination of the head (Table 3.1). This is obviously quite different from the traditional approach to the neurological examination suitable to the older child and adult.

The sitting examination

Spontaneous motility

Spontaneous gross and fine motility is assessed over a 3-minute period while taking the history from the parents. Both the quantity and quality of movements are assessed, each on a scale of 0–3. Speed, smoothness, and adequacy are the qualitative parameters. High scores in the quantity domain suggest attentional difficulties. However, note that the diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) is based on parent and teacher assessments of behavior, not office behavior.

TABLE 3.1

Soft Sign Examination in the Preschool Child

Sitting assessment

1 Spontaneous motility (3-minute observation)
2 Muscle power, tone, and mass
3 Reflexes
4 Sensory examination: finger localization, double simultaneous stimulation, graphesthesia, stereoagnosis

Standing assessment

1 Posture
2 Spontaneous motility (2-minute observation)
3 Posture with arms extended palms up and palms down
4 Assessment for involuntary movements (Prechtl's sign)
5 Mouth opening/finger spreading phenomenon
6 Diadochokinesis and associated movements
7 Finger-to-nose test
8 Fingertip touching test
9 Finger opposition test
10 Standing with eyes closed

Assessment of gait and station

1 Gait
2 Walking a straight line
3 Walking on tiptoes
4 Walking on heels
5 One-foot stand
6 Hopping on one foot
7 Catch a ball
8 Trunk

Prone or supine assessment

1 Examine spine
2 Knee-heel test
3 Sitting up without the use of the hands

Sitting assessment of the head

1 Musculature of face
2 Eyes
3 Ears
4 Mouth

TABLE 3.2

Anomalies Seen with ADHD

Head

1 Electric hair
2 Very fine hair that will not comb down
3 Fine hair that is soon awry after combing
4 Two or more whorls

Eyes

1 Epicanthus (where upper and lower lids join nose point of union)
  Deeply covered
  Partly covered
2 Hypertelorism: approximate distance between tear ducts:
  Greater than or equal to 1½ inches
  Between 1¼ and 1½ inches

Ears

1 Low-seated ears
2 Bottom of ears in line with
  Mouth (or lower)
  Area between mouth and nose
3 Adherent lobes:
4 Lower edges of ears extend
  Upward and back toward crown of head
  Straight back toward rear of neck
5 Malformed ears
6 Asymmetric ears
7 Soft and pliable ears

Mouth

1 High palate
2 Roof of mouth
  Definitely steepled
  Flat and narrow at the top
3 Furrowed tongue (one with deep ridges)
4 Smooth or rough spots on tongue

Hands

1 Fifth finger
  Markedly curved inward toward other fingers
  Slightly curved inward toward other fingers
2 Single transverse palmar crease
3 Index finger longer than middle finger

Feet

1 Third toe
  Definitely longer than second toe
  Appears equal in length to second toe
2 Partial syndactyly of two middle toes
3 Gap between first and second toe (greater than or equal to ¼ in)

Muscle power

Muscle power, tone, and mass are assessed in the same fashion as in the older child. Often functional assessment of the legs during gait maneuvers proves more useful than standard push-pull testing.

Assessment of reflexes

Reflex assessment is standard. Younger children sometimes show spread, for example, to the adductors when the knee is tapped, which is not necessarily pathological. Touwen and

Prechtl suggest that the plantar reflex be elicited by stroking with a sharp object or a thumbnail from toe to heel. The reverse technique prevents eliciting a grasp reflex as one approaches the toes.

Sensory examination

While the sensory exam is difficult to perform in the young child, there is information about the early development of sensory functions.

Finger localization

Many 3-year-olds (the percentages indicated in parentheses) and almost all 4- and 5-year-olds can oppose the thumb to the finger touched by the examiner (85%), find the fingers touched by the examiner with the contralateral hand (75%), oppose the thumb to the finger pointed to by the examiner (70%), find the fingers pointed to by the examiner with the contralateral hand (65%), and oppose the thumb to the finger indicated by the examiner while the subject's view is obstructed (50%) (Lefford *et al*. 1974). Finger imitation skills can be assessed in the 4- to 6-year-old (Levine & Schneider 1985). Sitting opposite the child, the examiner opposes his or her thumb to another finger on the same hand, holding that position for 5–8 seconds while the child imitates. Mirror movements and dyskinesias (opposition movements that are slow to release) should be noted. Children who require excessive visual input of their own hand movements may have true finger agnosia. Most 4- to 6-year-olds will perform correctly on three to four trials. Most 5-year-olds can even oppose the thumb to the proximal, distal, or middle phalanx of each finger when it was touched by the examiner out of the child's view (uncrossed localization) (Galin *et al*. 1977). However, it was not until age 8 or 9 that children were able to perform a crossed localization task – touch the homologous spot on the opposite hand with the opposite thumb. Difficulty with crossed localization is also seen in disconnection syndromes caused by surgical section of the corpus callosum. The young child may indeed look functionally acallosal in some respects. The more classic finger agnosia tasks of "How many fingers were touched, one or two?" and "How many between?" are too difficult for the preschooler. They are performed by only 30% and 15%, respectively, of 5-year-olds, 45% and 30% of 6-year-olds, and 85% and 65% of almost-7-year-olds (Kinsbourne & Warrington 1963).

Finger localization skill in kindergarten predicts reading and arithmetic achievement at the end of the first grade (Lindren 1978). Normal somatosensory system maturation may play a role in optimizing academic achievement. Furthermore, children with finger localization problems may try to compensate by adopting an awkward pencil grip, with resultant dysgraphia (Levine 1988). It is of particular interest that finger localization difficulties in the preschooler can cause dysgraphia and predict later arithmetic skill, because finger agnosia, dysgraphia and dyscalculia are three of the four (right–left disorientation the other) seen in Gerstmann's syndrome, which occurs on a developmental basis in perhaps 2% of school-age children (Suresh & Sebastian 2000).

Double simultaneous stimulation

Extinction to face on double simultaneous stimulation of hand and face is common in the child until about age 10 years, presumably because the face is more elaborately represented and because the facial sensory pathways mature earlier than those of the hand. In the preschool child there is also a right–left distinction, the testable child (sometimes as young as 2 years old) being more likely to extinguish the stimulus presented to the left hand, when right and left are touched simultaneously (Kinsbourne & Hicks 1978). Asymmetric lateralization of attention may be a phase of normal development (Roeltgen *et al*. 1986).

Graphesthesia

In the preschool child a matching format where the child picks out from drawings of a circle, line, square, and cross, the shape that has been made on his/her preferred hand can be used (Levine & Schneider 1985). Three of four correct is the norm for the 4- to 6-year-old.

Stereoagnosis

Using duplicate shaped pieces of wood, stereoagnosis can be tested in the preschooler (Levine & Schneider 1985). One by one, the forms are placed in the child's fisted hand and he or she is asked to pick visually the matching form. Most 4- to 6-year-olds will identify three of the four.

The standing examination

Posture

The standing exam begins with an assessment of posture. The posture of the preschooler differs from that of the older child. The 2-year-old has a rather broad based stance and often postures the arms even when just standing in place (Fig. 3.1a). The 3-year-old has a slightly broad-based stance. The 5-year-old holds his or her body straight and the base is narrow (Fig. 3.1b).

Spontaneous motility

Spontaneous motility is assessed in the standing position for 2 minutes, while the child is "standing around waiting for things to happen." Many preschoolers move around during a 2-minute observation period.

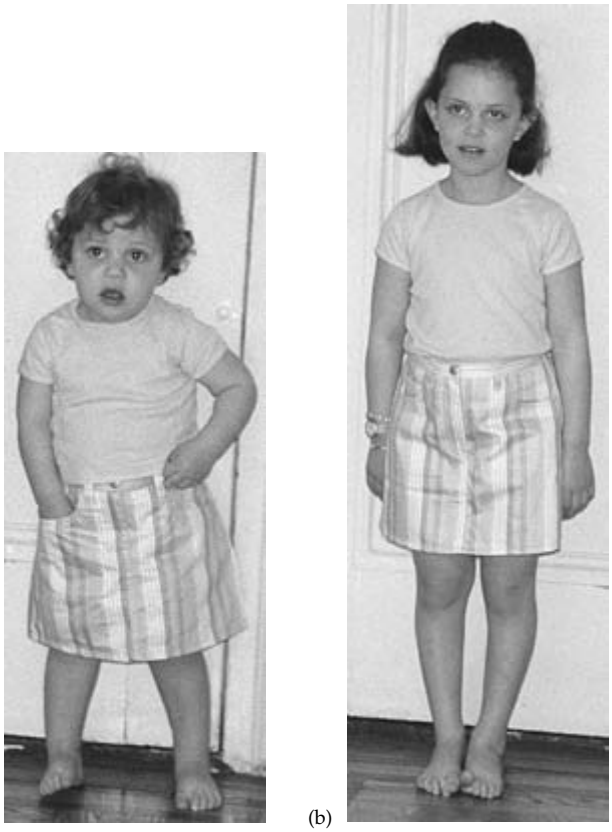


Fig. 3.1a and b The 2-year-old has a rather broad-based stance and often postures the arms even when just standing in place. The feet are not always flat on the ground. The 5-year-old holds her body straight and her base is narrow. Note the spontaneous striatal toe here, presumably reflecting a relatively immature basal ganglia. Photo by Nora Gross.

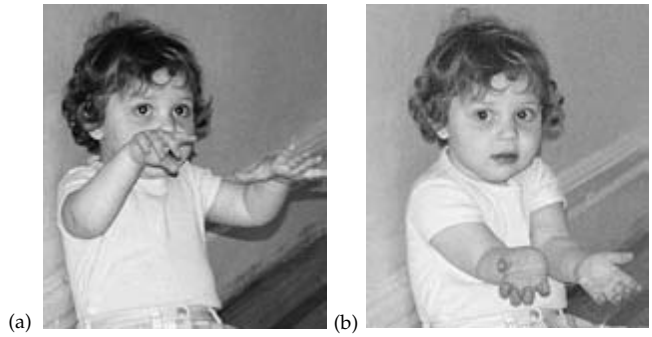


Fig. 3.2 The 2-year-old's arms drift up and down, as well as flexing at the elbows. The hands take on cupped and capped positions. Photo by Nora Gross.

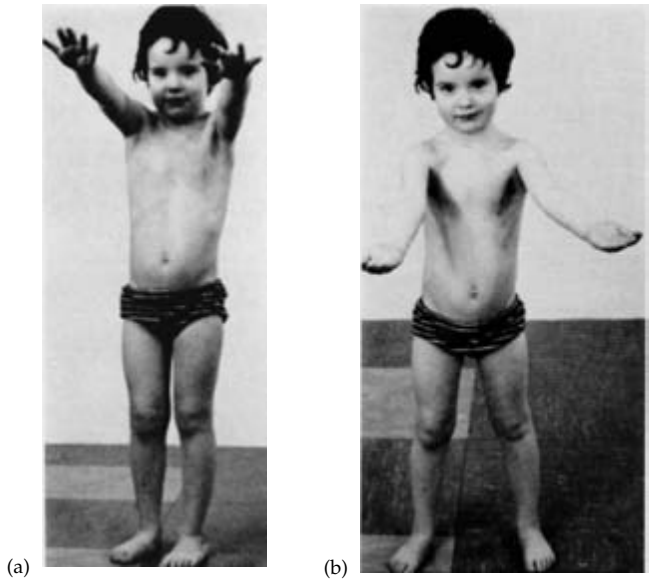


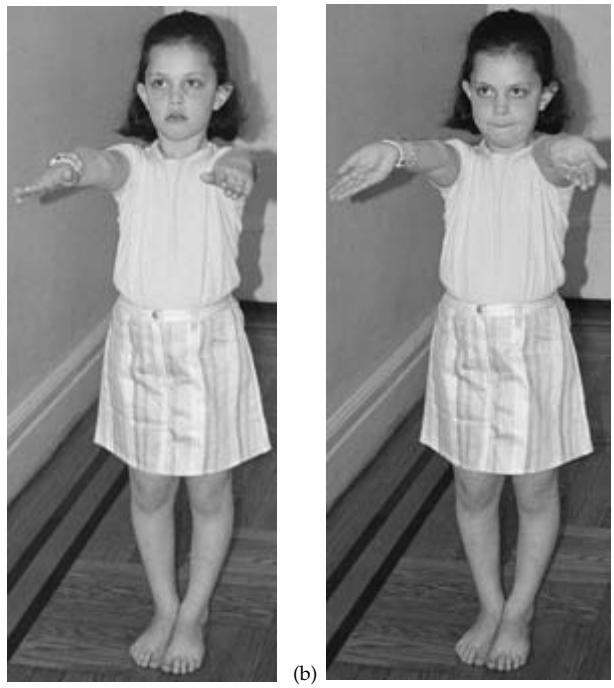
Fig. 3.3 The 3-year-old preschooler's arms tend to drift in the direction of the palms and to be laterally displaced on both tasks 30–60°. Reproduced with permission from Touwen BC, Prechtl HFR: *The Neurological Examination of the Child with Minor Central Nervous System Dysfunction*. London, 1970, Spastics International.

Posture with extended arms

Posture is checked in both the palms-up and the palms-down position for 20 seconds. The 2-year-old's arms drift up and down, as well as flexing at the elbows (Fig. 3.2). The 3-year-old preschooler's arms tend to drift in the direction of the palms and to be laterally displaced on both tasks 30–60° (Fig. 3.3). The older preschooler's arm doesn't drift up or down, but the child clearly has to concentrate to maintain a straight arm position (Fig. 3.4). Spooning of the wrist and hands is often present through age 5 years (Fig. 3.5).

Assessment for involuntary movements

Assessment for involuntary movements, including Prechtl's sign, is only accurate if the child can maintain a quiet general standing position for 2 minutes, i.e. passes the initial motility test. Thus, a reliable result is unlikely in the child under 4 years. To assess for choreiform movements, the child stands with feet together and with the fingers of the pronated outstretched hands apart for 20 seconds. Under 6 years the eyes are open, above 6 the eyes are closed. Normed data are not available on the frequency of Prechtl's sign in the preschooler, but it is probably very common.



(a) (b)

Fig. 3.4 The older preschooler doesn't drift up or down, but clearly has to concentrate to maintain a straight arm position. Note the different mouth position when palms are up and down. Photo by Nora Gross.

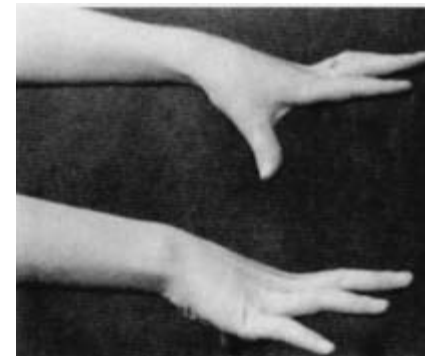


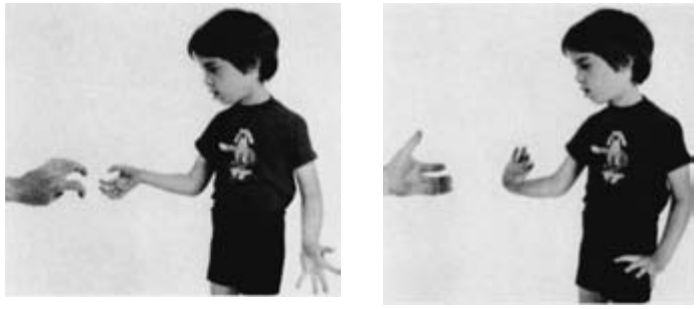
Fig. 3.5 Spooning of the wrist and hands is often present through age 5 years. This presumably reflects a relatively immature basal ganglia. Reproduced with permission from Touwen BC, Prechtl HFR: *The Neurological Examination of the Child with Minor Central Nervous System Dysfunction*. London, 1970, Spastics International.

Overflow movements

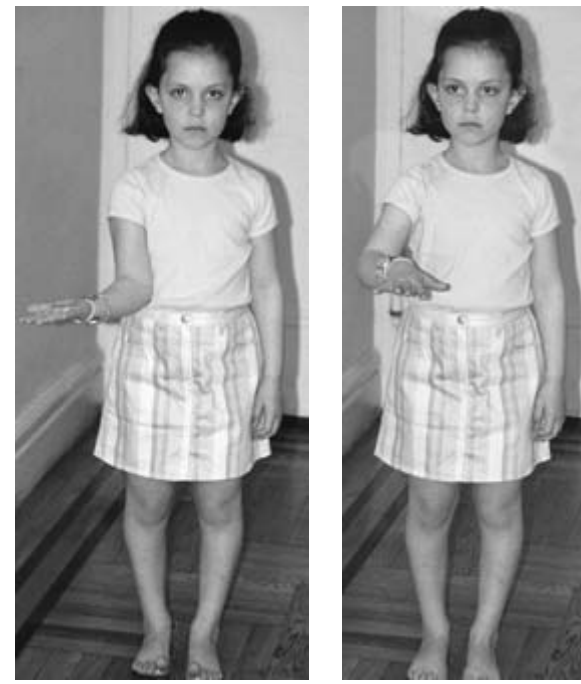
Examination for overflow movements is an important part of the soft sign assessment. Overflow movements, associated movements, and synkinesis are defined as movements occurring in parts of the body other than the part attempting the task; they may be symmetric or asymmetric. Mirror movements occur symmetrically. Overflow is common in young children and disappears around age 10 (Connolly & Stratton 1968), reflecting maturational changes in the motor system. For example, the crossed pyramid motor system, mediating rapid independent finger movements, matures later than the less specific medial motor system, which provides proximal limb and ipsilateral motor innervation. The uncrossed motor pathways may function tonically during childhood, resulting in mirror movements. With maturation, these noncrossing pathways come under the inhibitory control of the contralateral hemisphere via the corpus callosum (Dennis 1976; Nass 1985). Myelination of the corpus callosum is largely completed at about the same time that mirror movements disappear around age 10 years (Yakovlev & LeCours 1967).

Touwen and Prechtl (1970) suggest three tasks for assessing overflow and mirror movements: mouth opening/finger spreading, diadochokinesis, and the finger opposition test. The first task requires the child to open his or her mouth, close the eyes, and stick out the tongue while the extended arms, with hands and wrists relaxed, are supported by the examiner. The response of spreading the fingers is marked in the preschooler and muted by age 7–8 years. The second and third tasks are standard parts of the neurological assessment of cerebellar and motor function, respectively. On the diadochokinesis task (Fig. 3.6a and b) the preschooler will often mirror in the opposite limb (Table 3.3). Associated movements are scored as follows: 0, none; 1, barely visible or slight elbow flexion; 2, mirror movements without elbow flexion; 3, mirror movements with elbow flexion. On Denckla's (1973, 1974) time-for-20 version of this task about 20% of 5-year-olds evidence mirroring (Wolff *et al*. 1983).

The finger opposition test has been described by Touwen and Prechtl as five sequences to and fro of thumb to 2, 3, 4, 5, 4, 3, 2, 3, 4, 5, and so on, and by Denckla (1973, 1974; Rudel *et al*. 1984) as time to do 20 movements, i.e. five sequences of thumb to 2, 3, 4, 5, 2, 3, 4, 5, and so on. Although excellent for bringing out associated movements (65–90% of 5-year-olds show mirroring; Wolff *et al.* 1983), these tests are often too difficult for children under 5 years. Denckla's time-for-20 finger tapping task, thumb to index finger, can be performed by many children 3 years old and is, at least for the younger child, a good task for uncovering the overflow (30–45% of 5-year-olds show mirroring; Wolff *et al.* 1983), as well as looking at fine motor function (Fig. 3.7).



(a)



(b)

Fig. 3.6a and b On the diadochokinesis task the preschooler will often mirror in the opposite limb. The 3- to 4-year-old child has clear mirror movements with elbow flexion (a), while the 5-year-old has barely visible elbow flexion contralaterally (b). (a) reprinted with permission from Touwen BC, Prechtl HFR: *The Neurological Examination of the Child with Minor Central Nervous System Dysfunction*. London, 1970, Spastics International. (b) photo by Nora Gross.

TABLE 3.3

Mirror Movements

Score		Age				
		4	**4½**	**5**	**5½**	**6**
0	L	20	19	29	55	52
	R	0	14	14	10	24
1	L	60	57	43	40	28
	R	40	24	24	65	32
2	L	5	19	14	5	12
	R	35	43	29	20	36
3	L	15	5	14	0	8
	R	25	19	33	5	8

The percentage of children scoring 0–3 for mirror movements on the supination/pronation task is shown Vertically. The upper row (L) represents mirror movements on the left while the right arm voluntarily performs the task. The lower row (R) represents mirror movements on the right while the left arm voluntarily performs the task. From Njiokikjien C, Driessen M, Kabraken L: Development of supination-pronation movements in normal children, *Hum Neurobiol* 5:199–203, 1986.

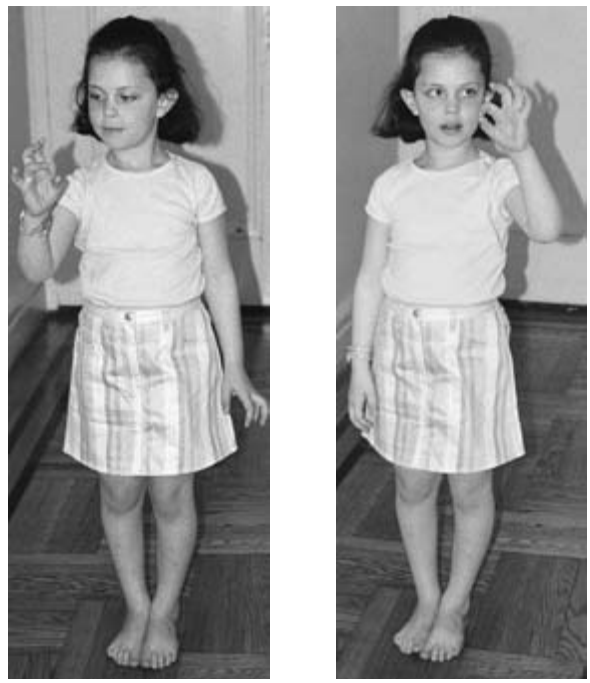


Fig. 3.7 Note the asymmetry in mirroring while this 5-year-old does a finger-sequencing task. It is marked in the nondominant hand and barely visible in the dominant hand. Photo by Nora Gross.

A number of other tasks have also been used to assess for associated movements, including clip pinching, finger spreading, and finger lifting (Wolff *et al.* 1983). Of these, only index finger lifting (passed by about 50% of 5-year-olds) would be a useful preschool measure (Fig. 3.6). Interestingly, at all ages there is little difference between dominant- and nondominant-hand performance for clip pinching and finger spreading. Thus, an asymmetry here might be a useful marker of a hemisyndrome, unlike a number of other gross and fine motor skills, for which dominance effects are common until age 7 years.

Cerebellar function

Tests of cerebellar function that Touwen and Prechtl (1970) perform in the standing position include diadochokinesis, the finger/nose test (the preschooler requires visual guidance and needs to hold his or her arm against the body for stabilization) (Fig. 3.8a and b), the fingertip touching test, and standing with eyes closed for 15 seconds (the preschooler may move ankles and toes a bit to maintain balance, but this does not seem to be clinically significant). Obvious asymmetries of function are suggestive of ipsilateral cerebellar disease. On the diadochokinesis task (Fig. 3.6a and b) the regularity of the movements and the presence of elbow movements are scored as follows (Touwen & Prechtl 1970); 0, no movement; 1, irregular with elbow movements of more than 15 cm; 2, irregular with elbow movements of 5–15 cm; 3, correct with elbow movements of less than 5 cm (see Fig. 3.4). The percentage of children scoring 1 to 3 for quality of movement is shown in Table 3.4. It is the exception rather than the rule for the preschooler to perform this task with precision. Pronounced deviation of the elbow during rapid alternating movements, rather than maintaining the action at the wrist, suggests overuse of proximal musculature around the shoulder. In the most children right arm performance is better than left (Njiokikjien *et al.* 1986). However, Denckla (1974) found little asymmetry on a time-for-20 pronation/supination task.

Assessment of gait and station

The standing exam is followed by an evaluation of gait (Touwen & Prechtl 1970). Children under 6 years generally show little arching of the foot when walking and little arm swing. The 2- to 4-year-old should have minimal gait asymmetry. The 2-year-old may have a lunging gait (Fig. 3.9). The normal gait width after age 3 is 11–20 cm. Narrowing may result from hypertonia of the leg adductors and widening from hypotonia or sensory or cerebellar disease. Children under 7 years may have difficulty with prolonged tandem walking. Difficulty with very simple line walking at age 4 is a risk factor for both hyperactivity and the neurological soft sign syndromes at age 7 (Nichols & Chen 1981).

TABLE 3.4

Score		Age				
		4	**4½**	**5**	**5½**	**6**
1	L	60	29	14	5	12
	R	45	19	10	5	8
2	L	40	71	71	65	72
	R	50	76	71	55	64
3	L	0	0	14	30	16
	R	5	5	19	40	28

The percentage of children scoring 1–3 for quality of supination/pronation is shown vertically. The upper row (L) represents the left arm; the lower row (R) represents the right arm score. From Njiokikjien C, Driessen M, Kabraken L: Development of supination–pronation movements in normal children, *Hum Neurobiol 5*: 199–203, 1986.

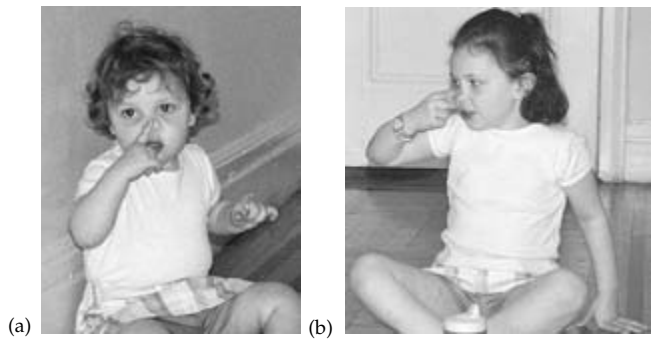


Fig. 3.8a and b The 2-year-old has to visually monitor her finger and shows marked mirroring in the other hand. The 5-year-old still monitors her movements visually, but her other hand is at her side. Photo by Nora Gross.

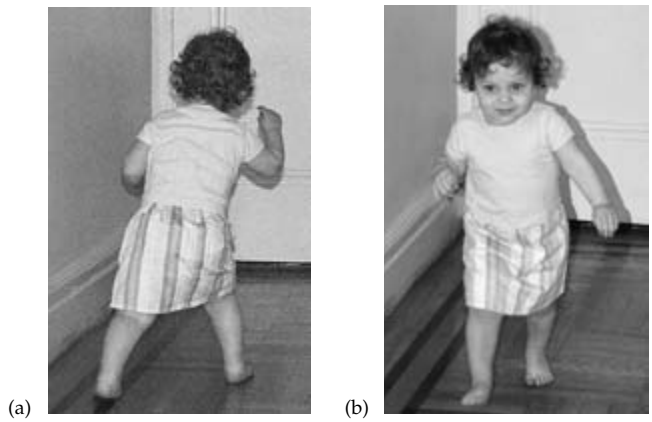


Fig. 3.9 The 2-year-old may have a lunging gait. Note the parallel arm movements. Photo by Nora Gross.

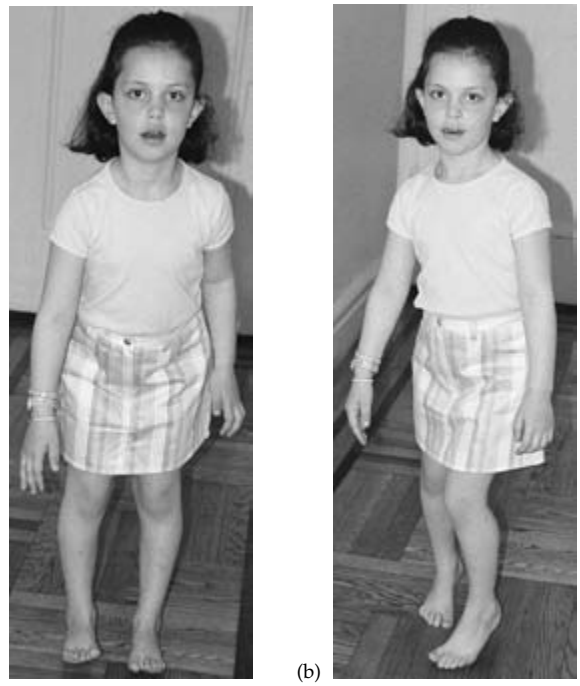
Children over 3 years should be able to walk on tip-toes. Any movements in upper extremities and face not present during the standard gait exam are counted as associated movements. Diminishing degrees of extension of arms, ventroflexion of the hands, and lip and tongue movements are seen through age 7 years (Fig. 3.10a). Clenching of the fists is counted as an associated movement only if the arms are also extended. About 25% of 5-year-olds evidence overflow (Wolff *et al.* 1983).

Heel walking can also be performed by children over 3 years. Again, any movements not seen during the normal walk are considered associated movements. They occur in about 50–80% of 5-year-olds (Wolff *et al.* 1983). Associated movements noted during heel walking persist longer, sometimes until 10 years, than do associated movements noted with toe walking (Fig. 3.10b). Arms are extended and wrists are dorsiflexed. Poor performance may also reflect hypotonia, paresis, or both. Paresis of the peroneal muscles may occur without other muscles being impaired to the same degree (Touwen & Prechtl 1970). Such children will walk on the outer side of the foot rather than the heels. Even children with mild spastic diplegia have trouble heel walking.

The ability to stand on one leg develops suddenly and matures rapidly. At 3 years only a few children can stand on one leg for more than a few seconds. The one-foot stand can be sustained for 10 seconds by a 4-year-old given a couple of false starts (Levine & Schneider 1985). By 5 years, most children can sustain the one-foot stand for about 10 seconds. There may be a marked difference between the performance on the dominant and the nondominant leg between ages 4 and 5 years, a finding that does not usually indicate a hemiparesis (Fig. 3.11).

Hopping on one foot also develops suddenly and matures rapidly. At 3 years only a few children are able to hop at all, and then only on the dominant foot. At age 4 years, 5 to 8 hops are normal and at age 5 years, 9 to 12. Prior to the age of 7 years, one leg is generally better than the other, although, as with the one-foot stand, the better leg may not be the one preferred for athletics. When the asymmetry is marked the possibility of a hemiparesis must be considered. Among a group of 150 5-year-olds 28% hopped more than 13 times on their left leg and 39% hopped more than 13 times on their right leg (Touwen & Prechtl 1970). In the National Collaborative Perinatal Project Study failure at age 4 on a hopping task was a risk factor for both hyperactivity and the neurological soft sign syndromes at age 7 years (Nichols & Chen 1981).

Ability to catch a ball can be assessed in the preschooler. The average 4- to 6-year-old will catch a 2-inch ball three to four of five tries (Levine & Schneider 1985). Associated movements of the face should be noted since they are not present in most preschoolers. In the National Collaborative Perinatal Project Study failure at age 4 years on a ball catch task was a risk factor for the neurological soft sign syn-



(a) (b)

Fig. 3.10a and b This 5-year-old is still having a hard time walking on her toes. Note how her foot toes in and her fingers flex. When she walks on her heels her wrists cock back. Photo by Nora Gross.

Fig. 3.11 This 5-year-old is still having a hard time standing on one foot. Note the tilt. This is common, particularly on the nondominant foot and should not be mistaken for a hemiparesis. Photo by Nora Gross.

dromes at age 7 years (Nichols & Chen 1981).

In general, motor system maturation often correlates with overall functioning at school age and beyond (Blondis *et al*. 1993; Gillberg 1989, 2003; Kadesjo & Gillberg 1999). In one study of children at the time of school entry four motor tests (standing on one foot, Fog test, design copying and diadochokinesis) combined with a brief structured clinical observation and a structured parent interview, identified 80% of children with disorders of attention, motor, and perception (DAMP) – and all those with severe DAMP – as well as a small number of false positives (Landgren *et al.* 2000).

Touwen and Prechtl (1970) suggest that assessment of trunk be performed while the child is standing. First the back is inspected and then the abdominal reflexes are elicited.

The prone or supine examination

Touwen and Prechtl (1970) begin this phase of the assessment by inspecting the spine. This is followed by inspecting the posture of the feet, legs, and hip joints. A 5-year-old can perform a sit up without using the hands only by lifting the legs off the table, whereas by age 7 years the legs stay in contact with the table, another marker of diminishing overflow.

Sitting assessment of the head

Musculature of the face

Assessment of the head begins with inspection of the musculature of the face for asymmetry at rest, during voluntary movement, and during an emotional response. Peripheral lesions of the 7th nerve affect both the upper and lower face. After early injuries improvement is often accompanied by synkinesias like crocodile tears. Bilateral facial nerve palsies are often the most prominent finding in the Mobius sequence, which consists, in addition, of gaze palsies, esotropia, and sometimes abnormalities of cranial nerves IX–XII. Generally, children present with feeding problems, lack of facial expression, and articulation difficulties (Smith 2000; Stromland *et al.* 2002). Central upper motor neuron 7th nerve deficits involve primarily the lower face, as the upper face is bilaterally innervated. The subcortically mediated emotional smile is relatively spared by supranuclear pathology, whereas with peripheral palsies the emotional smile is equally as impaired as the voluntary smile. Congenital absence of the depressor muscle of the mouth should not be confused with a facial palsy. In this disorder the abnormal side of the mouth is not pulled down when the child cries and the resting face is relatively normal. The side that appears to droop during crying is really the normal side. The diagnosis is important, as the incidence of associated abnormalities, particularly cardiac, is high (Nelson & Eng 1972).

Eyes

The examination of the eyes includes an assessment for strabismus. About 5% of normal children and about 50% of children with brain damage have strabismus. Strabismus is classified in several ways. Heterophoria is a latent condition that is brought out only in certain circumstances like fatigue and testing. A heterotropia is constantly present and may be either exo- (outward) or eso- (inward) in the horizontal direction or hyper- or hypo- in the vertical direction. Strabismus may be alternating, with the fixating eye switching back and forth, or it may be monocular. In monocular strabismus the involved eye is at risk for a disuse amblyopia, since the immature nervous system can suppress fixation in order to prevent diplopia. Paralytic or noncomitant strabismus is due to paresis of one or more extraocular muscles. It is worst on gaze into the field of the affected muscle and diplopia may be a symptom. Acquired paralytic strabismus raises concern for intracranial pathology. The one exception is the benign sixth-nerve palsy, which is sometimes seen in children in a parainfectious setting. This is, however, a diagnosis of exclusion. (Imaging should be performed to rule out intracranial pathology.) Congenital paralytic strabismus is usually caused by developmental defects of the extraocular system or birth trauma. Nonparalytic or commitant strabismus is the more common type. Extraocular muscles function normally and the defect is equal in all directions of gaze. Sometimes nonparalytic strabismus is due to underlying ocular or visual pathology; mostly it is idiopathic. Pseudostrabismus must be differentiated from true strabismus. The former is a reflection of certain anatomic variations like prominent epicanthal folds, a broad and flat nasal bridge, and hypertelorism.

Two simple tests can be used to identify strabismus. In the Hirschberg test the symmetry of the corneal reflex is

PEARLS & PERILS

- A position-oriented neurologic examination may be more useful in the preschooler than the classic systems-oriented examination.
- A Babinski reflex elicited from toe to heel avoids a false-negative result – the masking of a true Babinski sign by the grasp reflex, which is often still apparent in the toddler.
- Assessment for overflow movements can provide an index of neural maturation even in the preschooler, given the correct elicitation procedures. Excess overflow may be a marker of later learning disabilities.
- Gait and heel and toe walking are excellent sources of information about the neurologic status of the preschooler.
- Preschoolers often show dominance effects in both gross and fine motor skills. Beware of overcalling a left hemisyndrome.

documented. In the cover/uncover and cross/cover tests the eyes are observed for refixation movements. With the child fixing on a distant target, alternately covering the two eyes elicits no movement. With esotropia, the deviating eye will move outward as the fixating eye is occluded; with exotropia the deviating eye will move inward as the fixating eye is occluded. With a phoria the occluded eye tends to deviate, because binocular vision is temporarily disrupted, and refixation will be seen at the moment of uncovering.

Extraocular motility is then assessed. Congenital anomalies of the oculomotor system are often not brought to the attention of the physician until the preschool years. Distinguishing between congenital and acquired oculomotor problems has obvious therapeutic implications; old photographs are often very useful for this purpose.

Duane's retraction syndrome is of three types, all involving retraction of the globe and narrowing of the lid fissure on attempted adduction: (1) palsy of abduction with retraction on adduction, (2) palsy of adduction with retraction and intact abduction, and (3) palsy of adduction and abduction with retraction on attempted adduction. Occasionally the Duane's retraction syndrome is mistaken for an acquired sixth-nerve palsy; however, diplopia is rare with congenital palsies (Glaser 2000).

In Brown's tendon sheath syndrome, upgaze in the adducted position is restricted even during forced duction owing to the absence of the inferior oblique and thickening of the superior oblique tendon sheath. The deficit may be intermittent and even disappear during adulthood (Glaser, 2000).

A double elevator palsy has also been reported, involving both inferior oblique and superior rectus muscles. A homolateral ptosis is present but there is no diplopia and the pupil is spared. Preservation of Bell's phenomenon suggests that this is a supranuclear problem (Glaser 2000).

The Marcus Gunn jaw-winking phenomenon is a congenital trigeminal oculomotor synkinesis involving jaw and lid that is due to anomalous innervation. Generally the disorder presents in infancy as a (usually left) unilateral ptosis that jerks rhythmically upward during nursing. The jaw-winking phenomenon is an exaggeration of a normally existing reflex. The phenomenon often disappears over time.

Congenital fourth-nerve palsies are not uncommon and are often uncovered after minor head trauma. Review of old photographs will reveal the compensatory head tilt – head away from, chin toward the side of the paretic superior oblique muscle.

Examination of extraocular motility is concluded by assessment of the child's ability to converge. Accommodative esotropia tends to appear most commonly in the preschool years. This disorder is a reflection of excessive accommodation with over convergence.

The pupils should then be examined. Anisocoria, which may actually have been congenital, is sometimes not noted until the toddler years. In general, anisocoria in which the difference is maintained in different illuminations is not pathologic; however, anisocoria that increases or diminishes when the light changes should be considered pathologic. If the pupillary difference is more pronounced in bright light, it is the larger pupil that is abnormal; if the anisocoria is worse in dim light, it is the smaller pupil that is abnormal. In Horner's syndrome, seen for example with a brachial plexus palsy, anisocoria is more marked in dim light (which puts demands on the abnormal dilator mechanism) than in bright light (which puts demands on the intact constrictor mechanism) (Glaser 2000). If Horner's syndrome occurs before age 2, the iris is often hypopigmented.

The examination of the pupils is followed by an assessment of acuity and of the visual fields. Acuity can be measured in the toddler using a finger-mimicking game with alternating eye occlusion. The acuity is recorded as finger counting at X feet (20 feet equals 20/200, 40 feet equals 20/100) and is limited only by the distance that the examiner can stand from the child (Glaser 2000). Visual fields can be measured in the preschooler by finger mimicking of one, two, or five fingers flashed by the examiner. When fixation is a problem, the face may be turned so that the abducted eye can be moved no further toward the right or left (Glaser 2000).

Auditory acuity is then assessed with a ticking watch. The tongue and pharyngeal arches are inspected (cranial nerves IX–XII). Finally, the funduscopic examination is performed.

Mental status

Much information about the child's cognitive functioning can be gleaned from observation during the neurological examination. Attentional difficulties for example, are seen as an inability to stick with such tasks as motor stance or heel or toe walking. An impression about the child's general language skills can be gleaned from his or her contribution to the history and ability to follow verbal requests during the examination. However, a formal assessment of higher cortical function should nonetheless be attempted.

The assessment of higher cortical function in the preschooler is limited not only by the availability of appropriate measures, but by the cooperation of the child and the patience of the examiner. However, it is generally possible for the neurologist to get an impression of the child's functioning in the office and to obtain supporting and elaborating data from a psychometrician, neuropsychologist, and/or speech and language pathologist. In this chapter useful office measures for assessing the preschooler will be discussed.

Office measures

Historic

Although historic data are potentially biased by the parent/historian, the advantages in the preschool-age group

are temporal proximity and the cooperative nature of the informant.

The Anser system, developed by Levine (1996), includes parent and teacher questionnaires for the 3- to 5-year-old. Although it is biased toward behavioral issues, a useful medical and developmental history can also be obtained using the parent questionnaire.

The Denver Developmental Screening Test (DDST-II, Frankenburg & Dodds 1990) is a classic tool for assessing development in the personal–social, fine motor, language, and gross motor domains. By and large, except for the personal–social domain, assessment beyond 2 years requires the cooperation of the child. However, a prescreening developmental questionnaire filled out by the parent identifies over 80% of non-normal DDSTs (Frankenburg *et al.* 1987). An abnormal DDST predicts school problems at the end of the first grade with 84% accuracy (Sturner *et al.* 1985). However, the DDST is not as sensitive to speech and language problems as some specific language inventories (Glascoe *et al.* 1992) (see below).

The Early Screening Inventory (Meisels *et al*. 1997) for 3- to 6-year-old children and their parents and the Developmental Assessment of Young Children (Voress & Maddox 2003) are both new instruments that can be used in the office to perform a general developmental screen.

Language

Table 3.5 lists pertinent questions to ask the parents of preschoolers suspected of experiencing language delay (Schwartz & Murphy 1975). Tables 3.6 and 3.7 list anticipated 50th-percentile receptive and expressive language milestones from ages 1–5 years. Assessment of language functioning using these milestones provides a general idea of language level. Additional information can be gleaned from observations of communicative language use (pragmatics). Considering language in terms of its subcomponents of phonology, syntax, and semantics and evaluating prosody and pragmatics may provide the skilled clinician with enough information to make a subtype diagnosis from among the developmental language disorders (see Chapter 19). Rescorla and Achenbach (Rescorla & Achenbach 2002; Achenbach & Rescorla 2000) have recently developed and validated a brief screening checklist language inventory for 2-year-olds, which can be used to document the presence of an at least 50-word vocabulary and at least some two-word phrases. Coplan's (1987) Early Language Milestone Scale is useful through age 3 years. The clinical adaptive test/clinical linguistic auditory milestone scales (CAT/CLAMS), which can be administered in the office from ages 1–36 months, are both sensitive and specific to mental retardation and correlate well with Bayley scale scores of mental development (Capute & Accardo 1996; Hoon *et al*. 1993). To obtain a measure of receptive vocabulary skills that correlates with overall language status, the Peabody Picture Vocabulary Test (Dunn & Dunn 2001) can be administered from 2½ years on by secretary, nurse, or physician. The PEET and PEER (Levine & Schneider 1985; Blackman *et al*. 1986) have language subtests – including spatial directions, complex sentences, categories, temporal directions, word span, and rote language skills (e.g. counting, days) – that can be used in isolation or in conjunction with the whole exam for the 3- to 6-year-old. The Preschool Language Scale (Zimmerman *et*

TABLE 3.5

Pertinent Questions to Ask Parents of Preschool Children with Suspected Language Disorders

	Key questions	Likely parent responses
1	How old was your child when he began to speak his first words?	24 months or older
2	How old was your child when she began to put words into sentences?	36 months or older
3	Does your child have difficulty learning new vocabulary words?	Yes
4	Does your child omit words from sentences (e.g. do his sentences sound telegraphic)?	Yes
5	Does your child speak in short or incomplete sentences?	Yes
6	Does your child have trouble with verbs such as *is, am, are, was,* and *were*?	Yes
7	Does your child have difficulty following directions?	Yes
8	Does your child seem to have difficulty in understanding you if you use long sentences?	Yes
9	Does your child respond appropriately to questions?	No
10	Does you child ask questions beginning with *who, what, where,* and *why*?	No
11	Does your child use present and past tense verbs correctly?	No
12	Does it seem that your child has made little or no progress in speech and language in the last 6–12 months?	Yes
13	Does your child omit sounds from her words?	Yes
14	Do you feel your child's speech is more difficult to understand than it should be in view of his age?	Yes
15	Does it seem as though your child uses t, d, k, or g in place of most other consonants when she speaks?	Yes

From Schwartz A, Murphy M: Cues for screening language disorders in preschool children, *Pediatrics* 55:717–722, 1975.

TABLE 3.6

Receptive Language Skills

Years	Expected abilities of a child at this age
1	Understands "Where is mother?"
1½	Points to one body part
1½	Follows two-step commands two times out of three (*me spoon/mom ball*, *me ball/mom spoon*, *mom ball/cup me*)
2	Knows six body parts
2–2½	Understands concept of "one"
2½	Points to spoon, ball, cup by use
3	Recognizes day and night
3½	Knows three out of four prepositions (*on*, *under*, *in front*, *behind*)
4	Recognizes colors
4–4½	Understands concept of "three"
4½–5	Identifies right and left on self

TABLE 3.7

Expressive Language Skills

Years	Expected abilities of a child at this age
1	Knows two to four single words
18	Uses two-word sentences
2	Refers to self by name
2–2½	Uses plurals, *I*
2–2½	Converse in sentences
2½–3	Gives full name
3–3½	Comprehends *cold, tired, hungry*
3–3½	Can draw opposite analogies two times out of three (*fire/ice; mother/father; horse/mouse)*
4	Comprehends senses
4½–5	Defines words correctly six times out of nine (ball, lake, desk, house, banana, curtain, ceiling, hedge, pavement)

al. 2001) provides a more specific and extensive assessment of language, but also takes longer to administer.

Visual-spatial and motor

Tables 3.8 and 3.9 list anticipated 50th-percentile motor milestones from ages 1–5. Attention should be paid to crayon-holding posture. Egan (1990) describes several early grasps (Fig. 3.12): (i) supinate (pencil grasped at the distal end and often held vertically; present from 18 months but virtually gone by 36 months); (ii) pronate (pencil is grasped in the middle of its length with flexed fingers and thumb gone at 42 months): and (iii) tripod (pencil held near to the point with thumb, index and middle fingers functioning together). This grasp is used by 50% of children from 36 months onward. Eighty per cent of children have a tripod grasp at 48 months. The preschooler uses a rigid tripod – thumb opposed to index finger supported by middle finger, but without flexion extension of the interphalangeal joints, which becomes a dynamic tripod at age 6–7 years.

TABLE 3.8

Motor Milestones

Years	Expected abilities of a child at this age
1½	Walks up steps, throws overhand
2	Tricycles
2½	Balances on one leg for 1 second
3	Toe and heel walks
3½	Balances for 5 seconds
4	Hops, tandems
5	Hops 10 times
6	Tandems well

TABLE 3.9

Visuospatial and Visuomotor Milestones

Years	Typical abilities of a child at this age
1	Scribbles
2	Copies vertical line
2½	Copies circle
3½	Copies +, draws circle, Humpty-Dumpty
4½	Draws square, oblique lines, 6-part person
5–6	Draws triangle, 10-part person
6–7	Draws diamond

The Developmental Test of Visual Motor Integration (Beery & Buktenica 2003) can be administered in the office starting at age 2 years. Fig. 3.13 shows the particular drawings that should be copied by different ages. The PEET and PEER (Levine & Schneider 1985; Blackman *et al.* 1986) have visuomotor subtests including: visual matching, copying figures, and drawing from memory that can be used in isolation or in conjunction with the whole exam for ages 3–6 years. Having a child draw a person is a simple way to monitor development. Egan (1990) suggests that there are three main stages of development in drawing the human figure by the preschooler: (i) "Humpty-Dumpty" has a head and arms and legs are on the head; (ii) intermediate man, who has a head, no body, legs on head and arms at the right level on the legs. It is not clear that all children necessarily go through this intermediate stage, although some 25% do so; and (iii) mature man, with head, body and limbs on body (Fig. 3.14). Developmental delay should be suspected if a child of 42 months is not yet drawing at least a "Humpty-Dumpty" man, or a child of 54 months is still drawing a "Humpty-Dumpty" man. The Draw a Person Test (Goodenough & Harris 1963) can be used to generate a developmental quotient, as well as a projective about the child's emotional status (Jolles 1996). Drawings are scored for the presence of

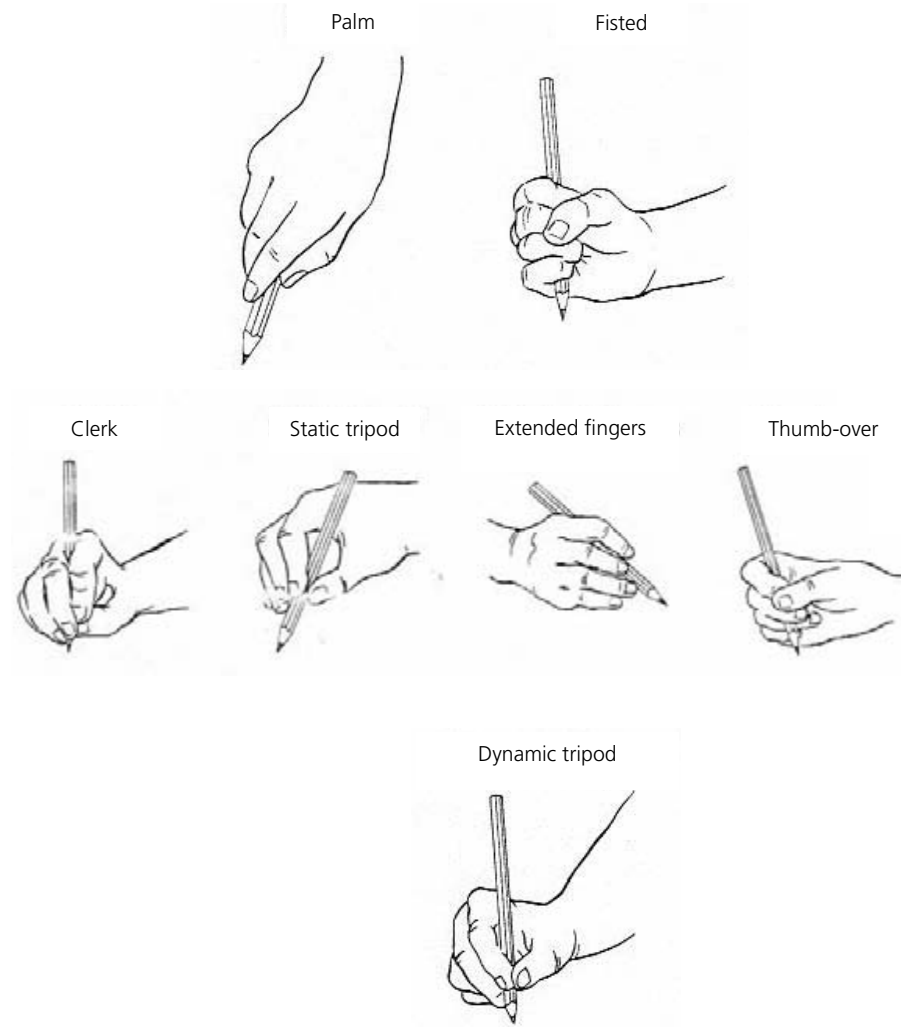


Fig. 3.12 Development of pencil grips: an ulnar/vertical is seen from 1½ to 3 years. A radial grip is acceptable until 3½ years. A static tripod is present in 50% of children by 3 years, and 80% by 4 years. Cleric, extended finger and thumb over-grips are seen in some children instead of a static tripod. Most children master the dynamic tripod grip by 5–6 years.

Age of acquisition	Form
2-10	|
3-0	—, O
4-1	+
4-4	/
4-6	□
4-7	\
4-11	X
5-3	Δ

Fig. 3.13 The age at which various shapes should be copied, as indicated in the Test of Visual-Motor Integration (Beery & Buktenica 1984) are shown here. (Modified from Beery KE, Buktenica N: *Developmental Test of Visual-Motor Integration*. Cleveland, 2003, Modern Curriculum.)

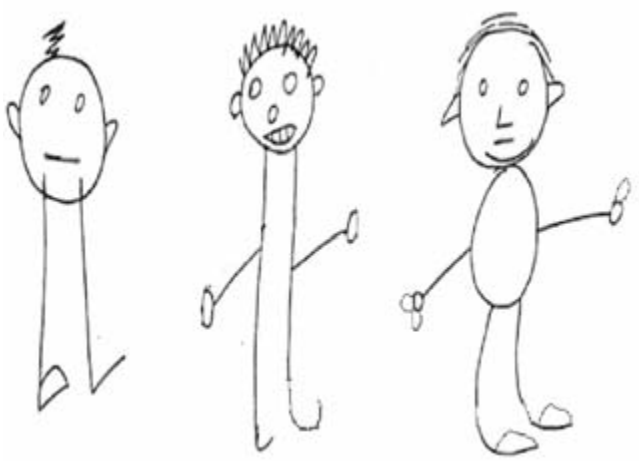


Fig. 3.14 Drawing of a person. *Left*, Humpty-Dumpty, drawn by 50% of children at age 3 years and 80% at 3½ years; *Center,* Intermediate form, drawn by 50% of children at age 4 years and 80% at age 4½ years; *Right,* Mature form, drawn by 50% of children at age 4½ years (modified from Egan D: Developmental examination of infants and preschool children, *Clinics of Developmental Medicine* 12:18, 1990.)

73 details. Raw scores are converted into standard scores distributed similarly to IQ scores. The number of body part details expected increases with age. Two parts are expected at age 3½, six parts at 4½, and ten parts at 5½ (Fig. 3.15).

Attention

Attentional deficits can be a problem in the preschool years (see Chapter 19) and are best assessed by observation and by history. Connor's questionnaire (1997) can be used, as can Levine's Anser questionnaires (1981), the Child Behavior Checklist (Achenbach & Rescorla 2002), the Preschool Behavior Questionnaire (Behar 1977), and the Early Childhood Inventory (Gadow & Sprafkin 2002).

Dominance

Finally, dominance should be assessed by demonstration: show me which hand you use for writing. A dominance battery (eye, hand, foot) filled out by the parents is a useful way of assessing for mixed dominance. In general, it is atypical for the eventual right-hander to declare strongly prior to age 1 year or to have failed to declare by age 5 years (Annett 1985). Left-handers tend to be more ambidextrous, so they declare later. Pathological left-handedness (a genetic right-hander who, perhaps because of perinatal injury to the left hemisphere, becomes a manifest left-hander) should be considered when the child is clearly left handed before age one. The increased frequency of left-handers among preterms may reflect this (Ross *et al.* 1987). Relatively little information is available about the right- versus left-hand skill of right-handers during the preschool years. Annett (1985) found a stable right-hand advantage on her peg-moving task from ages 3½ to 15 years. Berger-Gross *et al*. (1984) found

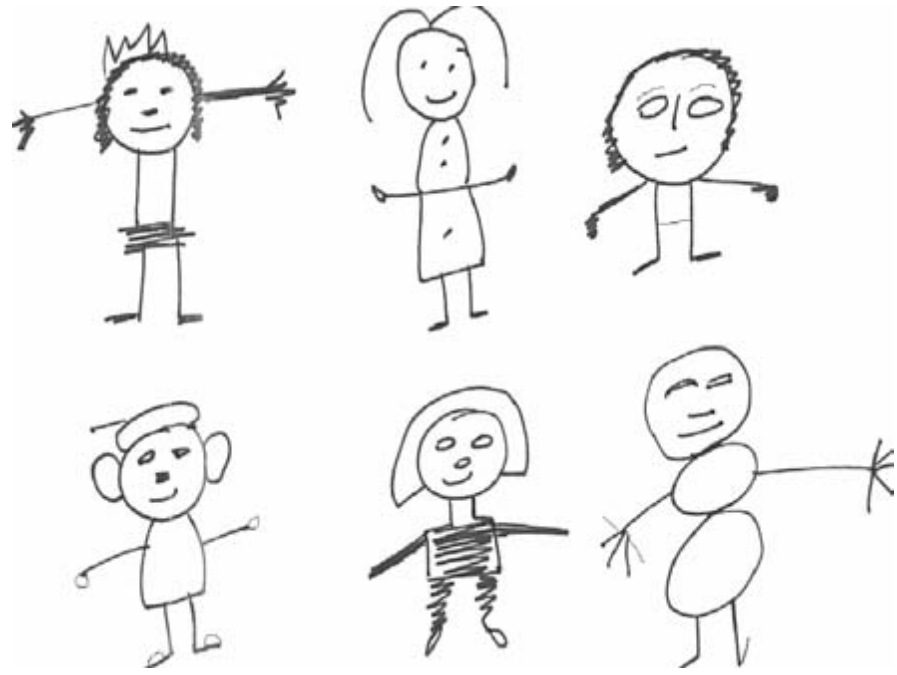


Fig. 3.15 Drawings of a person by 5-year-old children should contain at least 10 body parts.

a right-hand advantage on finger tapping and sequencing tasks paralleling the right-hand advantage to age 7 years found by Denckla (1973; 1974). Although left-handers are in general less strongly left-handed than right-handers are right-handed, the left hand of the young left-hander is the equal in terms of dexterous performance to the right hand of the young right-hander (Rudel *et al.* 1984).

Evaluation

Practice parameters have recently been put forward by several different groups with suggested workups of the young child with developmental delay (Committee on Children with Disabilities 2001; Filipek *et al*. 2000; Shevell *et al.* 2003).

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This is a comprehensive book on all aspects of dominance.

CONSIDER CONSULTATION WHEN...

- The exam shows unilateral soft signs.
- Testing shows a domain-specific deficit.
- Testing shows a learning disability, but there is no family history.

CHAPTER 4

The Neurologic Examination of the School-Age and Adolescent Child

Ruthmary K. Deuel, MD and Amy C. Rauchway, DO

OUTLINE

Items of the general physical examination
Appendix: school-age pediatric and neurologic examination scoring form

Virtually all items used in the neurologic examination of the adult may also be employed in the neurologic examination of the school-age child and adolescent. The items to be included must be chosen with care, commensurate with the information that is required from the examination.

Certain domains must always be evaluated in any neurologic examination. Thus, every neurologic examination should include an evaluation of the patient's mental status, cranial nerves, motor system, deep tendon reflexes, and responses to sensory stimulation. Depending on the presenting complaint and the general purposes of the examination, each of these domains may then be evaluated in greater or lesser detail. To aid in examination of developmentally delayed or anomalous children, specific variations of the neurologic exam may prove useful.

Rapport with the child is a major factor in ensuring an efficient neurologic examination. The examiner should bear in mind that the child's best effort on each item is more informative than grudging or partial performance. In general, a cheerful, positive attitude toward the child and a stubborn insistence on repeated efforts if the first response to a command is insufficient are rewarded by a better examination. Just as developmental norms are important for the neurologic examination at younger ages, they are important in the school-age child, particularly on the mental status and motor performance items. To obtain as much information as possible with the least amount of effort, it is good to use certain items in the neurologic examination to define more than one factor. For instance, response to commands and negative or positive reinforcement on the part of the examiner give considerable information about the child's compliance. Hand preference and fine motor performance are other aspects that are readily evaluated concomitantly with the ongoing examination. If the child is instructed to use "your fastest hand first" or "your strongest hand first" on unimanual motor items, a measure of hand preference will be obtained (Deuel & Moran 1980). The historic information gathered concerning the child's conduct should be supplemented by the physician's direct observations during the examination.

In the sections that follow, the individual items of the neurologic examination will not all be discussed in detail. An excellent standard text on the general subject is DeJong's *Neurologic Examination* (Haerer 1992). The chapter by Dodge and Volpe in Farmer's textbook *Pediatric Neurology* (1983) remains a detailed overview of the more specialized pediatric neurologic examination. A newer, very well referenced chapter is in Menkes and Sarnat: *Child Neurology Sixth Edition* (2000). The goal of conducting a neurologic examination in a school-age child is to arrive at the correct diagnosis. If one appropriately applies the formal examination to test hypotheses constructed from the chief complaint and history, and also observes the child's spontaneous actions and interactions, at the end of 30 or so minutes sufficient information should be available to make a positive diagnosis of localized or lateralized nervous system abnormalities. Mental retardation, specific learning disabilities, as well as attention deficit disorder, developmental language disorder, or developmental apraxia are equally identifiable. In addition, psychiatric disorders such as childhood depression, anxiety and conduct disorder may be positively identified by a versatile and thorough neurologic examination.

Items of the general physical examination

For a complete neurologic assessment, aspects of the general physical examination are pertinent and should always be evaluated. The number of the general examination items actually conducted is of course dependent on the question

that the examination is attempting to resolve. In infants and children, height, weight, and head circumference should always be accurately measured and plotted according to the percentile for chronologic age. For school-age children, the Nellhaus Composite International and Interracial Graph for head circumference is most accurate (Nellhaus 1968). Currently, there is controversy (Fessell *et al.* 2000; McIntyre 2003) about newer head circumference standards. Until resolution is obtained, reliance upon the older standard is recommended. Blood pressure and pulse rate are also part of the standard neurologic examination, as is evaluation of the head, eyes, ears, nose, throat, skin, skeleton, and thoracic and abdominal organs.

In observing the hair, texture and thickness are important. The skull should be palpated for bone defects and for unusual shape or contour, such as is seen in plagiocephaly or hydrocephalus. The facies should be described if any irregularities at all are observed. External examination of the eyes is important, including the anatomic structure of the lids, cornea, sclerae, conjunctivae, and iridies. Interpupillary distance should be recorded. Hypertelorism or hypotelorism is an important stigma of some chromosomal disorders (Pryor 1969). Excessive conjunctival vasculature is a subtle but important indicator of ataxia-telangiectasia (Taylor *et al.* 1975). The external examination of the ears likewise may yield information regarding branchial cleft and other less common anomalies. The otoscopic examination is best carried out after first testing for tympanic movement. A full examination of the mouth, lips, palate, and tongue structures is valuable. In general, facial and other dysmorphisms may be an indicator of specific acquired or genetic conditions. A detailed catalogue with developmental norms is *Handbook of Normal Physical Measurements* (Hall *et al*. 1995). An oral exam pertinent to speech mechanisms and articulation should be carried out in any child with speech or language delay (Spriesterbach *et al.* 1978). Dentition may give a clue to skeletal abnormalities. In certain syndromes, abnormal dentition is the rule (Beumer *et al.* 1973). Evaluation of the thyroid gland should be carried out by palpation and auscultation of the gland. The thorax should be examined, the heart and lungs auscultated, and pulses in the neck examined with auscultation of the head and neck after it is ascertained that the cardiac rhythm is regular and there are no intrinsic cardiac auscultatory findings. The radial, carotid, and femoral pulses also should be palpated. It is important to palpate the abdomen for enlarged organs. The genitalia should also be examined with a view to Tanner staging (Tanner 1962). This is particularly important in suspected sex chromosome aneuploidies (Waber 1979; Pennington *et al.* 1980; Ratcliffe 1982; Scriver *et al.* 2000). The spinal column should be examined with the patient prone, standing, and bending over to evaluate scoliosis and lordosis. The sacral region should be particularly carefully observed for dimples or bony defects, particularly if any lower extremity difficulties have been noted. Skin changes overlying the spine, such as hemangioma or hair tufts, are of importance because they may herald underlying bony and neural tube defects. Shagreen patches of tuberous sclerosis are also found in this location (Berg 1985). The extremities should be carefully evaluated for structural abnormalities that may yield the clue to various heritable syndromes, such as homocysteinuria, the mucopolysaccharidoses, and pseudohypoparathyroidism (Schimke 1965; Grossman & Dorst 1973; Scriver 2000).

During all phases of the history and examination, it is convenient to note whether the patient remains attentive to the examination, cooperative with commands, and responsive to positive and negative reinforcement. Because the physical examination is primary, we have called this latter group of assessments concomitant observations (see the Appendix). It is usually easy to find at least two or three opportunities to use positive reinforcement. For example, when the child opens his mouth, one can say, "That's good" or when she relaxes her abdominal muscles, one can respond with, "You're doing a good job at that. Would you keep it up?" Of course there are usually also opportunities for negative reinforcement, for example, "Don't breathe so fast" or "Don't put your shirt on yet." It is likewise valuable to consider the quality and quantity of the subject's distractibility. Observe the results of external interruptions (for example, comments from parents, knocks at the door) to determine if they distract the child from following instructions for the formal exam. Does the child become distracted without any obvious external stimuli? Finally, as a concomitant observation, is the child impulsive, interrupting the examination with sudden self-initiated actions or talk? Structured conscious rating of these responses is valuable and necessary to the evaluation of the cognitive, attentional, and motivational abilities of the child.

KEY CLINICAL QUESTIONS

A 9-year-old girl is brought by her family because of sudden onset, yesterday, of a "twisted" smile and an inability to close her right eye, without history of antecedent infection, trauma or toxic exposure. On exam you find no general physical abnormalities, and on thorough neurological exam only mild decrease in right 7th nerve functions, including taste discrimination, eye closure, lacrimation, and facial expression. You find no hyper- or hypoacusis. What is the most likely cause of the isolated 7th nerve paralysis you have defined? What should be done to protect the eye?

Comment: Most likely the child has idiopathic facial palsy (IFP), or Bells palsy. Use of an eye lubricant and a "pirate patch" are needed for corneal protection. Certain factors, such as severity of paralysis (if severe, minimal excitability of the facial nerve allows an estimate of residual nerve function if done soon after onset) or endemic Lyme disease should influence the intensity of your pursuit of underlying and treatment-demanding etiologies.

It is thus an integral part of the mental status examination. Although further testing may certainly be required to refine behavioral and cognitive observations, the directed pediatric and neurologic examination combination should suffice for initial detection and categorization of pervasive developmental, cognitive, attentional, motivational, and conduct disorders, as well as more specific entities such as cerebral palsy, Fragile X, and childhood migraine.

Children with deviant communication styles are usually sent to a physician for at least one diagnostic evaluation. Such children, however, present a major challenge to any physician's examining expertise. Careful initial consideration of the child's interactions with parents and objects in the room before paying overt attention to the child should direct the physician's approach to the hands-on examination. For example, nonverbal cues may be the operative ones for this particular child. In order to break the ice, the child may be handed a fascinating toy appropriate to his or her estimated cognitive level. Then very obviously attention is directed back to the adult historian while the child's reaction to the move, and interaction with the toy are covertly monitored. Does the child make some kind of attempt to retrieve the examiner's attention? If so, some valuable information has been gained about social abilities and communication style that is not available through quantitative testing. Is the child interacting appropriately with the toy? Is the child also attending to the examiner's interactions with the historian? Of course, carrying on an interview with a historian and at the same time observing the child may tax the physician's own attentional capacities, but it will be rewarded by observational material that is informative in and of itself, as well as affording a chance to plan strategy for completion of the fundoscopic examination and other items of the basic neurologic examination.

The neurologic examination

The neurologic examination is actually a series of functional tests aimed at determining whether different segments and subsystems within the nervous system are normal. Some of the functions assessed will vary, depending on the chief complaint of the patient. Thus, the "standard" neurologic examination is designed to answer pertinent questions regarding sensory motor, and higher cortical functions.

The subject of the examination cannot be passive during most tests but must comply and attempt to carry out commands. For example, any detailed sensory examination is impossible without good patient compliance. In children, the order of the neurologic examination items should be dictated by common sense and the need to maintain good compliance. It is more important to assess all the necessary items than to follow some set rule for their presentation. At the beginning of the examination of the school-age child, it is often useful to introduce yourself by asking some of the conversational items in the mental status exam. For example, an assessment of orientation is often a good opener. This allows an evaluation of the child's knowledge of where he or she is, who the doctor is, the day of the week, and, for older children, the date and year. Other items that can be used are the names of the child's school and school teacher. For junior-highschool-age children, the address and zip code of the child's school is a good item, as is the question about presidents of the United States.

Handedness may also be identified conversationally by inquiring about several everyday activities (Bryden 1977) (and later checking the responses with performance during pantomime on command and use of actual objects – Appendix items N115-N148) (Provins & Cunliffe 1972), such as "What hand do you use when you cut with a pair of scissors?," "What hand do you use when you eat with a fork?" The patient should be asked to identify his or her right hand and then given a three-part command using left and right items (for example, "Close your eyes and put your left thumb on your right ear").

If the chief complaint is failure or poor performance in school, the mental status examination should definitely include grade- and age-appropriate testing of school skills: letter identification or reading, copying shapes, and writing spontaneously as well as to dictation and copying. The writing should be evaluated for speed and the output for legibility. The child should be asked to count or work arithmetic problems, including word problems, as grade-appropriate. He or she should be asked to draw a picture of a person.

KEY CLINICAL QUESTIONS

A 14-year-old H.S. freshman reports excellent health and school grades since you saw him last 3 years ago, but gradually increasing difficulty in walking. General physical exam is normal with no change in growth parameters. On neurological exam, the mental status, cranial nerves, and complete sensory exam are also normal, as is the upper extremity motor exam. Power in all muscles of both legs is excellent, but gait testing reveals slow progression with intoeing and no heel-strike. Reflexes at the knees and ankles are 4+, and there is ankle clonus bilaterally, with bilateral upgoing toes. What descriptive diagnosis will you give the condition? What causes will you investigate? Irrespective of cause what therapies could be helpful to ambulation?

Comment: On the basis of your exam findings of spasticity in both lower extremities, the child has a progressive spastic paraparesis. There are multiple etiologies, most common of which is familial spastic paraplegia (FSP). Physical therapy is most helpful in prolonging ambulation in this slowly progressive degenerative disease.

Some of these tasks may be incorporated into an informal assessment of attention and memory: hand the child a clean sheet of unlined paper and a sharpened pencil with an eraser. Seat the child comfortably at a good writing surface. Tell the child to (1) write his or her full name, (2) draw a picture of a person, and (3) write a sample. The sample should be of the child's own composition, and the examiner should specify a grade-appropriate task (the alphabet, a word, a few words, a sentence, paragraph, or short essay on the subject of the child's choice). Have the child repeat the commands. When they have been repeated correctly, ask the child to carry out the tasks and (4) inform you when they are complete. This constitutes a complex developmentally appropriate four-part command that assesses attention and memory.

Then, out of the corner of the eye, while ostensibly discussing historic information with the parent, the examiner should observe several facets of the patient's performance: (1) how the hands are used, (2) how attentive the child is to the task, and (3) how rapidly or painstakingly the task is accomplished. To present a distractor, the examiner may ask the parent a question about a subject that is emotionally charged for the child. Several types of information may be derived from this exercise. First, if the child successfully follows the complex four-part command without interrupting the adult conversation, one has an estimate of his or her memory span, attention focus span, and compliance. If in addition to completing the assigned task, he or she has been monitoring the adult conversation, and interjecting comments about it, the examiner can be assured the child has adequate capacity (to be distinguished from actual everyday performance) to refocus attention on a task after having shifted attention to distractors. Second, the examiner can judge the age-appropriateness of the writing and drawing samples and note any major discrepancies in this factor between the two types of graphic production. The picture the child produces may be scored using the Goodenough criteria (Taylor 1959; Gunn 2002). The spontaneous writing sample may be judged for grade-appropriate configuration, spelling, and punctuation. Such screening allows the physician direct observational insight that may then be supplemented by formal individual psychometric and school achievement tests performed at a school or other facility.

The direct, first-hand testing of school skills by the neurologic examiner affords that examiner an opportunity to detect uneven development of different cognitive abilities. This portion of the examination should thus help evaluate the validity of any formal cognitive testing that may have been performed. More importantly, it may point up areas where more detailed and quantitative testing should be requested. Without direct examination of the cognitive aspects of the child's development, the neurologic examination will not be helpful in solving diagnostic dilemmas concerning attention, specific learning and language disorders. This is particularly relevant to the child with a pervasive attention or conduct disorder secondary to an underlying cognitive deficit. It is much less important in the evaluation of other common problems, such as seizures or neuropathy, in which case these added cognitive elements of the exam may be minimized.

KEY CLINICAL QUESTIONS

A 6-year-old boy is brought by his newly adopting parents because of his problems with kindergarten schoolwork. Birth, family, and developmental history are sketchy, but recent health has been fine. His pediatric exam shows macrocephaly, a long face, large protuberant ears, frequent inattention to commands, distractibility, and poor articulatory skills. On neurological exam, he is eager and interactive, but cannot explain where he is, cannot draw a triangle nor print his name. Otherwise he has only mild diffuse hypotonia. Given the history limitations, are you able to consider any diagnoses at this point? What further evaluations will you recommend?

Comment: The combined exam findings, namely large ears, long face, big head, moderate cognitive and language problems, attention difficulties, and mild hypotonia are in themselves suggestive of Fragile X, or other genetic syndromes. Given the unknown history (injury, abuse?) and large head (acquired?) a brain imaging study may be helpful. Psychometric, and speech and language evaluations should be planned, and possibly a stimulant trial.

Examination of the cranial nerves includes evaluation of the important special senses, vision, and hearing. It is usually unnecessary to test smell. However, if there is a question of frontal lobe or anterior fossa pathology, this examination should be performed. The use of commercially available tests allows one to present familiar fruit smells (orange and banana are most easily recognized by school-children) to each nostril. Confrontation visual fields are usually easily undertaken with one eye covered with a 3 × 5 index card in the 10-year-old and over. The optimal object is a small white-headed pin; The tester should sight on the subject's pupil and use her own visual field as a measure of the subject's visual field, placing the pin equidistant between the tester and the subject. With this technique, the blind spot that confirms accurate field mapping can usually be found in the alert cooperative school child (Traquiar 1949; Thompson 1979). In younger or less able children, fingers may be presented spontaneously to both fields or to one for at least a gross estimate of field integrity. In any child who will fixate, optokinetic nystagmus can be used to estimate responses to visual stimuli (Haerer 1992). Optokinetic testing should definitely be performed when there is a question of cortical blindness in a child of any age (Brindley 1969). Visual acuity can be tested using a standard Snellen chart at 6 m, in first graders or older

children.[1] Visual acuity testing should be performed with and without glasses. Eye position should be noted without glasses. A cover test – consisting of having the patient fixate with both eyes forward, then covering one eye and seeing if the position of the remaining uncovered eye changes – may be used if there is a question concerning extraocular muscle abnormality (Cogan 1956, Chapter 10). Versions of the eyes in conjugate following should also be tested. Pupillary symmetry and reactions to direct stimulation with light, and to light in the opposite eye, should be noted, as should nystagmus. Spontaneous and reactive nystagmus may have various connotations, depending on the type and direction of the movements (Cogan 1956, Chapter 5).

Funduscopy should be carried out so that both disks, both maculae, and the peripheral retina of each eye can be visualized. A short-acting pupillary dilator may be invaluable in achieving this end. If, for any reason, a satisfactory view of the fundi cannot be obtained and appears necessary for diagnosis, referral to a pediatric ophthalmologist is recommended. Jaw movements should be assessed. The symmetry of both the upper and the lower face should be evaluated. To test hearing crudely, finger rustling or whispering in the right and left ear with the other ear occluded is a reasonable test of conversation level. Deafness is still often undetected (Coplen 1987); losses in selected frequencies particularly may go unnoticed as a cause of "inattention," as are central auditory processing deficits. Taste is sometimes tested, and children older than age 4 usually readily respond to salt/sugar taste in the anterior two thirds for the seventh nerve or the posterior third for the ninth nerve of the tongue. Palate elevation must be tested, both voluntarily and as part of the gag reflex. The sternocleidomastoid muscle is tested by having the child turn the face away from the side of the muscle tested. Tilting the chin up toward the ear will make the contracting sternocleidomastoid more prominent for palpation. Shrugging of the shoulders also allows testing of the eleventh nerve. Tongue protrusion and lateral movements are evaluated to test the twelfth nerve. Repeated syllables such as PA-TA-KA (Spriesterbach *et al.* 1978) allow for evaluation of orobuccal agility. Obviously, it may be necessary to carry out further, more refined and quantitative tests of visual and auditory sensation, such as the measurement of visual evoked potentials or brainstem auditory evoked potentials (BAEP). It is well to bear in mind that measurement of BAEP to clicks (composed of multiple frequencies) is not designed for testing hearing thresholds.

Introducing the motor examination with gait testing allows the youngster a chance to stretch. Running should be tested with at least a 6-meter leeway; a hall is useful for this test. Children 6 years old or older should be able to skip or able to learn from a demonstration.[2] Tandem walking should be tested to evaluate lower extremity coordination. The Fog maneuver may be used, which requires the child to walk on the insides or the outside of the soles (Fog & Fog 1963). This is useful in determining whether there are adventitious movements in the face and hands during this "stress" gait (see items N93 and N94 in the Appendix). Toe and heel gait are also helpful to test active strength in the lower extremity muscle groups. The pronator drift test should be performed with the child standing, the arms extended, the palms up. The child should be asked to hold the posture for 20 seconds. To evaluate for chorea, the child should stand unsupported for 20 seconds with eyes closed, arms extended and hands pronated with wrists extended and fingers abducted and extended (Barlow 1974). Resistive strength testing of the upper and lower extremities may be carried out in standard

PEARLS & PERILS

Neurologic Examination of the School-Age Child

- There is no such thing as the standard neurologic examination. Rather, there are an infinite variety of neurologic examinations, the items of which depend heavily on the individual performing them and the hypotheses being tested. Even with a standard protocol, as in the Collaborative Perinatal Project, different neurologic examiners will ascertain somewhat different incidences of disorders (Nichols & Chen 1981).
- Mild degrees of hemiparesis may be markedly accentuated by the Fog maneuver that may elicit marked asymmetries of the upper extremities and assumption of a hemiparetic posture by the arm on the affected side (see items N93 and N94).
- Aneuplodies and their associated physical features are often accompanied by distinctive neuropsychologic profiles called "behavioral phenotypes" (Cassidy 2002). An example is Turner's syndrome with abnormal spatial understanding and motor skills, but normal verbal skills (Money 1993).
- Williams's syndrome and its associated physical features are also accompanied by a distinctive neuropsychologic profile, including a fluent receptive language disorder and clumsiness (Bellugi 2000).
- The nondominant hand is often more accurate in stereognosis discrimination than the dominant one (Witelson 1978).
- Most standardized psychometric tests – for example, the WISC-III (Wechsler 1991), Stanford-Binet (Thorndike *et al.* 1986), and Slosson (1998) – depend heavily on verbal instructions. They cannot therefore differentiate between general decreased intellectual powers and a more specific cognitive deficit as the underlying cause of pervasive, nonspecific symptom complexes such as "attention deficit disorder" or "conduct disorder."

[1] In first graders or older children, a Rosenbaum pack vision or screener may be used.

[2] Skipping requires a step on one foot, next a hop, landing on the first foot, then a step on the second foot, followed by a hop, landing on the second foot. If a child has no prior experience with skipping, he or she should be able to learn from one demonstration trial.

fashion in children 6 years old and older. For screening purposes, shoulder girdle, distal extremity, and hip girdle strength should be tested. Stair climbing or stepping up to the seat of a chair is an excellent test for hip girdle strength. If a musculoskeletal or neuromuscular disorder is suspected, more thorough testing of each muscle group should be carried out, with grading of muscle strength from 0 to 5. Of course, evaluation of sitting posture should be made during this portion of the exam.

Cerebellar coordination of the upper extremities is best tested with the finger-to-nose test. The elbow should come to full extension and the wrist to full pronation before the child's finger is allowed to touch the examiner's finger. It is best to require three positions – center, 30° to the left, and 30° to the right – with each hand, and to require two trials in each position for each hand. To evaluate coordination more proximally in the upper extremities, several tests are used. With all of them, observation of body parts not involved in the demanded action may yield information about synkinesis, particularly mirror movements. Resting tremor, intention tremor, titubation of the trunk or head, and other involuntary adventitious movements may also become apparent. To test wrist turning, alternating taps of the palm, and the dorsum of the hand on the knee should be done as rapidly as possible, or the child may be given an object, such as a reflex hammer, to turn back and forth in a regular rhythmic fashion. The child may also be asked to pretend to screw a light bulb into a ceiling fixture. Movements are normally in rhythmic alternating fashion. With cerebellar disorders, however, they frequently assume an extremely erratic, nonrepetitive pattern. The heel–shin knee–ankle maneuver further tests coordination of the lower extremities.

To assess isolated finger movements as a measure of pyramidal tract function, a finger-tapping task is often used, and has the advantage of standardization as to rate expected at different ages and for both sexes (Denckla 1973; Holden 1982). During such unimanual distal movements, it is valuable to have the other hand held in the air without support. One may then note whether associated mirror movements occur when the hand that is designated to be active is in fact carrying out the required action. Associated movements mirroring a variety of actions may occur in the hand not voluntarily engaged. Thus it is well to observe for them during the entire examination. Foot tapping can be done in the time-for-20 format described by Denckla (1974) and compared with standards. Hopping in place on either foot should be possible for any child older than 5 years of age.

Testing for developmental apraxia and clumsiness, a source of school and home failure that cannot be determined from paper and pencil tests, is very important in any child with school or attention difficulties. The tapping test just discussed is excellent to define clumsiness and accompanying adventitious movements but does not suffice to demonstrate apraxia. Apraxia (or dyspraxia) may be defined as the inability to carry out age-appropriate voluntary motor sequences in the absence of a primary motor or sensory deficit (David 1981). It is only determined by direct testing during the neurologic examination. Copying hand postures (using for instance the Luria Fist Test), pantomiming acts (pouring milk into a glass), and using actual objects (putting a flashlight together and turning it on) are the three types of performance that should be covered in any complete examination for apraxia (Damasio *et al.* 1985). A standard manual apraxia battery is incorporated in the neurologic protocol in the Appendix (items N115–N148) (Deuel & Doar 1990) and more fully discussed in Chapter 18.

Upper extremity reflexes should be tested with the arms relaxed and in a symmetric position. Relaxation can sometimes be accomplished by asking complex questions of the patient as the respective tendons are tapped or by reinforcement maneuvers. The Hoffman sign, otherwise called the "Babinski of the upper extremity," should be attempted with a flick of the index fingernail. Examination of reflexes in the lower extremities may be performed with the patient sitting and the legs in a symmetric dependent position, which is also advantageous for eliciting clonus. However, the deep tendon reflexes and clonus may also be checked in the supine position.

Sensation may be tested in 6- to 12-year-old children in the same manner as in adults. For a screening examination, light touch and position sense or light touch and vibration sense may be adequate. If there is any question of a spinal lesion, then examination of responses to thermal and pinprick stimuli becomes mandatory. Even in school-age children, it is wise to introduce the pin carefully before starting the examination, in which the entire dermatomal distribution should be tested, including the lower sacral segments. Stereognosis can be readily evaluated in this age group by using small common objects such as clips, safety pins, keys, and coins. Graphesthesia (writing on the skin) may be evaluated. Normative data for graphesthesia of a relatively psychometric quality is given in the Halsted–Reitan battery (Reitan 1969; Russell *et al.* 1970, Chapter 2), although the testing routine they recommend is lengthy. Bilateral simultaneous somatosensory stimulation with fingers on the face, the hands, and the legs should be part of every screening examination. Finally, autonomic responses, vasomotor responses, and sweating should be noted.

In conclusion, the neurologic examination is a versatile diagnostic instrument. Using it, one should detect localizing and lateralizing signs of nervous system abnormalities, and determine reliably the maturational level of cognitive, emotional, and motor capacities as well as physical growth and development. Supplemented by a careful comprehensive history, the examination frequently yields all the basic information necessary to make a full diagnosis, not only of neurologic disease but also of neuropsychiatric and developmental disorders of higher cerebral function. To analyze

quantitatively specific hearing and visual loss problems ascertained by the neurologic evaluation, or to evaluate nerve and muscle functions further, or to quantitatively characterize developmental language disorders, dyslexia, dysgraphia, and dyscalculia, standardized tests are usually helpful.

Appendix: school-age pediatric and neurologic examination scoring form

This scoring form is useful as a reminder about the types of subtests entailed in an extensive physical and neurologic examination. Of course, as the neurologic examination is an "à la carte" rather than a "table d'hôte" menu, individual items other than those catalogued here may be substituted, and some listed items may be omitted. The suggested scoring is meant to facilitate entry into a database. If an item is normal, the first box is checked. If an item is clearly abnormal, an 8 is circled; if it is not tested or indeterminate, a 9 is circled. Extra boxes are provided for concomitant observations on adventitious movements (see item P13), observed hand preference (first choice, see item N99; or hand used, see item N135), and quantitation (time in seconds, see item N101). For the dyspraxia items (N115–N149) there are three subscales, for use of actual objects (Object), imitation of nonsense gestures (Imitate), and pantomime (Pantomime). Of course, every time an abnormality is checked on the binary format, notes about its severity and quality should be made as usual. Note: This form may be reproduced for clinical use without further permission from the author or publisher.

Preschool and School-Age Pediatric and Neurologic Examination Scoring Form

Items with an asterisk are inappropriate for the preschooler; items preceded with PRE are alternate versions for the preschooler.

S Subject Identification

S1 Name _____ _____ _____
Last *First* *Middle*

S2 Birthdate _____ _____ _____
Month *Day* *Year*

S3 Age at examination _____

S4 Gender _____

S5 Handedness by subject report _____
R–L–A

a Fork (R–L)
b Scissors (R–L)
c Other hand better at anything else? (Y–N)

E Examiner Identification

E1 Examiner _____ _____ _____
Last *First* *Middle*

E2 Title _____

E3 Place _____ _____
Institution *Room Number*

E4 Date
Month *Day* *Year*

E5 Time education started (0–24 months; 24–60 months _____

P Pediatric Examination

P1 Weight _____ (kg) Percentile _____
P2 Height _____ (cm) Percentile _____
P3 OFC _____ (cm) Percentile _____
P4 Blood pressure (right arm) _____ (S)/ _____(D)
P5 Head shape and contour
☐ 8 9
P6 Hair
☐ 8 9
P7 Facies
☐ 8 9
P8 Eyes – structure (external exam):
palpebral fissures, lids, cornea, sclera, conjunctiva, iris, pupils
☐ 8 9
P9 Ears – size, shape, position
☐ 8 9
P10 Ears – otoscopic exam
☐ 8 9
P11 Nose: obstruction, mouth breathing
☐ 8 9
P12 Lips – structure
Upper lip length
Lips when meet in occlusion
☐ 8 9

P13 Lips – function
Protrude (whistling position)
Retract ("Show me your teeth.")
☐ 8 9 AM ☐

P14 Tongue – structure
Size in relation to dental arch
Fissures
Frenulum length
☐ 8 9

P15 Tongue – function: curl up and down
☐ 8 9 AM ☐

P16 Tongue – function: Say "tsk tsk tsk tsk."
☐ 8 9

P17 Hard palate: arch, width, integrity
☐ 8 9

P18 Velopharnygeal part: soft palate and uvula structure
☐ 8 9

P19 Dentition (include missing teeth in comments)
☐ 8 9

P20 Articulator function: Say "Pa–Ta–Ka."
☐ 8 9
Time in seconds _____
PRE: Say "Pa–Pa–Pa, Ta–Ta–Ta, Ka–Ka–Ka."

P21 Thyroid
☐ 8 9

P22 Thoracic wall
☐ 8 9

P23 Lungs
☐ 8 9

P24 Heart size
☐ 8 9

P25 Heart sounds
☐ 8 9

P26 Heart rhythm
☐ 8 9

P27 Heart rate
☐ 8 9

P28 Radial, femoral, and carotid pulses, bilaterally
☐ 8 9

P29 Abdominal wall
☐ 8 9

P30 Abdominal organs palpable
☐ 8 9

P31 Abdominal masses
☐ 8 9

P32 Genitalia
☐ 8 9

P33 Tanner stage – pubic hair
☐ 8 9
Stage number in Arabic _____

P34 Tanner stage – breasts or penis
☐ 8 9

P35 Lymph nodes
☐ 8 9

P36 Skin vascular nevi
☐ 8 9

P37 Skin – pigmented or depigmented nevi
☐ 8 9

P38 Skin – scars, eczema, vitigilous cyanosis
☐ 8 9

P39 Spine – dimples, sinus, scoliosis, lordosis
☐ 8 9

P40 Extremities – anatomy
☐ 8 9

P41 Cooperation
☐ 8 9

P42 Responsiveness to positive or negative reinforcement
☐ 8 9

P43 Attention to commands
☐ 8 9

P44 Attention shifts to external stimuli
☐ 8 9

P45 Attention shifts or lapses without obvious external stimuli
☐ 8 9

P46 Perseveration of attention in face of new command
☐ 8 9

P47 Impulsiveness – sudden self-initiated talk or action
☐ 8 9

P48 Impression of pediatric examination
☐ 8 9

Neurologic Examination

N1 Alert – oriented (person and place)
☐ 8 9

N2 Comprehends (numbers of fingers, age)
☐ 8 9

***N3** Subject right hand identification ("Show me your right hand")
☐ 8 9

***N4** Subject left hand identification ("Show me your left hand")
☐ 8 9

***N5** One-part command ("Make a fist with your left hand")
☐ 8 9

***N6** Two-part command ("Cover your left eye with your right hand.")
☐ 8 9

***N7** Three-part command ("Put your left thumb on your right ear and stick out your tongue")
☐ 8 9

***N8** Examiner left hand identification ("Point to my left hand")
☐ 8 9

N9 Finger identification – eyes open
☐ 8 9

N10 Finger identification – eyes closed
☐ 8 9

(*Continued*)

N11 Confrontation fields – right eye covered by card
☐ 8 9

N12 Confrontation fields – left eye covered
☐ 8 9

N13 Confrontation fields–bilateral simultaneous stimulation, upper and lower quadrants
☐ 8 9

N14 Visual acuity – right eye without glasses to Snellen chart at 20 ft
☐ 8 9

N15 Visual acuity – right eye with glasses to Snellen chart at 20 ft
☐ 8 9

N16 Visual acuity – left eye without glasses to Snellen chart at 20 ft
☐ 8 9

N17 Visual acuity – left eye with glasses to Snellen chart at 20 ft
☐ 8 9

N18 Visual acuity – binocular vision to near card without glasses
☐ 8 9

N19 Visual acuity – binocular vision to near card with glasses
☐ 8 9

N20 Position of eyes in forward fixation (4 ft) without glasses
☐ 8 9

N21 Cover test right eye (if *glasses*, use)
☐ 8 9

N22 Cover test left eye (if *glasses*, use)
☐ 8 9

N23 Extraocular muscles (right eye)
☐ 8 9
Extraocular muscles (left eye)
☐ 8 9

N24 Conjugate gaze – follow
☐ 8 9

N25 Conjugate gaze – command
☐ 8 9

N26 Pupils – symmetry
☐ 8 9

N27 Pupil
Right eye react to direct light
Left eye consensual
☐ 8 9

N28 Left eye react to direct light
Right eye consensual
☐ 8 9

N29 Conjugate gaze – converge
☐ 8 9

N30 Pupils – accommodation
☐ 8 9

N31 Nystagamus
☐ 8 9

O N32 Funduscopy – right eye macula
☐ 8 9

O N33 Funduscopy – right eye disk
☐ 8 9

O N34 Funduscopy – right eye retina
☐ 8 9

O N35 Funduscopy – left eye macula
☐ 8 9

O N36 Funduscopy – left eye disk
☐ 8 9

O N37 Funduscopy – left eye retina
☐ 8 9

N38 Facial sensation (cotton swab) – right V
☐ 8 9

N39 Facial sensation (cotton swab) – left V
☐ 8 9

N40 Jaw open, close – right V
Versus resistance
☐ 8 9

N41 Jaw open, close – left V
Versus resistance
☐ 8 9

***N42** Jaw move left and right
☐ 8 9

N43 Jaw jerk
☐ 8 9

N44 Upper facial symmetry – VII
☐ 8 9

N45 Lower facial symmetry – VII
☐ 8 9

N46 "Open your eyes wide"
☐ 8 9

N47 Finger rustle, right ear – VIII
☐ 8 9

N48 Finger rustle, left ear – VIII
☐ 8 9

N49 Palate elevation – IX, X (voluntary)
☐ 8 9

N50 Gag reflex – right IX, X
☐ 8 9

N51 Gag reflex – left IX, X
☐ 8 9

N52 Sternocleidomastoid – right XI
☐ 8 9

N53 Sternocleidomastoid – left XI
☐ 8 9

N54 Tongue protrusion – XII
☐ 8 9

N55 Tongue (left and right) lateral movements – XII
☐ 8 9

N56 Neck and trunk musculoskeletal anatomy (scoliosis, torticollis)
☐ 8 9

N57 Shoulder girdle musculoskeletal anatomy A
☐ 8 9

N58 Pelvic girdle musculoskeletal anatomy A
☐ 8 9

N59 Sitting posture
☐ 8 9

N60 Muscle power neck flexion
☐ 0–5 8 9

N61 Muscle power neck extension
☐ 0–5 8 9

N62 Muscle power, deltoid – right
☐ 0–5 8 9

N63 Muscle power, deltoid – left
☐ 0–5 8 9

N64 Muscle power, biceps – right
☐ 0–5 8 9

N65 Muscle power, biceps – left
☐ 0–5 8 9

N66 Muscle power, wrist dorsi – right
☐ 0–5 8 9

N67 Muscle power, wrist dorsi – left
☐ 0–5 8 9

N68 Muscle power, finger extension – right
☐ 0–5 8 9

N69 Muscle power, finger extension – left
☐ 0–5 8 9

N70 Muscle power, finger abduction – right
☐ 0–5 8 9

N71 Muscle power, finger abduction – left
☐ 0–5 8 9

N72 Muscle power, thumb–five oppose – right
☐ 0–5 8 9

N73 Muscle power, thumb–five oppose – left
☐ 0–5 8 9

N74 Muscle power, hip flexion – right
☐ 0–5 8 9

N75 Muscle power, hip flexion – left
☐ 0–5 8 9

N76 Muscle power, hip abduction – right
☐ 0–5 8 9

N77 Muscle power, hip abduction – left
☐ 0–5 8 9

N78 Muscle power, leg flexion – right
☐ 0–5 8 9

N79 Muscle power, leg flexion – left
☐ 0–5 8 9

N80 Muscle power, foot dorsiflexion – right
☐ 0–5 8 9

N81 Muscle power, foot dorsiflexion – left
☐ 0–5 8 9

N82 Muscle power, great toe dorsiflexion – right
☐ 0–5 8 9

N83 Muscle power, great toe dorsiflexion–left
☐ 0–5 8 9

N84 Muscle tone, upper extremeties
☐ 0–5 8 9

N85 Muscle tone, lower extremeties
☐ 0–5 8 9

N86 Gait (running in hall: 20 ft away, 20 ft toward)– speed, foot placement
☐ 0–5 8 9

N87 Gait (running in hall: 20 ft away, 20 ft toward) hand and arm movement
☐ 0–5 8 9

N88 Gait (walking in hall: 20 ft away, 20 ft toward) – foot placement posture
☐ 0–5 8 9

N89 Gait (walking in hall: 20 ft away, 20 ft toward) – hand and arm movement
☐ 0–5 8 9

***N90** Skip eight places in hall on command
☐ 8 9

N91 Tandem ten paces – coordination (balance, foot placement)
☐ 8 9

N92 Tandem ten paces – adventitious movements (hand, arm, and face movement)
☐ 8 9

***N93** Fog gait – feet inverted, five paces (adventitious hand, arm, and face movement)
☐ 8 9

***N94** Fog gait – feet everted, five paces (adventitious hand, arm, and face movement)
☐ 8 9

N95 Toe gait, five paces
☐ 8 9 AM ☐

N96 Heel gait, five paces
☐ 8 9 AM ☐

N97 Pronator drift (standing unsupported 20 seconds, eyes closed, arms extended, palms up)
☐ 8 9

N98 Choreaform twitch (standing unsupported 20 seconds, eyes closed, arms exteneded, fingers extended and abducted, palms down)
☐ 8 9

N99 Coordination (eyes open, standing unsupported) Subject finger to examiner finger to subject nose right hand
2 × 3 positions: left, center, right, arm full extension
☐ 8 9 First choice _____

N100 Coordination (eyes open, standing unsupported) Subject finger to examiner finger to subject nose – left hand
2 × 3 positions: left, center, right, arm full extension
☐ 8 9 First choice _____

N101 Coordination (sitting, alternating wrist supination, pronation): time for 20 – right (reflex hammer in cross–palm grasp in tested hand, both arms adducted to waist, flexed at elbows)
☐ 8 9 First choice _____

N102 Coordination (sitting, alternating wrist supination, pronation): time for 20 – left (reflex hammer in cross–palm grasp in tested hand, both arms adducted to waist, flexed at elbows)
☐ 8 9 First choice _____
AM ☐ Time in seconds _____

(*Continued*)

N103 Coordination (supination and pronation of wrist): time for 20 – right
☐ 8 9 First choice _____
AM ☐ Time in seconds _____

N104 Coordination (supination and pronation of wrist): time for 20 – left
☐ 8 9 First choice _____
AM ☐ Time in seconds _____

N105 Finger tap on thumb, time for 20 – right (Denckla instructions)
☐ 8 9 First choice _____
AM ☐ Time in seconds _____

N106 Finger tap on thumb, time for 20 – left (Denckla instructions)
☐ 8 9 First choice _____
AM ☐ Time in seconds _____

N107 Finger on successive fingers – left (Denckla instructions)
☐ 8 9 First choice _____
AM ☐ Time in seconds _____

N108 Thumb on successive fingers – left (Denckla instructions)
☐ 8 9 First choice _____
AM ☐ Time in seconds

N109 Hop in place, five times – left
☐ 8 9 First choice _____

N110 Hop in place, five times – left
☐ 8 9 First choice _____

N111 Foot tap – right (Denckla instructions)
☐ 8 9 First choice _____
AM ☐ Time in seconds _____

N112 Foot tap – left (Denckla instructions)
☐ 8 9 First choice _____
AM ☐ Time in seconds _____

N113 Heel–shin, knee–ankle – right (subject lying down)
☐ 8 9

N114 Heel–shin, knee–ankle – left (subject lying down)
☐ 8 9

N115 Object – hand throw, Nerf ball, 3 ft – right
☐ 8 9 First choice _____

N116 Object – hand throw, Nerf ball, 3 ft – left
☐ 8 9 First choice _____

N117 Object – one-foot kick, Nerf ball, 3 ft – right
☐ 8 9 First choice _____

N118 Object – one-foot kick, Nerf ball, 3 ft – left
☐ 8 9 First choice _____

N119 Object – "Erase this E"
☐ 8 9 Hand _____

N120 Object – Wind the watch three times
☐ 8 9
Hand that winds

N121 Imitate – two hands open, palms toward subject
☐ 8 9
PRE: Imitate – left, then right, hand up, fingers spread

N122 Imitate – left hand open, palm toward subject, right hand fisted
☐ 8 9

N123 Imitate – thumbs touch and index fingers touch (diamond shape)
☐ 8 9

N124 Imitate – thumb touching index finger of other hand, palms toward subject
☐ 8 9

N125 Imitate – thumbs and index fingers form interlocking circles
☐ 8 9

N126 Imitate – right hand fisted, palm toward subject, with index and little fingers raised. Expect non-mirror response (child must use his or her right hand)
☐ 8 9

N127 Imitate – begin in N113 position and climb up five times ("itsy-bitsy-spider")
☐ 8 9

N128 Imitate – Luria's fist test, one time quickly, right hand only) "Watch me. I'm going to show you what to do. I will do it only one time so look closely")
1 Fist down on lap
2 Hand open, hit radial border of hand on lap
3 Fisted hand again, palm side up in lap
☐ 8 9

N129 Imitate – Luria's fist test, one time quickly, left hand only) "Watch me. I'm going to show you what to do. I will do it only one time so look closely.")
1 Fist down on lap
2 Hand open, hit radial border of hand on lap
3 Fisted hand again, palm side up in lap
☐ 8 9

N130 Pantomime – "If this is a birthday cake show me how to blow out the candles"
☐ 8 9

N131 Pantomime – "Now, this is a knife, show me how you would cut a piece of the cake"
☐ 8 9
Hand (if single hand used) _____

O N132 Pantomime – "Show me how you light a match"
☐ 8 9
Hand that strikes _____

O N133 Pantomime – "Stand up and show me how you swing a baseball bat."
☐ 8 9
Hand on top _____

N134 Pantomime – "Here is a book. Show me how you turn the pages"
☐ 8 9
Hand that turns _____

N135 Pantomime – "If this is a comb, show me how you would use it to comb your hair"
☐ 8 9
Hand used _____

N136 Pantomime – "Show me how you pour milk into a glass"
☐ 8 9
Hand that pours _____

N137 Pantomime – "Show me how you would brush your teeth with a toothbrush"
☐ 8 9
Hand holding toothbrush _____

N138 Pantomime – "Show me how you would open a locked door with a key"
☐ 8 9
Hand holding key _____

N139 Object – Draw a square (8½ × 11 clean white paper, normal finish, #2 sharp pencil)
☐ 8 9 hand _____

N140 Object – Draw a triangle (8½ × 11 clean white paper, normal finish, #2 sharp pencil)
☐ 8 9 hand _____

N141 Object – Draw a rectangle (8½ × 11 clean white paper, normal finish, #2 sharp pencil)
☐ 8 9 hand _____
Pre: Object – draw a circle

N142 Object – Please draw a clock with an hour hand and a minute hand" (8½ × 11 clean white paper, normal finish, #2 sharp pencil)
☐ 8 9 hand _____

N143 Copy the box
☐ 8 9 hand _____

N144 Object – Hand preference ("Write your first and last names")
☐ 8 9
Hand for pencil _____
PRE: "Write your first name"

N145 Object – "Now write it with the other hand."
☐ 8 9

N146 Object – "Fold the paper neatly so it fits and put it into the envelope"
☐ 8 9
Hand that puts paper in _____

N147 Object – "Put the batteries into the flashlight and turn it on."
☐ 8 9
Hand that exerts torque _____

N148 Object – "Roll up the paper and then use it like a telescope to look at the doorknob"
☐ 8 9 Eye _____

N149 Object – "Roll up the paper and then use it like a telescope to look at something in a different direction than the doorknob"
☐ 8 9 Eye _____

N150 Romberg position, eyes open
☐ 8 9

N151 Romberg position, eyes closed
☐ 8 9

N152 Tremor, action – right hand
☐ 8 9

N153 Tremor, action – left hand
☐ 8 9

N154 Tremor, rest – right hand
☐ 8 9

N155 Tremor, rest – left hand
☐ 8 9

N156 Tremor, intention – right hand
☐ 8 9

N157 Tremor, intention – left hand
☐ 8 9

N158 Titubation
☐ 8 9

N159 Reflex, biceps – right
☐ 8 9

N160 Reflex, biceps – left
☐ 8 9

N161 Reflex, triceps – right
☐ 8 9

N162 Reflex, triceps – left
☐ 8 9

N163 Reflex, knee – right
☐ 8 9

N164 Reflex, knee – left
☐ 8 9

N165 Reflex, ankle – right
☐ 8 9

N166 Reflex, ankle – left
☐ 8 9

N167 Reflex, clonus, sustained (six+ beats) – right ankle
☐ 8 9

N168 Reflex, clonus, sustained (six+ beats) – left ankle
☐ 8 9

N169 Reflex, plantar – right
☐ 8 9

N170 Reflex, plantar – left
☐ 8 9

N171 Sensation (touch recognition), C4 – right (cotton swab, eyes closed)
☐ 8 9

N172 Sensation (touch recognition), C4 – left (cotton swab, eyes closed)
☐ 8 9

N173 Sensation (touch recognition), C7 – right (cotton swab, eyes closed)
☐ 8 9

N174 Sensation (touch recognition), C7 – left (cotton swab, eyes closed)
☐ 8 9

N175 Sensation (touch recognition), TI – right (cotton swab, eyes closed)
☐ 8 9

N176 Sensation (touch recognition), TI – left (cotton swab, eyes closed)
☐ 8 9

(*Continued*)

N177 Sensation (touch recognition), L2 – right (cotton swab, eyes closed)
☐ 8 9

N178 Sensation (touch recognition), L2 – left (cotton swab, eyes closed)
☐ 8 9

N179 Sensation (touch recognition), L4 – right (cotton swab, eyes closed)
☐ 8 9

N180 Sensation (touch recognition), L4 – left (cotton swab, eyes closed)
☐ 8 9

N181 Sensation (touch recognition), S1 – right (cotton swab, eyes closed)
☐ 8 9

N182 Sensation (touch recognition), S1 – left (cotton swab, eyes closed)
☐ 8 9

N183 Sensation, position, right great toe (five trials)
☐ 8 9

N184 Sensation, right index finger
☐ 8 9

N185 Sensation, position, left great toe (five trials)
☐ 8 9

N186, Sensation, left index finger
☐ 8 9

N187 Sensation, location of fingertip in space – right
☐ 8 9

N188 Sensation, location of fingertip in space – left
☐ 8 9

N189 Sensation, stereognosis (fine) – right (six trials)
☐ 8 9
PRE: Use four matching block shapes

N190 Sensation, stereognosis (fine) – left (six trials)
☐ 8 9
PRE: Use four matching block shapes.

N191 Sensation graphesthesia (fingertip writing) – right
☐ 8 9
PRE: Pick from drawn square, circle, cross

N192 Sensation, graphesthesia (fingertip writing) – left
☐ 8 9
PRE: Pick from drawn square, circle, cross

N193 Autonomic – vasomotor
☐ 8 9

N194 Autonomic – sweating
☐ 8 9

N195 Time examination ended (0–24:0–60)

I Impression

I1 Neurologic impression
☐ 8 9

I2 Mental status – mood and affect throughout pediatric and neurologic exams
☐ 8 9

I3 Estimated intellectual status
☐ 8 9

Preschool and School–age Pediatric and Neurologic Examination Scoring Form from David RB: *Pediatric neurology for the clinician*, Norwalk, CT. 1992, Appleton & Lange.

Annotated bibliography

Dodge PR, Volpe JJ: Neurologic history and examination. In: Farmer TW, editor: Pediatric neurology, 3rd edn. Philadelphia, 1983, Harper & Row, pp 1–41.
This chapter is very succinctly written and very well illustrated. In addition, it explains how to take a good history and provides excellent advice on how to engage the patient's interest and cooperation that is as pertinent today as it was 20 years ago. The chapter contains good detail concerning examination of the cranial nerves and gives various "tricks of the trade" for eliciting valid sensory responses from immature subjects.

Slosson R: Slosson intelligence test (SIT) for children and adults-Revised (SIT-R). East Aurora, NY, 1998, Slossen Educational Publications, Inc.
The Slosson is a quick-screening IQ test that, with proper precautions against testing artifacts, can be very useful to the neurologic examiner. However, like all screening tests, particularly if it provides an abnormal estimate, it should be checked by the more reliable (and complex, requiring a person fully trained in its administration) WISC-III or Stanford-Binet-4th Ed. All three of these "IQ measures" rely primarily upon the linguistic abilities of the child, and still different tests of cognitive abilities may be necessary in the language disabled child.

Spriesterbach D, Morris HL, Darley FL: Examination of the speech mechanisms. In: Darley FL, Spriesterbach D, editors: Diagnostic methods in speech pathology, 2nd edn. New York, 1978, Harper & Row, pp 215–231.
This chapter describes methods of examining speech mechanisms that are practical and often not covered by the medical school physical examination course. Examination of the speech mechanism is highly important in any school-age child suspected of having a language disorder but is often omitted for lack of familiarity with the proper method.

Wechsler D: Wechsler intelligence scale for children, 3rd edn. San Antonio, TX, 1991, Psychological Corp.
The W1SC-III is an individually administered, well-standardized test that breaks down cognitive function into "verbal" and "performance" scales. Although these scales (and the individual subtests that compose them) are useful, it is important to bear in mind that the WlSC-III (as well as most other standard individual IQ tests) exclusively uses verbal communication for instruction and communication with the child. Thus, a child with a language disorder will likely have a depressed performance as well as verbal score. Recourse to nonverbal instruments may then be in order.

Roid G, Miller L. Leiter: International performance scale – revised. Wood Dale, IL, 1996, Stoelting Company.

This test requires a highly trained psychometrician. It was specifically designed to be a nonverbal test of "IQ". As such the language medium is almost irrelevant (although the gestural idioms of the culture from which the tested child comes are important). Thus it is a much better reflection of cognitive ability in most language disabled children. However, the child with severe visual-spatial disabilities will not do well on the LIPS-R.

CHAPTER 5

Neurodiagnostic Laboratory Procedures

The Electroencephalogram

Warren T. Blume, MD, FRCP(C)

OUTLINE

The normal electroencephalogram
Electroencephalography and epilepsy
Certain central nervous system disorders

The normal electroencephalogram

To read the electroencephalogram (EEG) of a child or adolescent properly, one must be aware of several aspects that distinguish it from that of an adult. Many of its features are age dependent, and a brief review of these follows. Maturational and state factors create a wider variety of waveforms than are usually found among adults; such multiple waveforms may become superimposed to create sharply contoured waves that can be mistaken for spikes. Infants and young children often fall asleep during the recording, and the consequent EEG changes are more marked than those found in older age groups. These factors of maturation and state create wider fluctuations of EEG readings among normal children, a factor which commonly leads to overinterpretation of the recording. Finally, interhemispheric asymmetries of normal features occur commonly in youth, including alpha activity, mu rhythm, and the so-called "posterior slow of youth."

The sometimes bewildering array of components can be simplified by asking five questions for each state of alertness in determining whether a recording is normal:

1. In what state of alertness is the child?
2. Is the background activity appropriate for age?
3. Are there any asymmetries, beyond those normally accepted for certain waveforms, which cannot be ascribed to artifact?
4. Are there any definite spikes?
5. Is there any focal or diffuse excessive delta activity?

Maturation milestones

Wakefulness

The first discernable background frequency is 3–4 Hz, which appears at age 3 months. This frequency increases to about 5 Hz at age 5 months, to 6–7 Hz at 12 months, and to 7– 8 Hz at 2 years and by 6 years stabilizes at about a 9 Hz rhythm (Fig. 5.1). The mean frequency at 15 years is about 10 Hz. Alpha amplitude varies from 30 to 100 μV in the first year of life; it may increase to a maximum at 6–9 years and then decline. Gentle passive eye closure by the technologist may elicit background frequencies not otherwise apparent. An asymmetry of alpha is commonly seen in pediatric EEGs; it is usually higher right, but a higher left-sided amplitude is not clearly an abnormality. Asymmetries of amplitude are more accepted than asymmetries of frequency, and a left-to-right frequency difference exceeding 1 Hz usually indicates an abnormality on the slower side.

The rhythmic background activity in youth is commonly interrupted by 250- to 500-msec posterior waves occurring singly or repeating at 2–4 Hz. Their amplitude is equal to or slightly greater than that of the background rhythms (Fig. 5.2). Combination of such waveforms with alpha creates sharply contoured, spike-like deflections in the occipital regions, which are not as sharp as occipital spikes. Such posterior slow activity blocks with eye opening and generally waxes and wanes with alpha. The quantity and amplitude of such activity gradually increases in the first decade of life, reaching an apex in early adolescence. As with

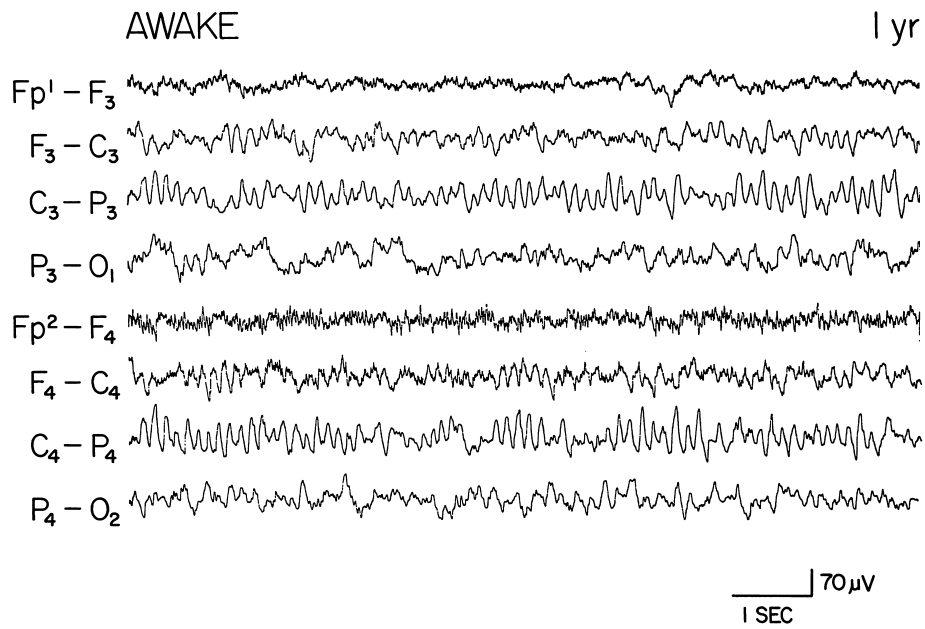

Fig. 5.1 Rich mixture of waveforms in alert infant. This tracing is dominated by 7- to 8-Hz central-parietal activity, but 1- to 2-Hz diffuse activity is also evident. The slightly greater quantity of delta on one side (left) is insignificant at this age. None of the apiculate waves is a spike. Normal recording.

the background activity, the abundance of such "posterior slow of youth" can be considerably greater in the right hemisphere as compared to the left. Such activity can be rhythmic at about 3–4 Hz and may appear in prolonged runs. In addition to an intermittent and rhythmic form, a halving of the alpha frequency occurs on occasion in children, usually with drowsiness. All such potentials occur only with the eyes closed.

In contrast, lambda waves may be particularly prominent as primarily electropositive, sharply contoured waves seen over the occipital head regions with the eyes open and particularly during scanning eye movements. Asymmetry of lambda waves is not an abnormality.

Theta (4–7 Hz) activity is present in varying amounts in the EEGs of children. Its quantity relative to other waveforms increases considerably in the first years of life, reaches a peak at age 5–6 years, and then declines somewhat thereafter. Therefore, with the eyes closed or open, theta is the dominant diffuse activity in recordings in the 2- to 5-year age group. With eyes closed, its quantity equals that of alpha activity at age 5–6 years, after which alpha becomes the more prominent. As with adults, theta activity tends to predominate over the left hemisphere at most ages. It would be very difficult to interpret a pediatric recording as containing excess theta activity, given its normal predominance.

Delta (1–3 Hz) and theta are approximately equal in quantity during the first year of life. Although the absolute quantity of delta increases during the first year and continues to do so to the fifth year, proportionally, it declines in relation to theta. However, low-voltage delta persists into adolescence in steadily declining quantities. Delta is never normally accentuated in drowsiness.

Persistent background activity develops earlier in the central (rolandic) head regions than in any other area. A 6- to 7-Hz rhythm may appear before 3 months of age and its frequency gradually increases to 8–10 Hz after 3 months. In the 1- to 5-year-old age group, the most prominent awake activity with eyes open resides in the central region (Fig. 5.1). Asymmetries of such activity appear commonly and usually shift back and forth between hemispheres. A persistent central rhythm asymmetry usually suggests an abnormality on the lower side unless there is some defect in the skull. As such central rhythms combine with other rhythms a sharply contoured appearance may result; this factor should be taken into account when identifying any central morphology as a spike.

The main purpose of hyperventilation in children's recordings is to elicit spike-wave discharges if they are not present during the resting recording. Regional spikes or excess slow waves are less commonly revealed in children than in adults. The accentuation of 2- to 3-Hz waves with hyperventilation is usually more marked in children than in adults, particularly around ages 10–12 years. Their location is often initially posterior in the early phases of hyperventilation, before becoming anterior.

Drowsiness

Because the EEG signs of drowsiness commonly appear before the child appears drowsy, the associated slowing of background rhythms may be misinterpreted as abnormal. Sinusoidal theta is the most common drowsy pattern in children from ages 3 months to about 5 years. Its frequency is 3–5 Hz in the first year of life, increasing gradually to 4–6 Hz by age 4 years. Its amplitude declines thereafter. From ages

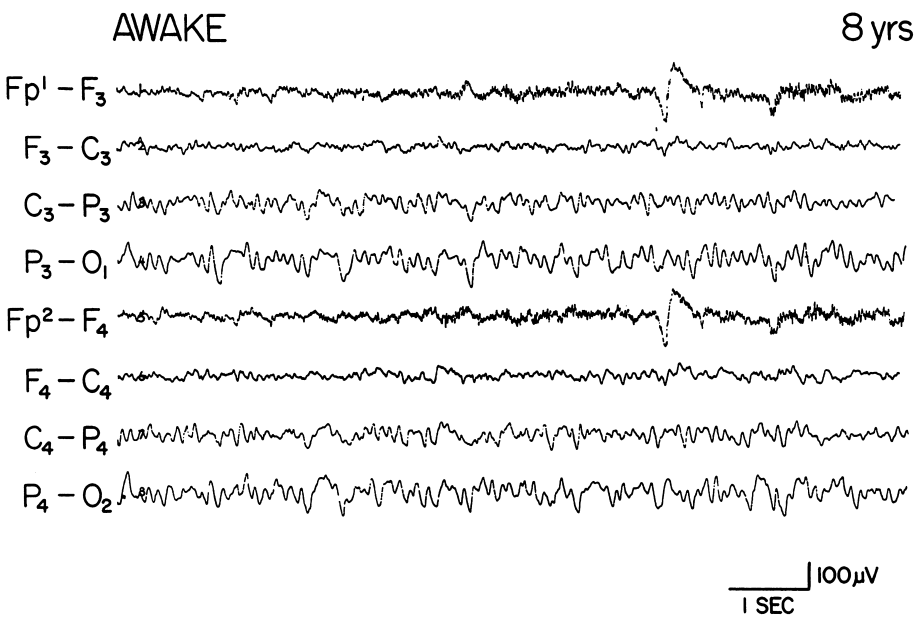

Fig. 5.2 Electropositive occipital waves of 200–250 msec separate the sharply contoured alpha to constitute the "posterior slow of youth," which can normally be abundant, as in this example.

6–16 years, rhythmic 5- to 7-Hz waves, maximum anteriorly, can accompany drowsiness.

Prominent generalized bisynchronous bursts of 2- to 5-Hz rhythmic activity occasionally attaining 350 μV or more can be seen over the frontal and central regions in drowsiness from age 14 months to about 10 years (Fig. 5.3). They are most common at ages 3–5 years. Such bursts are commonly mistaken for abnormalities. If sharply contoured background waves are intermingled, the composite can be falsely identified as spike waves.

Beta activity at 20–25 Hz becomes more prominent in drowsiness and light sleep and may be distributed diffusely with a maximum anteriorly. Alpha activity classically disappears in moderate drowsiness, but the aforementioned phenomena may appear before alpha wanes. In some children, the transition from wakefulness to sleep resembles an adult pattern, without the previously mentioned features.

Sleep

Rudimentary vertex (V) waves appear in light sleep as early as 3–4 months of age and become well developed by age 5 months. They achieve maximum expression as high-voltage sharply contoured monophasic or diphasic electronegative or electropositive waves at age 3–4 years and may be mistaken for rolandic spikes (Fig. 5.4). On bipolar montages, their amplitude may appear asymmetrical, but such asymmetries should shift from side to side. When in doubt, use a referential montage to assess the symmetries of such V waves.

Spindles appear first at age 3–4 months and are almost invariably present during ages 3–9 months if adequate quantity and different levels of sleep are attained. Occasionally, a child of this age may descend too rapidly to very deep sleep and omit the spindle phase. Spindles may shift in prominence from side to side, but the overall quantity should be approximately equal in the two hemispheres. Spindles are often at a maximum in the central and parietal regions in youth. After infancy, almost all recorded sleep is non-REM. Therefore, the features previously discussed describe this phase.

Delta activity (1–3 Hz) is invariably present in non-REM sleep. In children it should be accentuated posteriorly, a feature best illustrated by a bipolar anteroposterior montage or an ipsilateral ear reference. Such posterior delta activity may be sharply contoured.

Arousal

In infants younger than 2 months of age, arousal consists of a decrease in the voltage of ongoing activity. At age 3 months,

PEARLS & PERILS

The Normal Electroencephalogram

- Maturation criteria must be considered when reading a child's EEG.
- The modifications of the EEG with drowsiness are considerably greater for children than for adults, and such modifications vary with age.
- When assessing the frequency of background activity, make sure the child is not drowsy, as this will slow the rate.
- The rich mixture of normal activity in EEGs of children creates sharply contoured waves. Only those apiculate waves which contrast clearly with ongoing activity can be identified as spikes.
- A wide variety of normal findings exists in children's EEGs. Therefore, great caution should be exerted before stating that a mild abnormality exists.

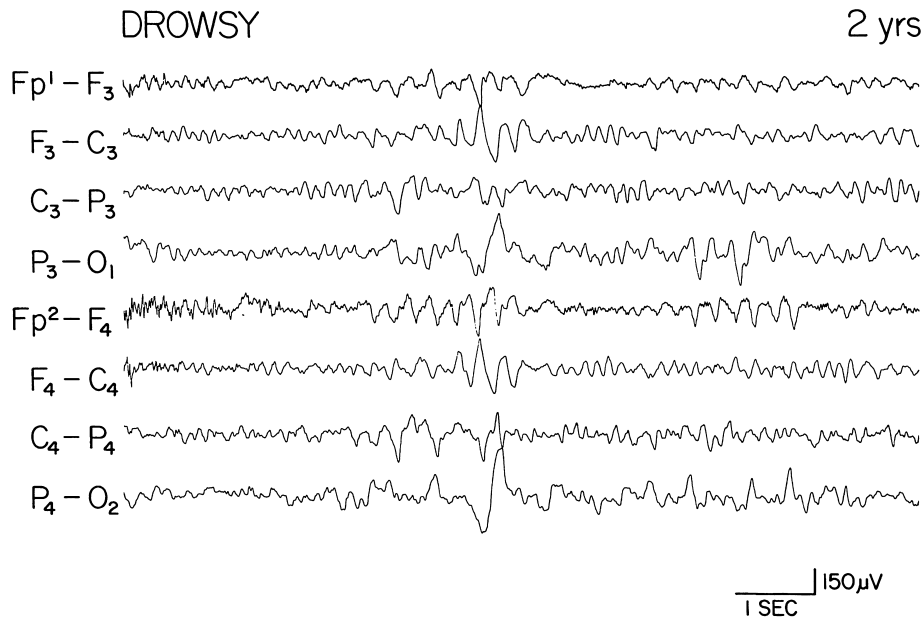

Fig. 5.3 Bursts of theta and delta in drowsiness, a normal phenomenon in childhood.

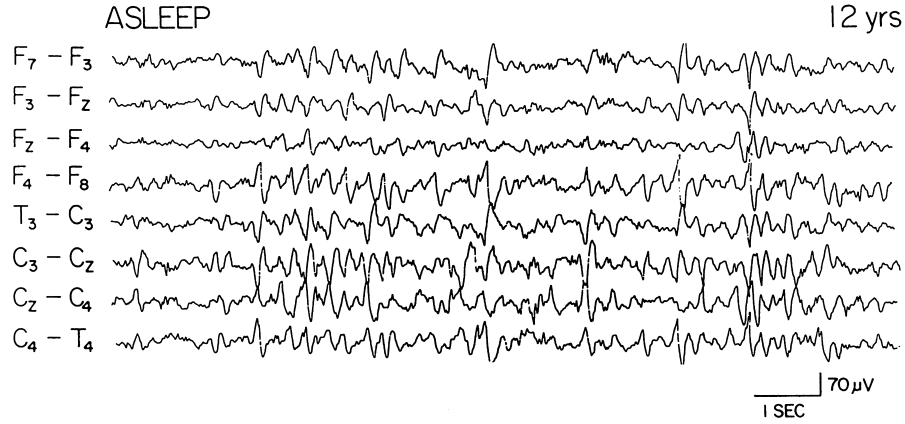

Fig. 5.4 Very apiculate V waves of varying morphology may appear in sequences, particularly in youth. Note their central-frontal (Cz–Fz) maxima.

a diphasic slow wave may occur in response to an afferent stimulus. This phenomenon, initially resembling a V wave, becomes better developed by 5 months, when it merges with a series of delta waves. If further arousal occurs, 4- to 8-Hz rhythmic theta lasting 1–5 seconds or more may appear in children age 7 months to 4 years. With continuing arousal, this theta is followed (paradoxically) by 1- to 3-Hz diffuse delta; this appears first at age 2–3 months, is maximally expressed at ages 12–18 months, and declines after age 5 years.

Electroencephalography and epilepsy

With access to a vast array of laboratory tests, the physician can easily forget that epilepsy is, and always will be, a clinical diagnosis – a differential diagnosis based on a painstaking history and physical examination. In many instances, these two effective, safe, and relatively inexpensive diagnostic procedures leave no unsolved questions. At other times, they will focus the attention on several questions to be addressed by the EEG, thus maximizing its clinical value: Is there a seizure disorder? Is it focal or generalized? If it is focal, is it unifocal (where?) or multifocal? How severe is the seizure disorder?

To answer such questions with confidence, a recording of high technical quality is required. It must be interpreted by a physician knowledgeable in pediatric electroencephalography.

Interictal electroencephalography

It is unusual for a patient to have an epileptic seizure in front of the physician, and a clinical seizure occurs only rarely in routine electroencephalography, with the occasional exception of absence attacks with 3-second spike waves. Therefore, interictal abnormalities, particularly spikes, are

in practice the chief correlate of the epileptic condition that can help answer the questions posed earlier.

A reasonable correlation between epileptiform activity in the resting EEG and seizure disorders exists in children. Of 242 children with spike foci, 82% were found to have epilepsy (Trojaborg 1968), whereas in another study epileptiform activity was found in only 1.9% of the 743 normal children (Eeg-Olofsson *et al.* 1971). Spikes occur in about 30% of children after a first seizure (Shinnar *et al.* 1994). Such discharges appear on an initial EEG in 50% (Carpay *et al.* 1997) to 76% (Yoshinaga *et al.* 2001) of children and adolescents with epilepsy. This incidence range likely reflects varying proportions of syndromes included in their studies. The Carpay study found that two EEGs will disclose spikes in ~ 66% of cases if sleep is included. Ninety-two per cent of the Yoshinaga study patients demonstrated spikes at some point over three EEGs. Younger children will more likely have spikes but spike specificity for epilepsy at this age may be lower (Pedley *et al.* 2003). However, two cautionary notes should be added. The first concerns the normal sharply contoured waves that appear ubiquitously in the recordings of children. In addition, several types of epileptiform waves, which can properly be called spikes, do not correlate with epileptic conditions (see Klass and Westmoreland 1985, for a review). These include small sharp spikes, 14-second and 6-second positive spikes, wicket spikes, 6-second spike-waves, and rhythmic midtemporal discharges. Definitions and descriptions of these phenomena are found in that article and in most electroencephalographic textbooks and atlases.

Generalized epileptiform abnormalities

Generalized spike-waves

The most classic of all EEG-clinical correlations is that observed between the bilaterally synchronous spike-wave complex with absence attacks. Usually, both the spike and the wave component emerge abruptly and distinctively from the background activity. However, occasionally the spike discharge is obscure, leaving only a burst of rhythmic 3- to 4-Hz bilaterally synchronous waves. Such "generalized" phenomena may be confined to the anterior head regions, to the posterior head regions, to one hemisphere, or even to a region of one hemisphere. When the phenomena are topologically confined, differentiation from focal spikes may be difficult. Descriptions of these phenomena appear in Weir (1965), Blume and Kaibara (1999), and Lemieux and Blume (1986).

About 97% of patients with bilaterally synchronous spike waves on the resting EEG or with hyperventilation have a generalized seizure disorder (Blume & Kaibara 1999). About 60% of these patients have absence attacks. The incidence of generalized tonic-clonic (grand mal) attacks varies considerably according to age at recording. A smaller number of patients with 3-second spike waves, usually in the younger age groups, have myoclonic seizures.

Because impairment of consciousness, as studied by reaction times, is most profound between 0.5 and 1.5 seconds after onset of spike-wave complexes (Browne *et al.* 1974), some have considered that even a single spike-wave complex represents an absence attack. Although this may be true theoretically, an absence attack is unlikely to be clinically detectable unless sequential spike-wave complexes last more than 5 seconds (Niedermeyer 1987).

Hyperventilation is the most effective means to elicit bisynchronous spike-wave discharges when they are not present in the resting recording. Hyperventilation was found to be more effective than a 6-hour recording in predicting clinical seizure frequency (Adams & Lueders 1981). Photic stimulation may also elicit spike waves, but these may appear in clinically normal subjects who do not have a history of spontaneously appearing seizures.

Continuous spike waves of sleep (electrical status epilepticus of sleep) is a condition in which sequential bilaterally synchronous spike waves are very abundant in non-REM sleep and therefore represent reiterative absence (Patry *et al.* 1971; Tassinari *et al.* 1984). In this disorder, atypical absences with atonic components are among the seizure disorders present in wakefulness as varying quantities of 3-Hz spike-wave discharges occur during the awake recording as well. Behavioral and mental deterioration, including a reduction in speech, occurs. Therefore, the syndrome shares clinical and electrographic properties with the Landau–Kleffner syndrome.

Bilaterally synchronous myoclonic seizures are usually associated with bilateral spike waves or polyspike waves. These may appear in an otherwise normal EEG, with slow spike waves in the Lennox–Gastaut syndrome, or with excess delta in degenerative central nervous system disorders and metabolic encephalopathies. Although the spike-wave complexes accompany the myoclonus, the specific timing between the spike and the myoclonic jerk varies (Gastaut *et al.* 1974).

The EEG may be normal in patients with generalized tonic-clonic (grand mal) seizure disorders such as juvenile myoclonic epilepsy. In other cases, it may show diffuse bursts of theta or may contain sporadic 4- to 5-Hz spike-wave or polyspike-wave complexes. Asymmetric or focal spike waves, or both, may appear commonly, but these can be considered fragments or regional expressions of essentially bilaterally synchronous phenomena (Aliberti *et al.* 1994; Lancman *et al.* 1994; Blume & Kaibara 1999). During the rarely recorded generalized tonic-clonic (GTC) attack, 20- to 40-Hz diffuse waves, slowing to about 10 Hz, appear during the tonic phase, followed by bilaterally synchronous and diffuse polyspike waves during the clonic phase. Unfortunately, muscle artifact rapidly obscures the tracing during GTC. Postictally, diffuse delta and theta predominate, with a return toward a normal recording within several minutes. No regional postictal abnormalities should occur if the at-

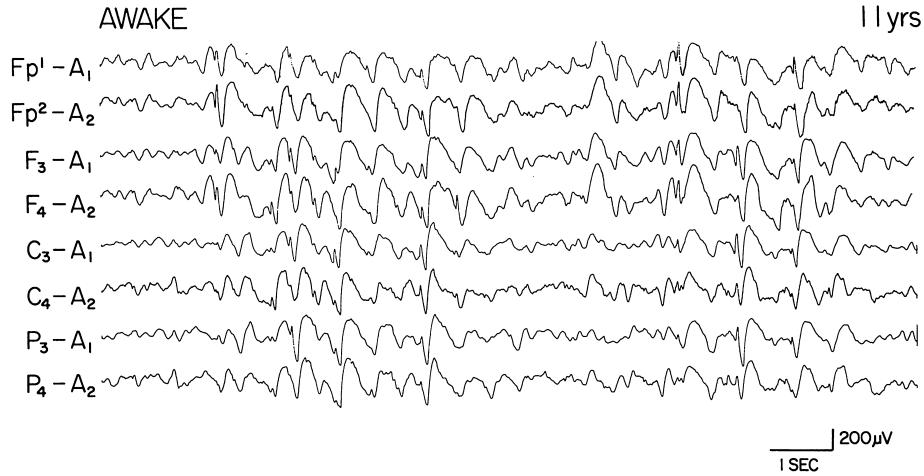

Fig. 5.5 Abundant bisynchronous 1.5- to 2.5-Hz spike waves are "slow spike waves" (SSW) seen with the Lennox–Gastaut syndrome or during absence status epilepticus. The unilateral (right) accentuation of some SSW occurs commonly and shifts from side-to-side. This is not secondary bisynchrony.

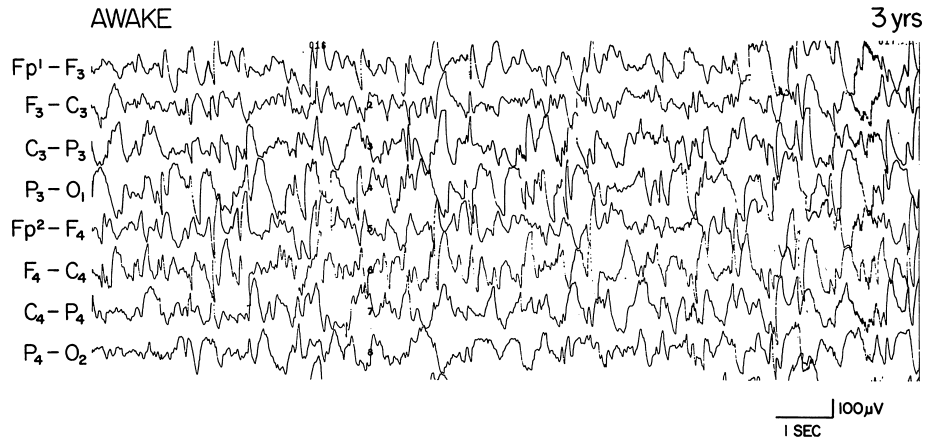

Fig. 5.6 High-voltage diffuse delta with abundant multifocal spikes comprise the hypsarrythmia pattern. These phenomena are at least moderately persistent in wakefulness but may appear in bursts in sleep.

tack was a primary generalized GTC. In those patients with secondarily generalized GTC, the attack itself may predominate in one hemisphere and its postictal effects would reflect the side or area of most intense involvement.

Slow spike waves

Gibbs and associates (1939) first distinguished slow spike and wave from the regular 3-Hz spike and wave; the former repeats at 1.5–2 Hz. The epileptiform component may be either a spike or a sharp wave. These bilaterally synchronous discharges occupy a considerably greater quantity of the awake resting recording than do 3-Hz spike-waves (Fig. 5.5). No clinical alteration may be discerned in such patients at the onset of a burst of slow spike waves in contradistinction to regular spike-wave discharges in which a closer correlation between the EEG and clinical findings occurs. As compared to 3-Hz spike waves, which appear principally in the 5- to 14-year-age group, the maximum incidence of slow spike waves occurs in children 1–5 years old (Blume *et al.* 1973). In earlier years, this pattern may be intermixed with hypsarrhythmia; in later years, it may merge with 3-Hz spike waves. The nonparoxysmal portion of the recording is abnormally slow, in contrast to the traditionally normal findings with 3-Hz spike waves. Hyperventilation less commonly elicits slow spike waves, and photic stimulation is not effective. Sinusoidal-like waves at 10–20 Hz may appear diffusely in such recordings (epileptic recruiting rhythm (ERR)), accompanied either by tonic seizures or absence attacks.

As with 3-Hz spike waves, about 98% of patients with slow spike waves have seizures. Tonic seizures are the most common, followed by atypical absence and myoclonic attacks. Intelligence varies inversely with age of seizure onset. Intractable generalized seizures and bilaterally synchronous slow spike waves and ERR on the EEG constitute the Lennox–Gastaut syndrome (Genton *et al.* 2000).

Hypsarrhythmia

High-voltage 1- to 3-Hz waves with multifocal asynchronous spikes and sharp waves of varying morphology and amplitude constitute the pattern known as hypsarrhythmia (Fig. 5.6). "Chaotic" is an appropriate description of the waveforms in their full expression. Virtually continuous during wakefulness when fully present, hypsarrhythmia may become discontinuous in moderate and deep sleep, and this effect of state should be considered whenever sequential EEGs are compared.

Hrachovy and coworkers (1984) described dramatic changes in the character of hypsarrhythmia over the course of recordings from all their 67 patients. In addition to the description already given, epochs of increased interhemispheric synchronization were found that may be the forerunners of slow spike waves. Hypsarrhythmia may predominate in one hemisphere or even be associated with a consistent focal spike discharge. Epochs of attenuation may interrupt the hypsarrhythmic pattern. Finally, asynchronous high-voltage delta activity with minimal epileptiform potentials can appear. The appearance of such varying EEG features depends on the duration of the recording, the clinical state of the patient, and the presence of structural abnormalities. For example, a large cystic defect in one hemisphere could impair the expression of hypsarrhythmia on that side, creating the asymmetric form. Attenuation is most common in deep non-REM sleep, as already mentioned.

Despite the abundance of spikes and abnormal slow waves, the hypsarrhythmic pattern is considered an interictal phenomenon, although one could consider the patient as being in an atypical absence during its presence. The most common clinical correlate of hypsarrhythmia is infantile spasms. During these spasms, the hypsarrhythmia pattern is abruptly and diffusely replaced by a single high-voltage wave with or without an accompanying spike. Immediately following this, a diffuse or regional attenuation of electrical activity occurs, occasionally accompanied by low-voltage, high-frequency activity. Such phenomena are termed "electrodecremental events" (EDEs) (Fig. 5.7).

The hypsarrhythmia pattern is not always present when infantile spasms first occur, but it ultimately appears. Therefore, the hypsarrhythmic pattern is helpful in differential diagnosis of epileptic and nonepileptic spasmodic conditions in infancy. Hypsarrhythmia is an age-related phenomenon, being confined usually to children age 3 months to 5 years, approximately paralleling the time course of infantile spasms. In younger patients, with the Ohtahara syndrome, a burst suppression pattern is characteristic (Ohtahara *et al.* 1976). In children of older ages, it may be replaced by slow spike waves, focal or multifocal epileptiform abnormalities, or nonepileptiform abnormalities.

No aspect of the hypsarrhythmic pattern has been found to correlate reliably with the ultimate evolution of mental development. Etiology and clinical course are more likely to be of value in this respect: Haga *et al.* (1995) found that those with focal ictal semiology had a poorer outcome.

Electroencephalographic changes during generalized seizures

In some instances, an electrographic seizure is manifested simply as sequential interictal potentials, such as a series of 3-Hz spike-wave discharges with absence attacks. Given the usual abundance of slow spike-wave discharges, at times it is difficult to determine whether the patient is having an atypical absence attack. Rhythmic waves of 10–20 Hz appearing diffusely may have absence or tonic seizures as the clinical correlate (Blume & Kaibara 1999) (Fig. 5.8). Generalized myoclonic seizures have high-voltage diffuse, bilaterally synchronous spike waves as the clinical correlate, even though the precise timing relationship between the EEG spike and the myoclonic jerk varies among patients and even in the same patient over time. GTC seizures combine many of these aforementioned EEG features: very-low-voltage high-frequency waves, 10- to 20-Hz rhythmic waves, or both appear during the tonic phase. These waves are then interrupted by 300- to 400-millisecond bilaterally synchro-

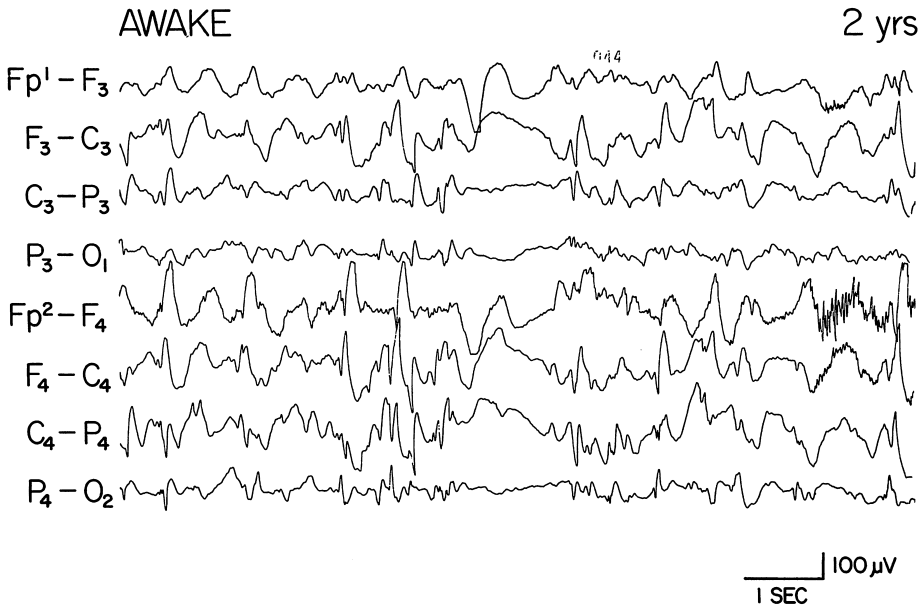

Fig. 5.7 An electrodecremental event. Sudden regional or diffuse (center) attenuation may interrupt the hypsarrhythmia or slow spike-wave pattern. Although no clinical change was evident on this occasion, such change may be associated with infantile spasms. Note chaotic hypsarrhythmia and bisynchronous slow spike-wave patterns here.

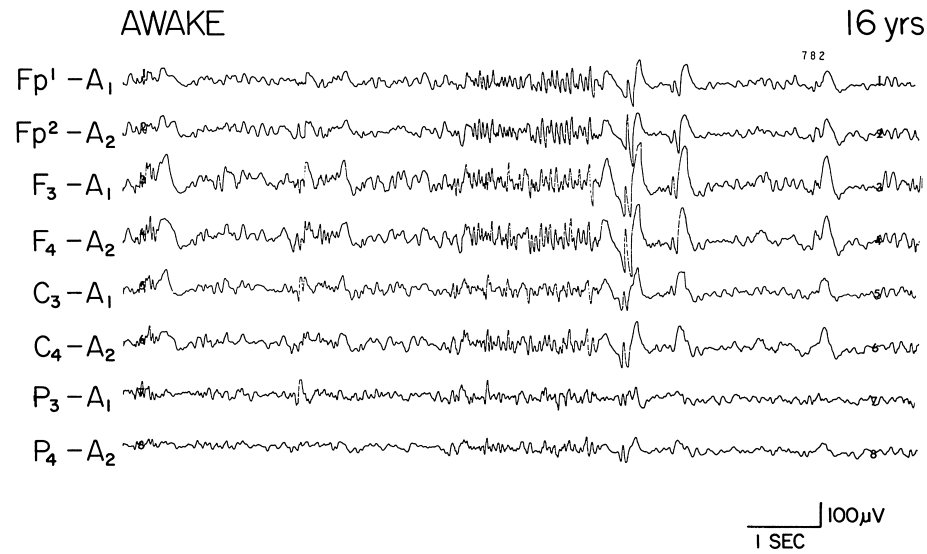

Fig. 5.8 Fast rhythmic waves (epileptic recruiting rhythm) appear bilaterally in a 2-second burst *(center)*, followed by bisynchronous slow spike waves. Such fast waves may be associated with either absence or tonic seizures, but this burst ended before any clinical change could be discerned. The short (0.05) time constant of this segment abbreviated the slow waves of the slow spike waves.

nous slow waves to constitute polyspike-wave discharges during the clonic phase. The ictal phase of infantile spasms and hypsarrhythmia has been described. See Gastaut and Broughton (1974) for a full discussion of these ictal EEG-clinical relationships.

Focal epileptiform potentials

Rolandic spikes

Confined to children and adolescents, rolandic spikes are frequent, stereotyped, and distinct discharges that have as their most prominent component a downward deflection on anterior-posterior bipolar montages (Fig. 5.9). This prominent downward deflection reflects the dipolarity of its field distribution, which can be proven by referential montages with simultaneous anterior positivity and posterior negativity (Blume 1982). Although the negative component of the field is usually over the central-parietal regions with extension to the midtemporal areas, a sagittal or even parietal-occipital location may be seen, all identified by the characteristic morphology and abundance. Such spikes may be virtually limited to one hemisphere in a recording but can be seen independently bilaterally and even synchronously bilaterally, in which case they resemble spike waves. Rolandic spikes appear more abundantly in sleep; in some patients they occur exclusively in sleep. Beydoun and colleagues (1992) noted generalized spike waves in 15% of patients with rolandic spikes and other foci in 10%. The clinical course of patients with these features did not differ from those with rolandic spikes alone. Distinction of these spikes from mu rhythm may be difficult. Mu is more confined to central regions (C3,4); Rolandic spike quantity would increase in non-REM sleep when the mu rhythm disappears.

When such spikes are abundant, they may be accompanied by slow waves in the same region. With this exception, the remainder of the EEG should be normal. Rolandic spikes do not usually represent a structural lesion. However, when a persistent attenuation of background activity or focal delta appears, particularly if independent of spikes, then a structural lesion might be present.

The associated seizure disorder is benign epilepsy of childhood with rolandic spikes (BECRs), which occurs most commonly during non-REM sleep as GTC with occasional unilateral predominance. During the daytime, partial sensory-motor attacks appearing principally in the face or arm may occur. Intellect and neurologic examinations are normal. Both the seizure tendency and the spikes tend to disappear by midadolescence, but the quantity of spikes bears no relationship to the quantity of epileptic seizures. About 50–70% of patients with rolandic spikes have seizures (Niedermeyer 1987). Therefore, it is possible to find this pattern by chance in an EEG performed in the course of looking for another condition. For example, this author has seen this pattern in patients with definite syncope. If a patient has a seizure disorder the characteristics of which are not those of BECRs, then additional electrographic abnormalities must be sought for correlation. Conversely, if a patient with a seizure disorder implicating the rolandic region does not have classic Rolandic spikes, then an epileptogenic lesion should be sought if a second EEG including sleep fails to disclose such discharges.

Occipital spikes

Occipital spikes are well-defined electronegative spikes that appear unilaterally or bilaterally in synchronous or independent fashion over the occipital lobes and may spread to the posterior temporal or parietal regions. They are more abundant with the eyes closed and therefore can be distinguished from lambda waves which, in contrast, are normal electropositive potentials that occur when scanning a complex field.

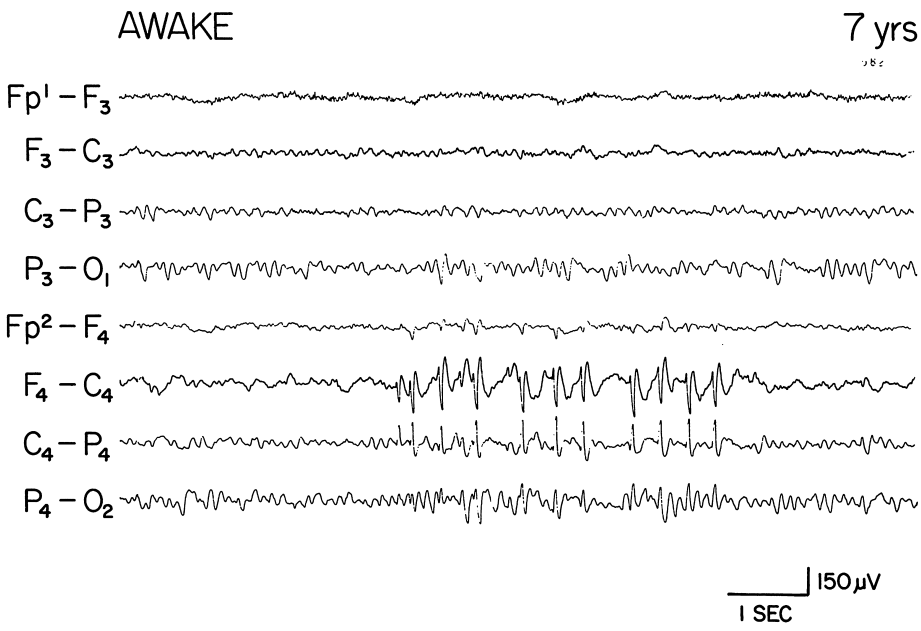

Fig. 5.9 Right rolandic spikes. Their abundance is usually considerable, *not* in keeping with the infrequent associated seizures.

Eeg-Olofsson and associates (1971) found occipital spikes in less than 1% of their normal children. Occipital spikes are the most common focal discharges in children younger than 4 years of age, and they appear most commonly at that time. Smith and Kellaway (1964) found epilepsy in only 54% of their children with occipital spikes. However, Maher *et al.*'s 1995 study of occipital spikes in a referral center laboratory found 29 of 31 children to have seizure disorders.

There are several types of occipital spikes and several conditions in which they appear. Discharges resembling rolandic spikes may appear in the occipital region and may be associated with a benign partial epilepsy of childhood consisting of visual, hemisensory-motor, autonomic, oculoversive and limbic-like seizures (Gastaut 1992; Panayiotopoulos 1999). Not all children with occipital spikes that attenuate with eye opening have easily controlled seizures, and therefore gradations between benign and more therapy-resistant syndromes occur (Cooper & Lee 1991). Very brief occipital spikes may appear in congenitally blind children without any occipital lesion or seizure disorder (Lairy *et al.* 1964). Syndromes encompassing migraine, occipital and other seizure disorders, and occipital spikes have been described (Andermann 1987). Occipital spikes associated with other focal occipital EEG abnormalities occur in children with epileptogenic lesions in this area including arteriovenous malformations, tumors, and cortical developmental abnormalities. Gobbi and coworkers (1991) described patients with occipital spikes, epilepsy, and calcifications in association with celiac disease. The seizures gradually become intractable. Finally, patients with a progressive myoclonus epilepsy such as Lafora body disease may have occipital spikes and light-sensitive seizures (Tassinari *et al.* 1978).

Photic stimulation may elicit occipital spikes in patients with both regional (Jones & Blume, unpublished results) and generalized encephalopathies, such as neuronal ceroid lipofuscinosis (Pampiglione & Harden 1977).

Anterior temporal spikes

Although anterior temporal spikes are thought to be more common among adults, they do appear in childhood and have similar clinical correlates. This is not surprising, because temporal lobe seizures may begin as early as 3–4 years of age. Montages that distinguish these discharges from the temporal extension of rolandic spikes are necessary; rolandic spikes extend principally to the midtemporal or posterior temporal region and are less prominent anteriorly and inferiorly. Eeg-Olofsson and colleagues (1971) found temporal spikes in less than 1% of their series of normal children.

The etiology of such spikes includes any anterior temporal chronic lesion including mesial temporal sclerosis (MTS), malformative lesions with or without MTS, and tumors (Falconer & Taylor 1968; Blume *et al.* 1982; Pringle *et al.* 1993; Aicardi 1994).

Periodic epileptiform phenomena

Periodic lateralized epileptiform discharges (unilateral, PLEDs; bilateral, BIPLEDs) appear in children. More precisely, PLEDs are repetitive regional discharges as they seldom repeat with metronomic regularity (Gross *et al.* 1999). These discharges usually reflect acute conditions with metabolic/electrolytic derangements complicated by seizures. Two-thirds of patients in a study by Chen *et al.* (2003) had central nervous system (CNS) infections, particularly herpes simplex encephalitis. All 15 patients of Garg *et al.* (1995)

had seizures of whom eight had status epilepticus; only one of seven survivors was seizure-free.

Periodic discharges may also accompany the hemispheric epileptiform and nonepileptiform abnormalities of Rasmussen's encephalitis.

Periodic high-voltage broad spikes occur in subacute sclerosing panencephalitis (SSPE). These 100–1000 μV complexes appear as 1–3 Hz waves with intermingled spikes that may occur at 2–20 second intervals and may be distributed diffusely or regionally. These waves correlate irregularly with brief axial or proximal limb myotonic phenomena.

Electroencephalographic changes during focal seizures

Focal seizures are characterized by the regional appearance of sequential waves that differ from background, the morphology of which evolves over the course of the seizure (Blume *et al.* 1984). Such waves may resemble single or multiple sine wave sequences or a series of spikes or sharp waves (Fig. 5.10).

Activation procedures

Any method which may elicit an EEG abnormality that has not occurred in a routine recording falls under the broad category of an activation procedure.

Hyperventilation

From age 4 years, children can cooperate with hyperventilation; their enthusiasm for the procedure is usually greater than among adults. Consequently and for reasons of brain immaturity, the effect of hyperventilation is more prominent in children than among adolescents and adults. Rhythmic theta and delta activity appears initially posteriorly and then diffusely. It may not remit when the technologist asks the patient to stop hyperventilation because some patients may continue hyperventilating. Hypoglycemia may augment the response. Therefore the quantity of this response and its persistence are not criteria of abnormality.

Photic stimulation

Four types of results occur with photic stimulation: (1) "driving," that is, response of varying morphology that is time-locked to the flash rate; (2) frontal myoclonic potentials, also time-locked, reflecting myoclonus of periocular and scalp musculature; (3) photoparoxysmal response, described later; and (4) no apparent effect. Full discussions of these phenomena can be found in electroencephalography textbooks and atlases.

The most clinically significant phenomenon with photic stimulation is the photoparoxysmal response, a bilaterally synchronous polyspike or polyspike-wave discharge that is not time-locked to the flash rate and that may continue beyond the cessation of the flash stimulus (Reilly & Peters 1973) (Fig. 5.11). This response is most readily elicited with flash rates of about 14–18 per second, particularly on eye closure. It appears in about 3% of all patients referred for EEG and of those with partial seizure disorders, and in about 20–50% of patients with GTC, myoclonic, or absence attacks (Takahashi 1987). As the photoparoxysmal response may be seen in normals and in patients with metabolic or drug withdrawal conditions, a diagnosis of a seizure disorder cannot conclusively be made on this basis. Moreover, relatives of patients with primary generalized seizures may demonstrate a photoparoxysmal response without necessarily having a seizure disorder. On the other hand, such polyspike waves may confirm questionable spike-wave discharges on the resting recording. A photoparoxysmal response in a child with febrile convulsions suggests that these may be the first manifestations of a myoclonic epilepsy of childhood (Dalla Bernardina *et al.* 1982; Dravet *et al.* 1985). The photoparoxysmal response suggests that seizures of patients with primary generalized seizures may be precipitated by light flashes. Spike-wave discharges to photic stimulation are uncommon in children younger than 5 years of age, and the incidence in children age 5–15 years is relatively stable.

Ambulatory electroencephalography

To record sporadic, usually unpredictable clinical events in the patient's habitual environment is the goal of ambulatory monitoring (AM) which provides long-term recording without continuous technical supervision.

Although collodion-applied disk electrodes is currently the most reliable method to achieve stable long-term recordings (Ebersole *et al.* 2003). Young *et al.* (2003) have developed a small subdermal needle electrode even less susceptible to artifact.

Ebersole's group (Leroy & Ebersole 1983) devised montages to emphasize the anterior temporal and frontal regions, as most epileptiform discharges arise in these areas. With careful adherence to conservative standards of montage design and electrode application, about 80% of focal epileptiform abnormalities could be accurately identified and localized and 100% of seizures detected by ambulatory monitoring as compared to inpatient telemetry. Both systems were superior to routine electroencephalography in this respect (Leroy & Ebersole 1983; Bridgers & Ebersole 1985). Routine electroencephalography is probably superior for nonepileptiform abnormalities.

Ambulatory electroencephalography may help distinguish epileptic seizures from nonepileptic events such as pseudoseizures, syncope or sleep attacks. It could assist in determining seizure quantity, particularly absence. Classification of known seizures, e.g. temporal lobe from absence, may be accomplished. Technical limitations must be acknowledged, particularly when localization of seizure onset is paramount. Epileptiform activity could arise from areas not covered by the limited montages and the design of such

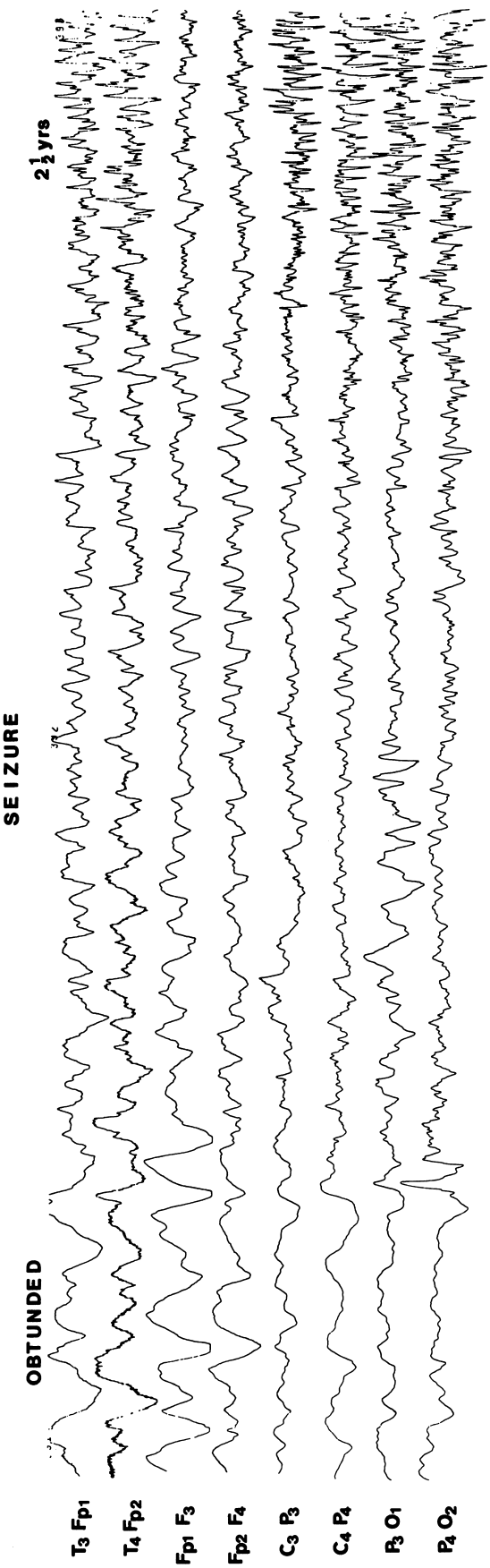

Fig. 5.10 From an excessively slow, delta-dominated background, a seizure gradually begins – first as theta *(center)*, then as sequential polyspikes *(right)*. Note left-right alternating montage.

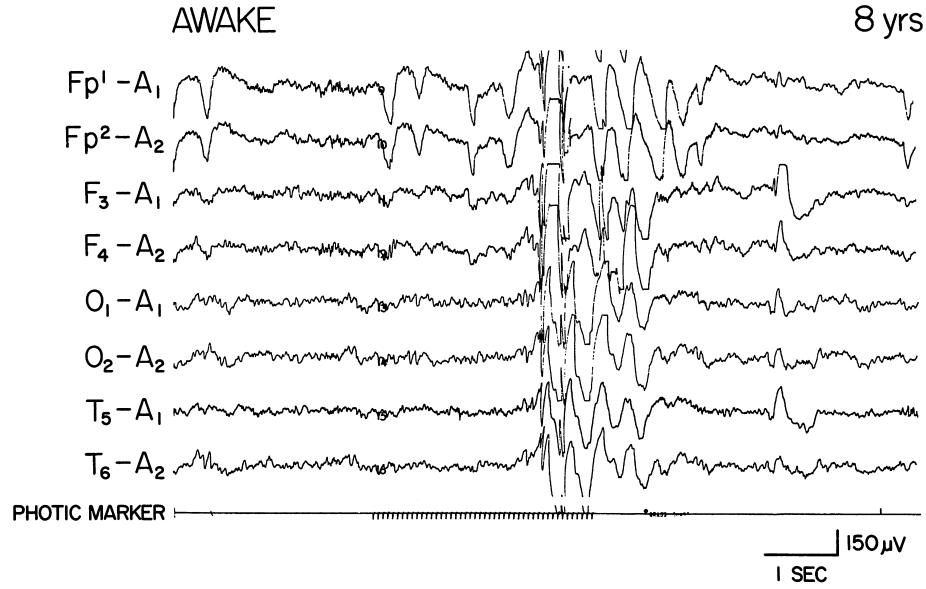

Fig. 5.11 The photoparoxysmal response, consisting of spike waves that have a repetition rate which is wholly independent of the flash rate and that outlast termination of the photic stimulation. Such spike waves correlate better with a generalized seizure disorder than do spike waves that are time locked to the stimulus and do not outlast the flash.

montages should be flexible. Patient selection and technical factors may affect yield. Thus, while Saravanan *et al.* (2001) obtained clarification of management in only 31%, Olson (2001) obtained useful information in 84% of 167 children.

Outpatient video-electroencephalography

In instances where the clinical description and standard EEG fail to identify the nature of some events, combining video-recording and EEG in a 2–3 hour session has been diagnostically helpful in 50–90% (Kramer *et al.* 1995; Chen *et al.* 1995; Carmant *et al.* 1996; Al-Qudah 1999; Valente *et al.* 2003). Distinction of epileptic seizures from other intermittent episodes, reclassification of known epileptic seizures and management changes have been realized in these studies.

Certain central nervous system disorders

Febrile seizures

Three mechanisms may predispose a child to seizures with a fever. The classic febrile seizure represents a genetically determined susceptibility to generalized seizures occurring only with fever. A second group of patients have seizures with fever because of a cerebral lesion occurring either before or during the febrile episode. A third group consists of children who have a chronic generalized epileptic condition that first becomes evident as seizures during a febrile episode.

Complex febrile seizures are those that last more than 15 minutes, are unilateral or focal, or are repeated within a single febrile episode. Such attacks tend to occur in patients whose neurologic development before the febrile attack was already abnormal and are usually associated with a higher risk of later epilepsy. Conversely, a single, brief, generalized febrile seizure may have a relatively favorable prognosis. However, in practice, classifying each episode into either the simple or the complex category may be clinically difficult, as may be the determination of prognosis. Therefore, electroencephalography may help categorize the mechanism of the febrile seizure if its nature is clinically ambiguous.

EEGs obtained less than a week after a febrile seizure may show various quantities of delta activity appearing either diffusely or posteriorly, with the quantity depending on the duration of the febrile seizure and the interval between its termination and the EEG recording. Such bilateral delta activity would fail to reveal the febrile convulsion mechanism. A postictal EEG with regionally accentuated delta or focal spikes would suggest that the seizure with a fever represented the second category outlined previously, that is, a seizure secondary to a previous or current regional central nervous system abnormality.

Electroencephalography could be valuable in the emergent situation for any patient who fails to regain conscious-

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EEGs and Epilepsy

- Slow spike waves are characteristically more abundant than 3-Hz spike waves.
- Rolandic spikes are characteristically abundant, even though seizures are rare.
- Distinction between sharply contoured mu rhythm and rolandic spikes can occasionally be most difficult. When in doubt, consider the phenomenon mu.

Central Nervous System Conditions with Epilepsy

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- The patient with a simple febrile seizure does not necessarily need an EEG.
- Sporadic spike-wave discharges in a patient with febrile seizures do not necessarily indicate that epilepsy will supervene.

ness within a reasonable time after the apparent end of a febrile seizure to exclude the possibility of continuing seizure activity.

The presence of generalized spike-wave discharges on a routine EEG in a patient with febrile convulsions does not increase the incidence of nonfebrile generalized convulsions later in life. For example, about 20% of the patients of Frantzen and colleagues (1968) had sporadic generalized spike waves that were not predictive of the recurrence of febrile seizures or the later development of nonfebrile seizures. Such spike waves appear more commonly after age 4 years. On the other hand, abundant spike waves suggest that the febrile seizure is the first manifestation of a generalized nonfebrile seizure disorder particularly if a photoparoxysmal response is readily elicited (Dalla Bernardina *et al.* 1982; Dravet *et al.* 1985).

An EEG is not mandatory in most patients with a simple febrile seizure. Clinical judgement would be required as to whether an EEG could help unravel the mechanism of a more complex attack.

Hemiconvulsion-hemiplegia-epilepsy

The hemiconvulsion-hemiplegia-epilepsy (HH & E) syndrome described by Gastaut and coworkers (1960) consists of a unilateral or predominantly unilateral prolonged motor seizure, a postictal hemiplegia that may or may not persist, and a focal epileptic seizure disorder, either as seizures from the temporal lobe of the implicated hemisphere or focal motor and possible secondarily generalized seizures. Because the young child is often febrile at the onset of the status epilepticus, a distinction from predominantly unilateral febrile seizures is clinically and nosologically impossible. Postictally, high-voltage 1- to 2-Hz delta activity may be seen bilaterally with emphasis on the implicated hemisphere, and this EEG abnormality may persist in less prominent form for several years. Multifocal spikes chronically appear independently in either hemisphere but principally over the clinically implicated hemisphere. Secondarily generalized spike waves are also a feature.

Acquired epileptic aphasia (Landau–Kleffner syndrome)

Continuous spike-waves during slow sleep (CSWS)

Synonymous with electrical status epilepticus during sleep (ESES) (Patry *et al.* 1971; Tassinari *et al.* 1982; 2000), the EEG features of this rare syndrome consist of abundant (~ 85% of slow-wave sleep) bisynchronous spike waves and slow spike waves with occasional regional expression, usually best expressed over the frontal-central regions (Pedley *et al.* 2003). Spike waves and slow spike waves also appear in wakefulness, but less abundantly. These phenomena appear principally at 4–7 years of age, but the associated generalized and focal seizure disorder may begin 1–2 years earlier. The CSWS phenomenon persists for 1–6 years; it gradually resolves along with the associated seizure disorder leaving cognitive, behavioral and motor deficits in some.

The Landau–Kleffner syndrome is closely associated with the CSWS syndrome (Veggiotti *et al.* 1999; Dulac 2001). Abundant spikes or spike-wave complexes appear bilaterally with predominance over the temporal, parietal, and occipital regions in acquired epileptic aphasia, with the emphasis shifting from side to side. Background activity is normal (Hirsch *et al.* 1990). Sleep onset and non-REM sleep may augment spike quantity, but they may persist in REM sleep (Roger *et al.* 1993). Such EEG abnormalities become less prominent in adolescents, in rough parallel with the decline in the seizure disorder for most patients. This syndrome and electrographic status epilepticus of sleep may be variants of the same disorder.

Malformations of cortical development

Several EEG phenomena may be associated with cerebral malformations, including a paucity of EEG activity either focally or diffusely, monorhythmic theta, or diffuse or focal delta activity. Encephalopathy caused by perinatal insults such as infection or trauma may have similar constellations of abnormalities, depending on the severity. In patients with relatively restricted abnormalities, such as porencephaly, most cerebral activity may be normal except in the implicated area, where paucity of activity, excessive slowing, or spike discharges may appear. Agenesis of the corpus callosum may be associated with a normal EEG or with hypsarrhythmia in infants with Aicardi's syndrome.

Patients with focal cortical malformations who have epilepsy may show multifocal spikes that extend beyond the lobe of the malformation (Palmini *et al.* 1991), but these are usually principally seen in the region of the malformation.

Such epileptiform discharges may be very abundant and may appear in repetitive sequences, paralleling the very frequent seizures with which these patients are afflicted (Raymond *et al.* 1995; Gambardella *et al.* 1996).

Trauma

The magnitude of EEG changes following trauma is considerably greater in children than in adults with the same neurologic status. A mild head injury in a child may produce prominent EEG changes that do not necessarily connote irreversible brain injury. Posteriorly accentuated excess delta activity is the most prominent single abnormality in the acute phase. The frequency of this delta activity is lower in the younger age groups. Such delta declines rapidly after the second week postinjury (Silverman 1962).

Because a head injury involves both direct and contrecoup effects, it is possible that the EEG would reveal dysfunction that is not clinically apparent. For example, the author has seen hemispheric arrhythmic delta activity ipsilateral to trauma-produced hemiplegia.

In addition to direct cerebral injury, other mechanisms may pertain. Carotid artery injury in neck trauma may produce a dissection-related stroke. Hypoxia from a chest injury would give diffuse abnormalities. Fat embolism from long bone fractures may rarely occur.

When assessing the effects of head injury on EEG, the presence of preexisting EEG abnormalities must always be considered; for example, a 3-Hz bilaterally synchronous spike-wave pattern is most unlikely to be the result of trauma.

Epileptiform abnormalities are a not uncommon late consequence of trauma. To ensure the relative or complete absence of these abnormalities, one or more recordings, including one taken during sleep, may be required.

Encephalitis

Normal background rhythms are replaced by theta and excess delta activity. These slow waves are usually diffuse but may have regional accentuation. Although the abnormalities correlate reasonably well with the neurologic state of the patient, both the severity of the encephalitis and any associated systemic disease with metabolic derangements may contribute. Electrolytic derangements alter the EEG more prominently in children than in adults.

Epileptic seizures may complicate encephalitis, and their clinical manifestations may be unusual or subtle. The EEG, particularly if adequate recording time is allowed, can detect electrographic seizures or at least abundant epileptiform activity. In this manner, it may also monitor the effectiveness of anticonvulsant therapy.

Periodic broad spikes are particularly characteristic of herpes simplex encephalitis; such phenomena may be diffuse, temporal-frontal, unilateral, or bilateral in a shifting manner.

In the past, electroencephalography was useful in localizing focal or multifocal abscesses, but advances in neuroimaging have largely supplanted this role in the privileged countries.

Meningitis

If the meningitis has a minimal encephalitic component, the associated EEG changes could be slight. Moreover, they may also represent any metabolic or electrolytic derangements attendant on the acute condition. Once again, focal delta activity should alert the clinician to the possibility of abscess or cerebral vein thrombosis as a complication.

Coma

Because the clinical examination of a patient with a subnormal level of consciousness, particularly coma, is primarily confined to assessment of brainstem function, the EEG provides a valuable adjunct by recording cortically originating activity.

Several phenomena can be seen in comatose conditions. The most common is diffuse persistent excess delta and theta activity. Lack of attenuation or other alteration of this activity by afferent stimuli indicates deep coma. The occurrence of triphasic waves in association with a depressed level of consciousness indicates a metabolically induced comatose condition (Bickford & Butt 1955; Sundaram & Blume 1987). Periodic lateralizing epileptiform discharges may be seen in patients with overriding regional abnormalities (Chatrian *et al.* 1964).

When recurrent seizures complicate the situation, the effectiveness of anticonvulsant treatment can be monitored by assessing the abundance of clinical and subclinical electrographic seizures and the quantity of spikes (Fig. 5.10).

Burst suppression activity may appear in deep coma: Bursts or brief runs of intermixed theta, delta, and spikes are separated by equal or longer periods of relative or complete inactivity, either diffusely or regionally. In other situations, diffuse, nonreactive sinusoidal patterns in the theta or alpha range have been described by several authors (see Bauer 1987, for review).

The prognosis of any of these patterns depends on the etiology of the comatose condition, its duration, and the direction of which sequential EEG recordings are headed. Thus, if anesthetics or other central nervous system depressants have been used, the value of EEG patterns in prognosis is virtually nil. Metabolic and toxic states usually have a better prognosis than structural or anoxic encephalopathies for a given EEG picture. Within this context, prognostically favorable signs are EEG reactivity to exogenous stimuli, spontaneous variability, and normal sleep potentials. The

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Acute Conditions

- Electroencephalography can help monitor the effectiveness of anticonvulsant medication in acutely ill patients whose epileptic seizures may have subtle or bizarre manifestations.
- Sequential EEGs are often of greater prognostic value than a single EEG in assessing the prognosis of a comatose child.
- Electroencephalography can be helpful in assessing whether coma is irreversible, but its value is considerably less than that of clinical data in this respect.

following suggest an unfavourable outcome: lack of reactivity to deep painful afferent stimuli, the burst suppression pattern, monorhythmic alpha or theta frequencies, a very low-voltage EEG, or electrocerebral inactivity.

Pampiglione and Harden (1968) carried out EEGs within the first 12 hours of cardiac arrest in children aged 1 day to 10 years. Those children whose EEGs contained at least some normal features appropriate to age, either on the initial recording or within a few hours, recovered well. Patients with continuous delta that failed to resolve over several hours and those with burst suppression or electrocerebral inactivity died.

The electroencephalogram in determination of irreversible coma

Bobele and colleagues (1993) found clinical examination to more reliably predict outcome or death in newborns and infants than either EEG or radionuclide cerebral perfusion scans.

With respect to the EEG, even apparent electrocerebral inactivity cannot be equated with total cessation of cortical function. A limiting factor is machine noise, from which cerebrally originating potentials of less than 2 μV cannot be distinguished. Neuronal discharges from the thalamus have been recorded when no EEG activity is apparent (Carbonell *et al.* 1963; Jonkman 1969; Visser 1969). Ashwal and Schneider (1979) showed the presence of EEG activity in patients up to 30 months of age who fulfilled other criteria for brain death; none of these five patients survived.

Instead of requiring physicians to use EEG in the determination of irreversible coma, it could be suggested as an ancillary test in situations during which full evaluation of brainstem function is not possible from a practical standpoint. This would occur when trauma to structures reflecting brainstem function had occurred. Even in this circumstance, EEG data would not necessarily assume primary importance but would be considered along with other data in arriving at a clinical decision of irreversible coma.

If one accepts the concept of irreversible coma instead of brain death, demonstration of complete cortical electrical inactivity may not be required. Reactivity of any pattern to afferent stimuli would assume paramount importance. Technical requirements can be found in many publications, particularly in the work of Bauer (1987).

Reye syndrome

Aoki and Lombroso (1973) demonstrated a close relationship between clinical staging of neurologic impairment and EEG. Although the prognosis at each stage has likely improved since their original publication because of improvements in management, the close clinical-EEG relationship may be useful in monitoring patients who have been pharmacologically paralyzed as part of management.

As with any comatose condition, unfavorable EEG prognostic signs would include lack of reactivity to afferent stimuli, very low-voltage activity, electrocerebral inactivity, and the burst suppression pattern.

Cerebral palsy

Among patients with cerebral palsy, those with hemiplegia have the highest incidence of EEG changes (90%), followed by quadriplegics (85%) (Gibbs & Gibbs 1964). Because the pathology is more deeply seated among patients with paraplegia and athetosis, EEG abnormalities are less common.

Asymmetries of awake and sleep potentials may appear among patients with hemiplegia, the side of lower voltage corresponding to the clinically implicated hemisphere. Such abnormalities would be less common for patients with athetosis or diplegia.

Multiple independent spike foci are probably the most common single EEG abnormality. Usually these spike foci are more common over the implicated hemisphere, but if both hemispheres are extensively damaged, the spikes may be better expressed over the relatively healthy side.

Syncope

Sequential electroencephalographic events occur in fortuitously recorded syncope: loss of alpha, a brief period of low-voltage beta, then rapidly augmenting diffuse theta, then delta activity followed by transient electrocerebral inactivity, then progressive recovery. Nonetheless, diagnosis of syncope does not depend on demonstration of this sequence, as was thought in the past.

The danger of performing an EEG in patients with syncope is that some irrelevant abnormality or anomaly might be disclosed. Therefore, the purpose of the recording should be thoroughly communicated to the patient and parents before the fact. When myoclonic or tonic movements are a prominent or prolonged feature of the syncopal attack (brief myoclonies are common), the clinician may be justified in wondering if a generalized epileptic condition is so represented. However, this is a rarity and an EEG is unnecessary in almost all cases of syncope.

As syncope may reflect cardiac arrhythmias, scrutiny of the electrocardiac (ECG) monitor recorded during the EEG is prudent although this single ECG lead would not be a sufficient cardiac examination in itself.

Headache

Although a high percentage of nonspecific abnormalities may be seen in children and adults with migraine or other forms of headache, the value of such abnormalities in differential diagnosis has never been adequately established. Thus, an EEG would be of less value than clinical judgement in evaluating the cause of headache.

Progressive disorders

The EEG does not play a major role in the differential diagnosis of most degenerative diseases encountered; of greater significance are age, symptoms, neurological examination, family history, and the course of the disease. However, EEG changes are often prominent and, therefore their unexpected presence may signal the existence of a degenerative disorder.

Slowing then disappearance of normal background rhythms combined with excessive delta or theta activity is a common finding whether gray or white matter is primarily involved. Spike discharges are more common in primarily gray matter disorders, whereas delta activity is relatively more prominent in white matter disorders; however, these distinctions are not absolute (Gloor *et al.* 1968).

At younger ages, patients with neuronal ceroid lipofuscinosis may respond to low-frequency flash stimulation with large occipital spikes (Pampiglione & Harden 1973). Early-onset degenerative conditions such as globoid leukodystrophy or phenylketonuria may be represented by the hypsarrhythmic pattern.

High-voltage posteriorly situated delta activity during wakefulness may represent adrenoleukodystrophy in any patient in whom more likely causes of this EEG phenomenon, such as recent seizures or trauma, are not present.

The electroretinogram (ERG) may help in the differentiation of some degenerative conditions. For example, in GM_2 gangliosidosis (Tay–Sachs disease), the ERG remains normal, whereas it may become abolished with neuronal ceroid lipofuscinosis.

Chronic Conditions

- History and neurologic examination are better than an EEG in diagnosing syncope and determining the cause of headache.

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Electroencephalography in progressive myoclonus epilepsies

Slowing of background activity and frequent generalized spike-wave and slow spike-wave discharges characterize this group of disorders. In mitochondrial encephalopathy with ragged red fibers (MERRF) focal abnormalities and photosensitivity may appear. Normal physiological sleep patterns may be abolished. In ceroid lipofuscinosis, low-frequency flashes may elicit high-voltage posterior polyphasic spikes. Visual evoked potentials are also large in this disorder. In Lafora's disease, focal occipital paroxysms may be seen in the same recording that demonstrates generalized polyspike waves. In Unverricht-Lundborg disease, photic stimuli may elicit polyspike-wave discharges in about 90% of patients, particularly in the early phases of the disease (Genton & Roger 1993).

Epilepsy and brain tumors

The classic EEG sign of brain tumor is persistent regional delta activity with spike discharges in the same region if the tumor is slowly growing. Thus we found persistent EEG delta activity in 10 of 16 patients whose tumors presented as chronic uncontrolled partial seizure disorders (Blume *et al.* 1982). However, multiple independent spike discharges occurred in a majority of epileptic patients with tumors; 4 of the 16 with tumor had generalized spike-wave discharges. Thus, the type and distribution of epileptiform discharges does not distinguish patients with tumors, but persistent focal delta activity over several recordings may suggest its presence. Of course, improved neuroimaging has lessened the EEG's value in tumor detection.

Angelman syndrome

Characteristic EEG features are bursts of high voltage rhythmic anterior-predominant delta activity that may appear in one or more forms: (1) hypsarrhythmic – with multifocal spikes, (2) rhythmic delta bursts only, (3) superimposed spikes creating a slow spike-wave or notched appearance, and (4) triphasic morphology (Valente *et al.* 2003). Although one or more of these appeared in 96% of their patients, Hou *et al.* (1997) indicate that clinical features become obvious before characteristic EEG features appear. Similar delta bursts may appear posteriorly and may be precipitated by eye closure (Rubin *et al.* 1997).

Rett syndrome

Reflecting the severe epilepsy that afflicts most girls with Rett syndrome, epileptiform activity is prominent in the EEGs. Slow spike waves are a major feature, and these waves usually achieve maximum expression posteriorly, as compared to the usual anterior field distribution of slow spike waves

in the Lennox–Gastaut syndrome (Niedermeyer & Naidu 1987). Multifocal spikes may also appear. Needle-like central spikes, occasionally evoked by stimulation of the contralateral fingernails, are characteristic (Nordli *et al.* 2003) (Fig. 5.12). Trauner and Haas (1985) also found disorganized and slow background activity during wakefulness and quasiperiodic bursts of high-amplitude delta or theta with interspersed epochs of attenuation lasting 3 to 4 seconds. These features develop particularly between ages 2–10 years when seizures and neurological signs appear (Nordli *et al.* 2003). Although EEGs of Angelman and Rett syndromes differ substantially (Nordli *et al.* 2003), features of each have been found in the same patient (Laan & Vein 2003).

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This textbook covers the topic of the electroencephalogram in greater detail.

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A more complete series of illustrations can be found in this atlas.

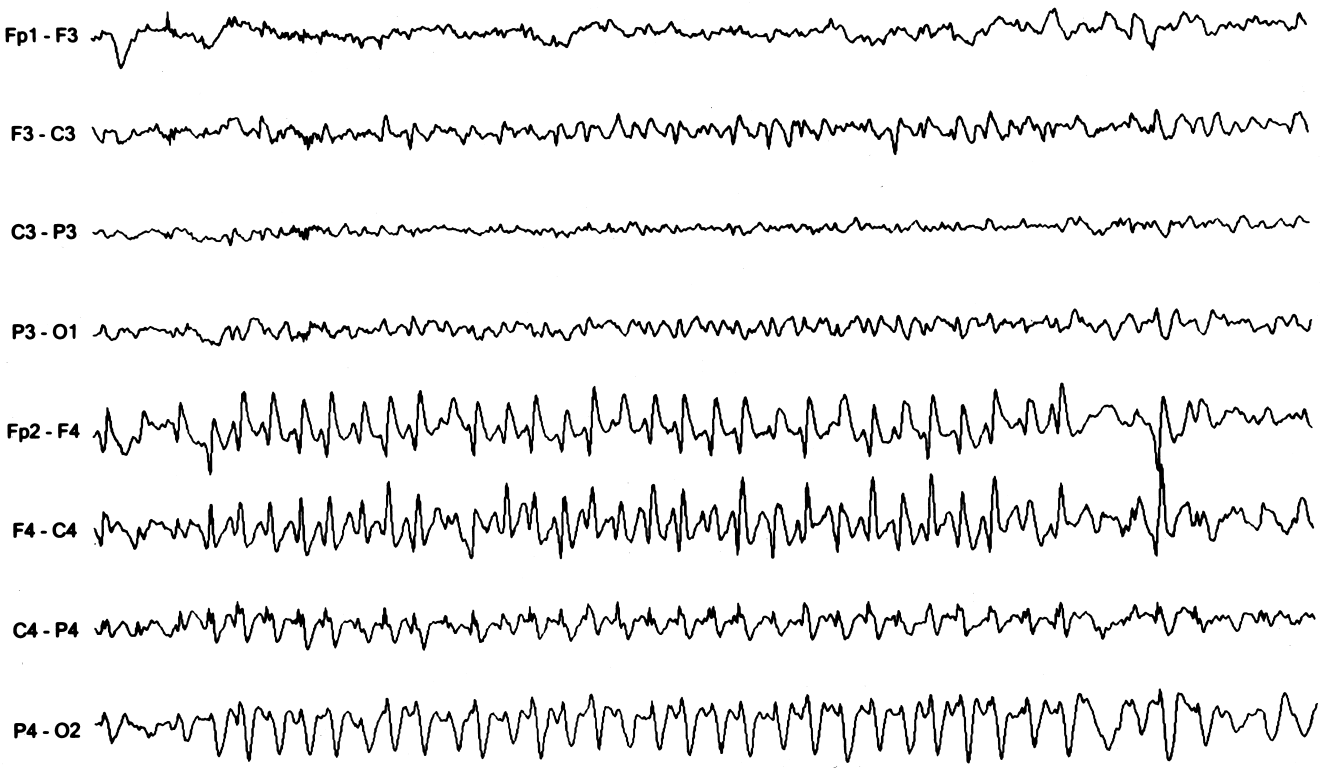

Fig. 5.12 A burst of repetitive multiphasic right hemisphere spikes in a patient with Rett syndrome. Note the characteristic brevity of at least one phase of these spikes.

Electrodiagnostic Evaluation of Pediatric Neuromuscular Disease

Laurie Gutmann, MD and Jack E. Riggs, MD

OUTLINE

Challenges of pediatric electromyography
Abnormalities in pediatric electromyography
Examples of questions to be addressed by pediatric EMG

This section on electrodiagnostic studies in the evaluation of pediatric neuromuscular disease will review the special challenges encountered and the types of electromyographic abnormalities that the physician can reasonably expect to detect in this age group. No attempt has been made to describe the actual performance of pediatric electromyography (EMG). Since specific neuromuscular disorders are reviewed elsewhere in this text, we will not review the specific electrodiagnostic abnormalities associated with each of these disorders. This chapter will review the specific questions that are commonly addressed by EMG in the evaluation of pediatric neuromuscular disease.

Challenges of pediatric electromyography

Pediatric EMG presents both the physician ordering the study and the physician performing the study with an array of special challenges. These challenges reflect the limited capacity of the young child or infant to cooperate with the study, the large surface area to body mass of the young child or infant, the absolute small dimensions of the limbs of the young child or infant, the observation that normal conduction values change dramatically over the first couple of years of life, and the challenges associated with performing EMGs in the intensive care unit setting. These potential pitfalls can greatly affect the interpretation of the EMG study. These challenges are so prevalent that a few words are devoted to each of them.

Limited capacity to cooperate

The limited capacity of infants and young children to cooperate during an EMG has several practical implications. Foremost, before ordering an EMG on a young child or infant, the physician should be able to explicitly ask the electromyographer a specific question that is to be addressed by the EMG study. Pediatric EMG is not a reliable or frequently useful screening test. Since young children may not be able to cooperate with the examination, the study is often performed in a nonstandard sequence. The electromyographer may need to alter the examination in such a way as to obtain information as the opportunity arises. The examination may have to be curtailed without doing all that was initially planned. If the electromyographer does not have a specific question to address, he or she will not know how to prioritize the examination.

Conscious sedation is not utilized in our EMG laboratory, although some laboratories use it with success. We encourage the presence of parents in the laboratory up to about age 7–8 years, which is the earliest age when the child can begin to understand why the study is being done and is able to cooperate with the study. Before that age, the presence of the parent is comforting and reassuring to the young patient. After that age, the child can usually be reasoned with and reassured by the examiner that no harm is intended. After age 7–8 years, the young child is more likely to react to the parent's anxiety.

If the physician ordering the EMG does not have a specific question for the electromyographer, everyone involved would be better served by referring the patient first to a physician with experience in pediatric neuromuscular disease. Similarly, if the electromyographer does not have experience in performing EMGs on young children or infants, it is best to refer the patient to an electromyographer with such experience. Much time can be wasted and ill feelings can evolve when parents suspect that physicians and electromyographers are not sure what they are looking for or how to interpret what they have done, particularly when it has involved repeatedly sticking needles into and delivering electrical shocks to their children. Parents may not allow these studies to be repeated elsewhere, thereby hindering the diagnostic process.

Large body surface area to body mass

The relatively large body surface area to body mass of a small child means that children are more prone to cooling. Abnormal temperature of the patient during nerve conduction studies and EMG can alter the results of the test, giving either a false-positive or a false-negative result. Although the importance of maintaining normal body temperature when screening for defects of neuromuscular junction transmission is widely acknowledged, the patient's temperature is also important when obtaining standard nerve conduction studies and needle EMG. A false-positive diagnosis of a mild demyelinating generalized peripheral neuropathy can occur if the patient is too cool. Distal latencies may appear to be mildly prolonged and nerve conduction velocities may appear to be mildly slowed. These alterations are partially due to alteration of the Na^+/K^+ pump activity and Na^+ channel open time.

On the other hand, conduction block in demyelinating disease improves with cooling. Sodium channel open time is prolonged with cooling, allowing for depolarization of the nerve in demyelinated areas. Sodium channel open time is shortened with warming. Warming can actually enhance the abnormalities in focal compressive lesions such as carpal tunnel syndrome, improving the accuracy of the test. However, warming will not make a normal study look abnormal.

On needle EMG, fibrillation and fasciculation potentials are reduced with focal cooling, and in early disease, fibrillation and fasciculation potentials may even disappear. This effect could result in a normal appearing study in a patient with axonal loss or early motor neuron disease.

At the neuromuscular junction, cooling will enhance neuromuscular transmission, resulting in a less prominent decrement with repetitive stimulation, despite a defect of the neuromuscular junction. The alterations from cooling are complex, having to do with a combination of Ca^{2+} influx and prolonged half-life, reduced acetycholinesterase activity, and vesicle and acetylcholine binding. However, warming or cooling will not give you an abnormal result in a patient without disease. The safety margin in a normal neuromuscular junction is high enough to compensate for temperature effects.

In our EMG laboratory, blankets are utilized to warm young children or infants if their extremity skin temperature is low. While utilization of heat lamps might be faster, we do not use them on young children or infants who cannot reliably notify laboratory personnel if they become too hot.

Absolute small dimensions

Since nerve conduction velocities are calculated using measured distances on the child's extremities, any measurement inaccuracies will be magnified as the size of the patient decreases. For example, an inaccuracy of 5 mm is relatively greater if the interelectrode distance is 50 mm than if it is 300 mm. Studies of children, especially infants, require accurate measurements for calculations of conduction velocities. Because of the small distance available for stimulation in a small limb, a slight inaccuracy in measurement can result in an "abnormal" velocity. In addition, until age 2 years, children have slower conduction and may have smaller amplitudes. Tables are available for the expected range of normal values in young children and infants.

The effect of limb length must also be taken into account for parameters such as F-wave latency and H-reflex. There are calculations available to correct for limb length.

Nerve Conduction Techniques

PEARLS & PERILS

- Nerve conduction techniques can help differentiate among the many similarly presenting disorders of the motor unit by outlining the types of nerve fibers involved, the pattern of involvement and the type and degree of the physiologic insult.
- The referring physician plays a critical role in the successful completion of the examination by appropriately preparing the parent and child, as well as by developing a differential diagnosis and set of specific questions from which the electromyographer plans the examination.
- Infants under 12 months of age will frequently sleep through nerve conduction studies if the examination is timed to take advantage of a natural sleep period and the stimuli are well spaced.
- Children who have had a negative experience with painful medical or dental procedures benefit from special preparation for their examination with consideration being given to use of guided imagery or self-hypnosis and use of analgesic medication or conscious sedation.
- The presence of a parent or familiar adult frequently improves the quality of the study by maximizing patient relaxation and cooperation.
- Normal values depend on the technique used and change dramatically between preterm infants and toddlers. Slower maturational changes occur between toddler age and adulthood. If adequate normative data do not exist for the technique being used, the sensitivity of the test greatly diminishes.
- Inaccurate results can be caused by imprecise distance measurements, excessive shock artifact or cool extremity temperatures.

Intensive care unit settings

As in adults, electrophysiologic testing is prone to electrical interference and artifacts, particularly in the intensive care unit setting. We prefer to perform the study in the EMG laboratory, if at all possible, to reduce some of these artifacts. When

this is not possible, needle EMG can be difficult to interpret. Sensory nerve action potentials may also be obscured, due to their small amplitudes. It is important to be aware of these limitations and to make the family aware of them as well.

Abnormalities in pediatric electromyography

The motor unit includes the motor neuron, peripheral nerve (motor axon), neuromuscular junction, and the muscle fiber. Electrodiagnosis of abnormalities of the motor unit can often be readily demonstrated using routine nerve conduction and electromyographic studies. EMG is an integral part of the neurologist's diagnostic armamentarium. It is important to remember that nerve conduction studies (NCS) and EMG results alone are not pathognomonic of any specific disease and do not give a definitive diagnosis. However, in conjunction with a good history and physical examination these studies often clinch a diagnosis.

Abnormalities of the motor neuron

Fibrillation potentials are the most frequent EMG abnormality seen that indicates the presence of a possible underlying motor neuron disorder. In the floppy infant syndrome, the implications of fibrillations are so grave that care must be exercised in calling this abnormality. One must be certain not to confuse the fibrillations seen with motor neuron disease with the fibrillations seen, for example, with myofiber necrosis in muscular dystrophy (Fig. 5.13). In addition, although motor units may have some polyphasia, they may not be large, as seen in adult motor neuron disease. Increased size and polyphasic motor units are evidence of denervation with reinnervation.

Abnormalities of peripheral nerve

After correcting for age-related maturational effects on nerve conduction parameters, nerve conductions studies are a very reliable method of detecting the presence of peripheral nerve disease in a child. Peripheral nerve disease may be a diffuse problem or a focal abnormality. NCS in combination with the needle EMG can help to distinguish whether the nature of the problem is demyelinating, axonal, or conduction block, as well as generalized, focal, or multifocal. NCS look at the latency (ms), amplitude (mV or μV), and conduction velocity (m/s) of a response to an electrical stimulus over the nerve.

Before age 2 or 3 years, normal values are much reduced. Premature infants have even slower velocities and prolonged latencies. Gestational age is more important for determining these values than is age from birth. Normal values for infants and young children are available in most electrophysiology texts.

Abnormalities of the neuromuscular junction

Repetitive nerve stimulation is useful in the evaluation of infantile botulism. Repetitive nerve stimulation is also useful in the evaluation of the congenital myasthenic syndromes, although these syndromes are extremely rare. To ensure accurate findings on repetitive stimulation, it is important that

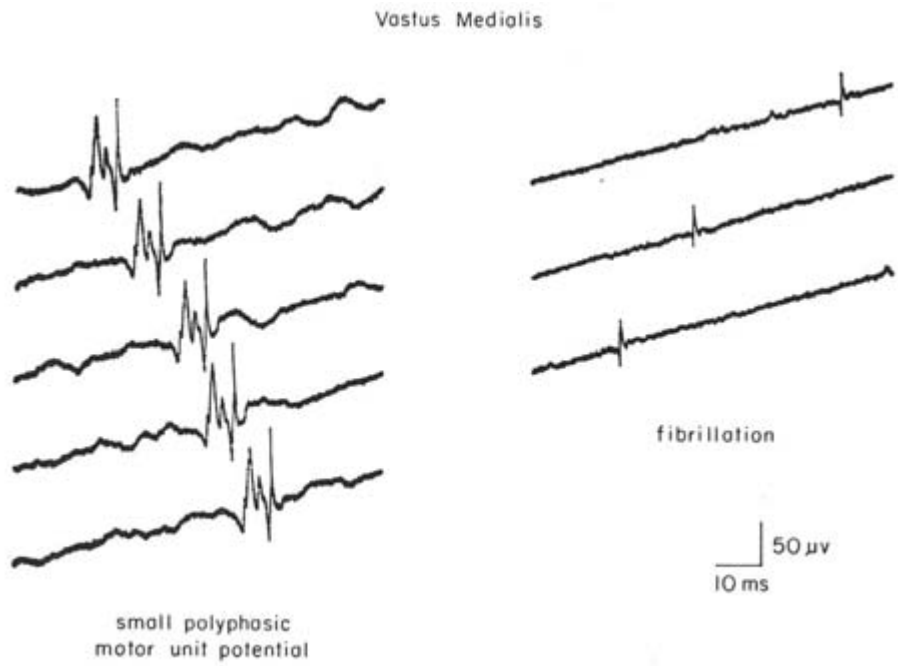

Fig. 5.13 Duchenne muscular dystrophy with small MUAPs and fibrillation potentials.

the patient be warmed to enhance the neuromuscular junction defect (see above) and, if they are old enough, understand exactly what is expected of them. Movement artifact can give a seemingly abnormal response. If the amplitudes of the responses go up and down, the patient is either moving or the limb is not being stabilized during the testing. The repetitive stimulation response with progressive decrement over all nine responses indicates movement, most often movement of the stimulating electrodes slowly off the site of nerve stimulation. The amplitude of the CMAPs during repetitive stimulation should not show a decrement after the fourth response if due to a pathophysiological response at the neuromuscular junction.

For infants and children who cannot exercise for the testing, either due to severe weakness or poor cooperation, it may be necessary to use 50 Hz stimulation (Fig. 5.14). Although 50 Hz is more uncomfortable than slower rates of stimulation, it is especially important to use it if there is suspicion for a presynaptic defect of the neuromuscular junction, such as botulism. Most other times, 2–3 Hz repetitive stimulation is adequate, especially when used before and after exercise.

If there is concern about a postsynaptic defect of the neuromuscular junction, prolonged 50 Hz stimulation may give a false-positive result in an infant, especially a premature infant. The immaturity of the neuromuscular junction in this case results in a poor safety factor and a decremental response that can be seen in healthy infants at such a high rate of stimulation. Slower rates of stimulation (2–3 Hz), with some mild sedation to reduce artifact and improve cooperation, would be preferred in this situation.

Although single fiber EMG also gives useful information in patients with defects of the neuromuscular junction, it requires a significant amount of cooperation and concentration from the patient. Single fiber EMG is also time-consuming and requires patience from both the examiner and the patient. Most children cannot participate in single fiber EMG before the age of 8 years.

Abnormalities of muscle

EMG is frequently not helpful in the evaluation of congenital myopathies. Mild degrees of polyphasia are often very difficult to assess in infants or young children. Fibrillation potentials associated with myofiber necrosis or myositis are often readily apparent, especially if associated with the early recruitment of many small motor unit potentials. The presence of fibrillation potentials may make it difficult to rule out a neuropathic process, as noted above.

Loss of insertional activity during needle examination may occur with fibrotic replacement of muscle in some myopathic processes.

Myotonic discharges, with their characteristic waxing and waning dive-bomber sound, may be an unexpected finding. The discharges are seen with needle insertion in a muscle at rest. In infants, the myotonic discharges may be absent or less sustained and quieter than in adults. Sometimes they can be confused with end-plate noise.

Examples of questions to be addressed by pediatric EMG

Floppy infant – myopathy, neuropathy, or central weakness?

Muscle weakness is one of the more frequent reasons why pediatric patients are seen in our EMG laboratory. In this situation, trying to differentiate between a central nervous system cause versus a peripheral cause for the weakness may be the primary question. Hypotonic infants who are weak from either cause may have similar clinical presentations. Newborns or infants who have respiratory difficulties or feeding difficulties with no central nervous system etiology may have spinal muscular atrophy, a myopathy (such as myotonic dystrophy or other congenital myopathies), or infantile botulism. For myotonic dystrophy, the parents

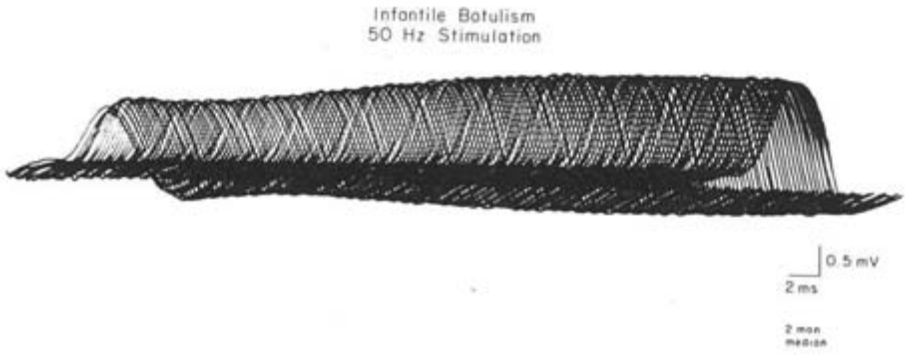

Fig. 5.14 50 Hz stimulation in a 2-month-old child with botulism.

should be studied for myotonic discharges, with the mother most likely being the disease carrier when a newborn has the above-mentioned clinical presentation. The myotonic discharges may not be present in the newborn, but will typically be found in the mother.

For other congenital myopathies, abnormal motor unit action potentials on needle EMG may be seen. Small amplitudes in motor NCS may be seen in motor neuron disease, motor neuropathies, botulism, or significant myopathies. It is important to remember that fibrillation potentials may occur in some myopathic disorders as well as neuropathic disorders (Fig. 5.15).

H-reflexes are long latency responses that are present in the ulnar nerve in infants, disappearing by about 1 year of age. Their presence in this nerve is due to lack of CNS myelination. Reoccurrence or persistence at a later age would be indicative of CNS demyelination or continued lack of myelination.

Is a neuropathy present?

Loss of sensation, with or without associated weakness, may occur with neuropathies, both acquired and hereditary. Ascending numbness may be from a central nervous system (spinal cord) lesion or an acquired neuropathy, such as acute inflammatory demyelinating polyneuropathy. Hereditary neuropathies are more common than toxic/metabolic neuropathies in children. We frequently do nerve conduction studies on parents of children with abnormal nerve conduction studies and EMG findings consistent with a polyneuropathy.

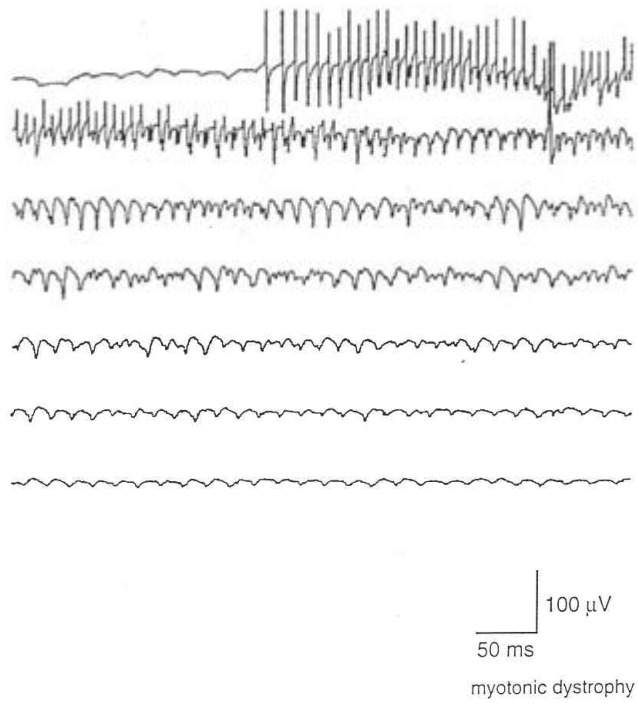

Fig. 5.15 Myotonic discharge in a 7-year-old child with myotonic dystrophy.

PEARLS & PERILS

Needle Electromyography

- Standard needle EMG can reliably differentiate neurogenic processes from other motor problems in infants and children.
- Needle EMG can provide important information about the pathophysiology of the disease process, for example, the presence or absence of ongoing reinnervation.
- Many myopathic processes – carrier states or subclinical phases of muscular dystrophies as well as congenital, structurally distinct myopathies – can produce motor unit potentials with characteristics and recruitment patterns that are too difficult to differentiate from normal values for age.
- Muscles that are going to be biopsied should not be studied by needle EMG within several weeks before biopsy because the muscle trauma incurred can produce changes that are difficult to differentiate from disease states.
- Serum muscle enzymes should be drawn before needle EMG, because the repeated needle insertions involved in most studies can produce a transient elevation of muscle enzymes that may confound the diagnostic effort.

Pediatric patients may have both central and peripheral nervous system involvement causing their weakness. This combination is uncommon in adults. Most commonly, this combination is a hereditary demyelinating disorder, such as metachromatic leukodystrophy or Krabbe's disease.

When attempting to differentiate between an acquired demyelinating neuropathy and a hereditary neuropathy, the time course of the illness is an important clue. The other clue is the presence of temporal dispersion and/or conduction block of the CMAP. This is more noticeable with proximal stimulation of nerves but can be seen with distal stimulation as well. The latencies and conduction velocities will be prolonged in both hereditary and acquired neuropathies, so the numbers may be very similar. However, the pictures of the waves show the spread of the conduction velocities in all the axons, based on the varied amount of demyelination throughout the nerve. Hereditary neuropathies have a more even distribution of demyelination.

When should the EMG be performed?

Timing for the EMG study can be important. With infants and children, the electromyographer may only get one opportunity or very limited opportunities to do the test, with parents and/or patient refusing a repeat study. In a mononeuropathy or plexopathy, if the question involves prognosis, waiting 3–4 weeks after the onset of the symptoms would be appropriate. However, if the question is that of

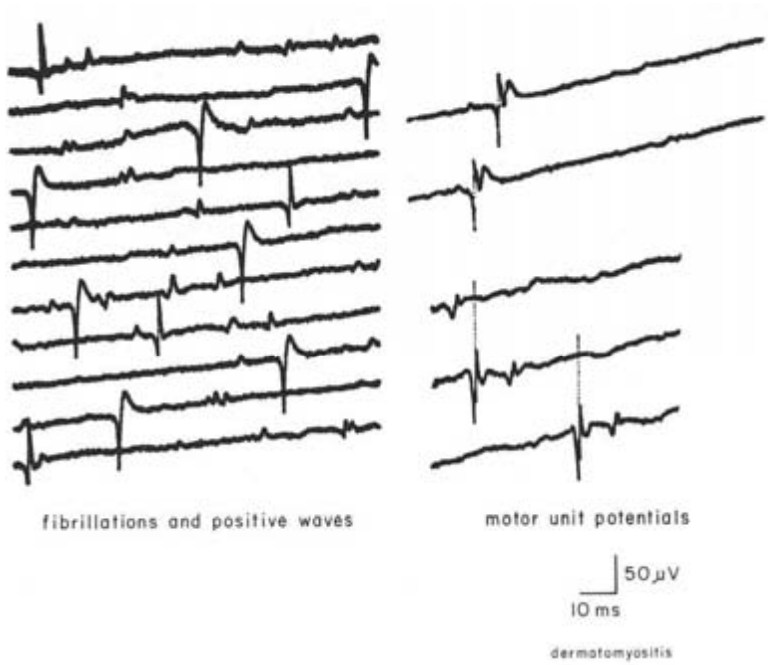

Fig. 5.16 Fibrillation potentials and small polyphasic MUAPs in a 4-year-old child with dermatomyositis.

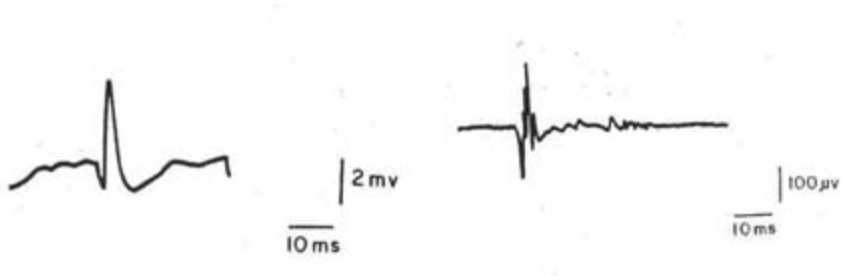

Fig. 5.17 MUAPs from neuropathy and myopathy – note difference in scale and presence of polyphasia in both.

postpartum brachial plexopathy, an early EMG may help answer the question of whether or not the plexopathy occurred *in utero* or in the perinatal period. Fibrillation potentials take 7–10 days to develop. Their presence soon after delivery would indicate a prenatal onset.

If the EMG is being performed for prognosis, the presence of motor unit action potentials, either large/rapidly firing or small, nascent units, in a plegic muscle are encouraging. Lack of motor unit action potentials and continued presence of fibrillation potentials would be discouraging. Parents and patients should be warned that repeat study may be necessary for continued assessment of prognosis in the latter case.

Concluding remarks

Electrodiagnosis is an important part of the diagnostic evaluation of children with neuromuscular disease. Even at large centers, large numbers of pediatric EMGs are not done, and the importance of having an electromyographer who is familiar with doing EMGs in children cannot be overstressed. The key component in successful electrodiagnostic studies in pediatric cases remains being aware of the limitation of the information that can be obtained and knowing what question you need to have answered.

Annotated bibliography

Jones HR, Harmon RL, Harper CM, Bolton CF: An approach to pediatric electromyography. In: Jones HR, Bolton CF, Harper CM, editors: Pediatric clinical electromyography. Philadelphia, 1996, Lippincott- Raven, pp. 1–36.

This reference provides a nice technical summary of the issues covered in this chapter as well as normal values for infants and young children along with appropriate additional references.

Gutmann L: Pearls and pitfalls in the use of electromyography and nerve conduction studies. Semin Neurol 23:77–82, 2003.

This reference provides an introduction for many of the technical issues introduced in this chapter along with appropriate additional references.

Clinical Evaluation with Evoked Response Modalities

John F. Kerrigan, MD

OUTLINE

Basic principles
Electroretinography
Visual evoked responses
Brainstem auditory evoked responses
Somatosensory evoked potentials
Intraoperative evoked potentials
Conclusion

Evoked potentials (EPs) are a noninvasive tool for evaluating the functional integrity of peripheral and central sensory pathways. As such, they complement the neurological examination, and information provided by other testing modalities.

The relative clinical utility of EPs (and neurophysiological studies in general) has been diminished in the era of modern structural imaging technology. The pace of new innovation in the structural imaging modalities has been nothing short of phenomenal, and continues to expand rapidly, while the pace of new developments in the neurophysiological realm over the past one or two decades has been much more modest. Nevertheless, EPs remain an important component of the diagnostic armamentarium, providing information regarding functional integrity of neurological pathways, localization of conduction deficits through these pathways, and changes in functional integrity over time that may not be accessible by standard physical examination or imaging techniques.

EPs may be expected to provide clinically useful information in the following situations:

1. Evaluating integrity of sensory (or motor) pathways in those patients unable to cooperate with conventional methods of neurological examination. This may apply to patients who lack behavioral maturity and voluntary cooperation, or who are otherwise impaired due to various pathological states, such as coma, obtundation, or retardation.
2. Providing specific diagnostic clues in selected patients that may complement other diagnostic or imaging studies.
3. Providing evidence for or against possible sites of pathological localization that may elude other diagnostic or imaging studies.
4. Providing a means of functionally evaluating sensory pathways during surgical interventions or other procedures that place these anatomic pathways at risk in a sedated or anesthetized patient.

PEARLS & PERILS

Evoked Potentials

- All evoked potential (EP) modalities change dramatically during development, particularly during early infancy. Results must always be compared to age-related normal standards.
- The EP technology staff must be well trained, experienced, and able to take the extra time required to work with infants and children. The quality of the interpretation rests upon the quality of the waveforms available for review.

In contemporary practice, the most common clinical applications for EPs in children are (1) screening of high-risk neonates and infants to identify possible hearing loss, and (2) intraoperative monitoring. However, all EP modalities are important in selected clinical circumstances. This chapter seeks to provide an overview of EP modalities in the context of evaluation and management of infants, children, and adolescents with neurological concerns or established neurological disease. The study of evoked responses is appropriate for neurologists and neurosurgeons, as well as a host of practitioners in other disciplines that deal with sick or impaired children, including audiologists, ophthalmologists, and anesthesiologists. These techniques also shed light on the basic maturational processes that subserve sensory function in the developing newborn and infant.

Basic principles

This section provides the interested clinician with a basic understanding of the indications, diagnostic potential, and pitfalls of each of the various EP modalities, while abbreviating technical aspects of study performance. Several excellent texts are available to the reader with more advanced interests (Russell & Rodichok 1995; Chiappa 1997; Aminoff 1999; Levin & Luders 2000).

Electrical activity of the brain is continuously present as "resting" or baseline activity, with distinct features that allow identification of waking, sleeping, or encephalopathic states. However, the nervous system will also demonstrate evidence of responsiveness (activation) that is time-locked to external events or stimulation, typically conducted by sensory pathways. EP studies attempt to record and quantify evidence of this neural activation, serving as a functional assessment of the sensory pathway in question. Most of the electrical potentials elicited by these sensory stimuli possess very low amplitude features, and consequently repeated stimulation of the afferent system, and subsequent digital averaging of a large number of individual stimulation events, is required to separate the evoked signal from the background neurophysiological "noise" of on-going activity. (The exception to this rule is familiar to all electroencephalographers, as the occipital response to photic stimulation may be visually detectable with just a single stimulus.) Typically two trials (two sets of repeated stimulation) are performed and visually compared by overlaying the waveforms, in order to determine reproducibility of the findings.

Evoked potential teaching tends to imply that each waveform can be attributed to an individual nucleus or to a single specific structure within the sensory conduction pathway. The reality is more nuanced. Peripheral waveforms may be attributed to a specific structure, such as the Erb's peak response with somatosensory evoked potentials resulting from the passage of an axonal volley through the brachial plexus. However, central nervous system responses usually defy such easy attribution, as the individual waveforms consist of a composite of waveform responses from multiple structures, potentially including both near-field and far-field responses. Fortunately, in most cases, the predominant feature of an identified waveform can be assigned to activation of a particular structure, often based upon lesion studies in humans (usually adults). We will identify the "primary" generator of the principal waveforms for each EP modality, which serves to provide localizing information for focal sensory conduction deficits.

The technical features of each EP modality are unique. Details regarding the stimulation system (including such features as simulation intensity, duration, and repetition rate), and the recording system (relating to features such as electrode placement, sweepspeed, gain, and bandpass) are discussed in the comprehensive references noted above. Ideally, a clinical neurophysiology laboratory performing such studies has sufficient volume and experience to maintain a high level of expertise and "practical know-how." Waveforms resulting from clinical disease or physiological changes in conduction must be differentiated from artifact. In comparison to other areas of diagnostic science, neurophysiological techniques possess relatively poor signal to noise ratios, even more so in children. The expertise of the interpreter, examining a study after its performance, cannot make up for the mistakes made by a careless or inexperienced technologist. Oversight of the technical performance of these studies is of paramount importance.

Electroretinography

Anatomic considerations

Functional integrity of the retina (or, at least, certain cellular elements of the retina) can be assessed with electroretinography (ERG). A light flash delivers photic energy to the retina, and evokes predictable changes in photosensitive cells and secondarily in their supporting cellular network. The a-wave identified in normal individuals is due to activation of the photoreceptor layer. The b-wave is generated by activity of supporting glial elements (Müller cells) and probably other cells within the bipolar layer (inner nuclear layer) of the retina (see Figs 5.18a and 5.18b).

Testing of cone cell responses (mediating high resolution, color, light-adapted vision) can be preferentially performed with bright white-flash stimulation in the light-adapted state, and also by evaluating the retinal response at rapid flicker rates (the "frequency-following" response). Rod responses (mediating lower resolution, dark-adapted vision) can be preferentially tested by a lower intensity blue-flash stimulation under dark-adapted conditions.

Flash stimulation is diffused over the entire retina, and consequently ERG tends to be a study that is more sensitive for diffuse retinal disease processes, and relatively less sensitive for macular degenerations (even when utilizing the light-adapted, cone predominant stimulation conditions). Focal ERG techniques (for regional evaluation of the retina) have been developed, but as yet do not enjoy widespread usage.

Technical issues

Typically, monocular flash stimulation is utilized, with both eyes recorded simultaneously. The opposite (unstimulated) eye then serves as a negative control. Recording features vary significantly from laboratory to laboratory, most importantly with respect to electrode placement. Corneal electrodes,

KEY CLINICAL QUESTIONS

ERG studies are helpful for…

- Evaluation of children with unexplained visual loss and/or nystagmus.
- Differentiating pigmentary retinopathy from normal variants of retinal pigmentation.
- Confirming visual dysfunction in the retina prior to pathological changes in the fundoscopic examination.

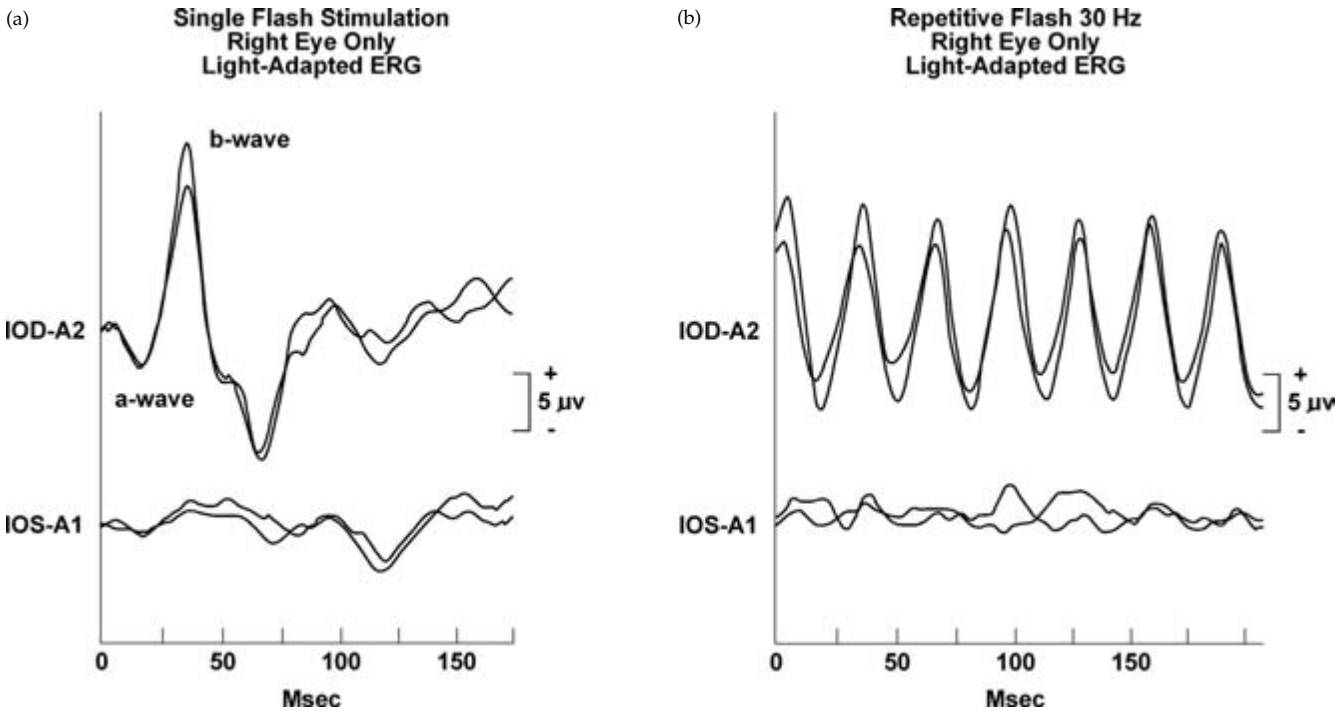

Fig. 5.18 (a) The principal ERG waveforms, with monocular stimulation of the right eye, identifying a-wave and b-wave responses. This response was obtained to bright full-field flash in a light-adapted state. (b) The "frequency following" response to repetitive flash stimulation of the right eye.

similar to contact lenses, provide the highest amplitude (and best signal to noise features) but require adequate sedation and placement by trained personnel, and carry significant risk of corneal abrasion in unskilled hands. Many laboratories, including our own, make use of periorbital skin electrodes, typically in an infraorbital position.

Developmental changes

The a-wave and b-wave responses are present at birth in term newborns, but typically show lower amplitude features, and slightly longer latencies. Mature a-wave and b-wave latencies are usually seen by 6 months of age, and fully mature ERG responses (considering both light-adapted and dark-adapted conditions) are typically obtained by age 1 year (Flores-Guevara 1996).

Clinical aspects

ERG studies, often together with visual evoked responses (VER), can be helpful in evaluating children with visual loss and/or nystagmus, either due to disease processes that affect the eye alone, or in conjunction with other features of neurological disease. These studies are ordered only *after* ophthalmologic examination, including fundoscopy, has been performed, in order to exclude the presence of disease states that affect the pre-retinal structures of the eye, such as corneal opacification, cataract, or diseases of the vitreous. However, it is also important to recognize that abnormalities of the ERG may be present in disorders of retinal function, including certain neurodegenerative conditions, prior to observable changes in the retina by direct fundoscopic examination (Harden 1989).

Retinal disorders

A large number of disease states in children affect the retina without associated neurological involvement. ERG studies in this group are usually ordered by the pediatric ophthalmologist, and the role of the child neurologist in these cases, if any, is often to exclude coexisting neurological problems.

The single most common genetic cause of childhood blindness is Leber's congenital amaurosis, an autosomal

PEARLS & PERILS

Electroretinogram (ERG)

- Most ERG techniques use flash, and do not require cooperation for visual fixation on a target.
- The ERG is more sensitive to diffuse retinal diseases than to diseases affecting the macula (maculopathies).
- ERG abnormalities usually precede fundoscopic findings in Leber's congenital amaurosis and neuronal ceroid lipofuscinosis.

recessive retinal dystrophy that affects both cones and rods. This disorder is genetically diverse, mapping to a number of different loci. Some of the specific gene mutations have been identified. These children present in infancy with visual inattention and nystagmus. Initially, the fundoscopic examination is normal. However, ERG responses in both light-adapted and dark-adapted conditions are markedly abnormal, if not entirely absent, and, accordingly, assist with the diagnosis of this disorder.

Pigmentary retinal degenerations, including retinitis pigmentosa (RP), also show abnormal ERG results. RP typically presents with night-blindness, and progressive restriction of the visual fields. It is largely a rod degeneration, with relative sparing of the cone-predominant macula, and thus, central vision. At the point in time during the clinical course where pathological pigmentary changes are seen, the ERG, particularly for dark-adapted or rod-mediated conditions, should always be abnormal (Baker 1995). Consequently, the ERG can be of great practical usefulness in distinguishing pathological pigmentary changes of the retina from the wide range of normal variation in retinal pigmentation seen in children.

Leber's congenital amaurosis and RP represent two of the more common "pure" retinopathies where ERG analysis can assist with the diagnosis. There are a large number of "pure" retinal disease states, both progressive and nonprogressive in nature. Detailed discussion of these disorders, and their ERG findings, is beyond the scope of this chapter. A partial list of these conditions is shown in Table 5.1.

TABLE 5.1

Disorders Associated with ERG Abnormalities

"Pure" retinopathies (modified from Kriss 1992)
Static
Congenital stationary night-blindness
Color blindness, complete and incomplete subtypes
Albinism
Progressive
Leber's congenital amaurosis
Retinitis pigmentosa
Cone dystrophies
Cone-rod dystrophies
X-linked juvenile retinoschisis
Neuro-ophthalmologic disorders (modified from Baker 1995)
Nonprogressive syndromes
Usher syndrome (multiple subtypes)
Laurence–Moon syndrome
Bardet–Biedl syndrome
Joubert's syndrome (some subtypes)
Degenerative diseases
Neuronal ceroid lipofuschinosis (infantile and juvenile subtypes)
Gangliosidoses
GM2 Type I (Tay–Sachs disease)
GM2 Type II (Sandhoff's disease)
Mucopolysaccharidoses
MPS Type I H (Hurler syndrome)
MPS Type I S (Scheie syndrome)
MPS Type II (Hunter syndrome)
MPS Type III (Sanfilippo syndrome)
MPS Type VII (Sly syndrome)
Mucolipidoses
Type IV
Peroxisomal disorders
Zellweger syndrome
Neonatal adrenoleukodystrophy
Hyperpipecolic acidemia
Infantile refsum disease
Abetalipoproteinemia

Neuro-ophthalmologic disorders

More commonly, the child neurologist is called upon to evaluate children where neurological symptoms, in addition to visual disturbance, are part of the clinical presentation. Most children with brain disorders and visual inattention will be determined to have cortical visual impairment (the preferred term to "cortical blindness," since most of these children have some partial retention of visual function). Although usually unnecessary, an intact ERG can help make the case that visual disturbance originates posterior to the retina.

Several nonprogressive syndromes can include retinopathy, and an abnormal ERG may assist with the diagnosis. Usher syndrome, combining sensorineural hearing impairment and visual loss secondary to a pigmentary retinopathy, has several clinical subtypes. Linkage studies have shown that it is a genetically diverse syndrome, but usually inherited in an autosomal recessive fashion. Abnormalities of the ERG may pre-date the changes of pigmentary retinopathy on fundus exam, and therefore can help to establish the diagnosis in a child with congenital deafness. Bardet–Biedl syndrome, and the phenotypically similar Laurence–Moon syndrome, combines pigmentary degeneration (and an abnormal ERG) with other features including retardation and hypogonadism. Some subtypes of Joubert's syndrome include retinopathy and visual loss.

Abnormal suppression and eventually complete loss of ERG responses is seen in several neurodegenerative diseases that affect children.

The infantile and juvenile subtypes of neuronal ceroid lipofuscinosis show striking and early abnormalities of the ERG due to progressive retinopathy, even before clinical visual disturbance may be evident. Of interest, and somewhat counterintuitive, is the observation that ERG responses can be completely flat in the presence of preserved flash visual

evoked responses. The late infantile form of the disease (Jansky-Bielschowsky) actually shows VER waveforms with potentially excessive amplitude features ("giant VERs"), despite suppressed or absent ERGs. Roughly 70% of the late infantile cases will show diagnostic abnormalities of the CLN2 gene.

ERG results are also abnormal in GM2 gangliosidosis (but not the Type III subtype), some forms of mucopolysaccharidoses, mucolipidoses, and peroxisomal diseases. Some of these disorders combine corneal opacification and retinal degeneration, making interpretation of the ERG more problematic (Baker 1995).

In summary, ERG abnormalities are relatively common in many of the neurodegenerative disorders that predominately affect neurons, and are classified as gray matter degenerations or poliodystrophies. Conversely, ERG abnormalities are generally not to be expected with the leukodystrophies. See Table 5.1 for a more detailed list of those disorders associated with ERG abnormalities.

Visual evoked responses

Anatomic considerations

Neurophysiological evaluation of the visual pathways posterior to the retina is performed with the visual evoked response (VER). The latency and amplitude of the waveform response generated by occipital cortex provides information about visual conduction through the visual pathways (optic nerves, chiasm, tracts and radiations), as well as the functional integrity of the visual cortex itself. The major waveform response (the P100) appears to be generated by postsynaptic potentials in the pyramidal cells of layer IV of occipital cortex, primarily from the macular area of representation (Ducati 1988). As the name implies, this peak occurs roughly 100 msec following stimulation with a pattern-reversal checkerboard. Negative potentials precede and follow the major positive peak (N85 and N135, respectively). These negative peaks have lower amplitude features, and can be more difficult to identify (Fig. 5.19).

While localization of the abnormality is relatively imprecise with VER, the presence of an asymmetrical response to monocular stimulation suggests a conduction defect in anterior (optic nerve or chiasm) pathways. In the absence of ocular pathology or retinal abnormality demonstrated by ophthalmologic examination or ERG, this type of pattern strongly suggests an optic nerve disturbance. Conversely, an asymmetrical field to the VER over the occipital region to monocular stimulation of *both* eyes suggests a unilateral or asymmetrical postchiasmal visual conduction defect or unilateral dysfunction of visual cortex. It is important to be aware that in some patients the field potential of the occipital (visual) cortex to VER stimulation may actually project its maximum to the contralateral side of the head, potentially resulting in false lateralization. Correlation with structural imaging would be recommended. The visual pathways are shown in Fig. 5.20.

Technical issues

The preferred method of pattern-reversal VER stimulation requires an awake and cooperative patient so that visual fixation can be maintained on the visual target of the checkerboard shift pattern. Consequently, flash stimulation

Visual Evoked Responses (VER)

PEARLS & PERILS

- Pattern-reversal testing is the most useful, but requires a cooperative patient for visual fixation, often not possible in children.
- Flash VER can be obtained simultaneously with the ERG.
- Asymmetrical responses over the occipital region may falsely lateralize to the side opposite of the abnormality (due to tangential projection of the electrical field). Confirmation with structural imaging is recommended.
- ERG and VER abnormalities must *always* be correlated with ophthalmoscopic examination. Ocular problems such as corneal opacification and cataracts should be excluded.

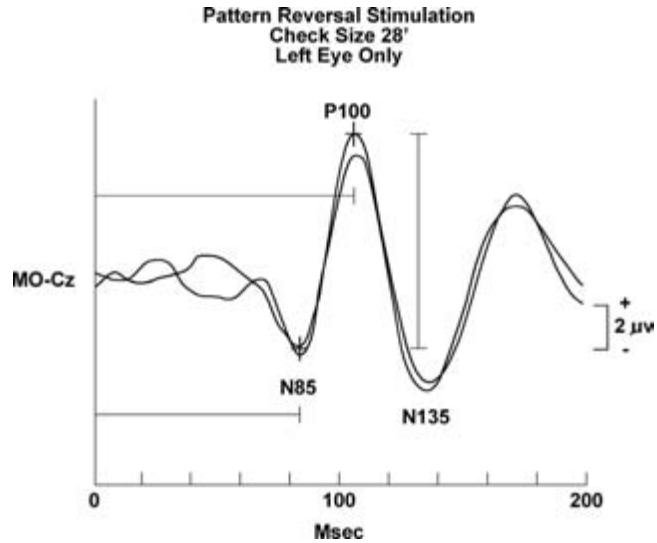

Fig. 5.19 Normal VER waveform, showing major positive peak (P100), and smaller negative peaks preceding and following (N85 and N135). Measurements relating to peak latency and amplitude (trough of N85 to peak of P100) are shown. A scalp positive electrical field shows an up-going deflection. Some laboratories use a reversed polarity convention, however, with the P100 showing a downward deflection. MO = midline occipital electrode, Cz = vertex electrode.

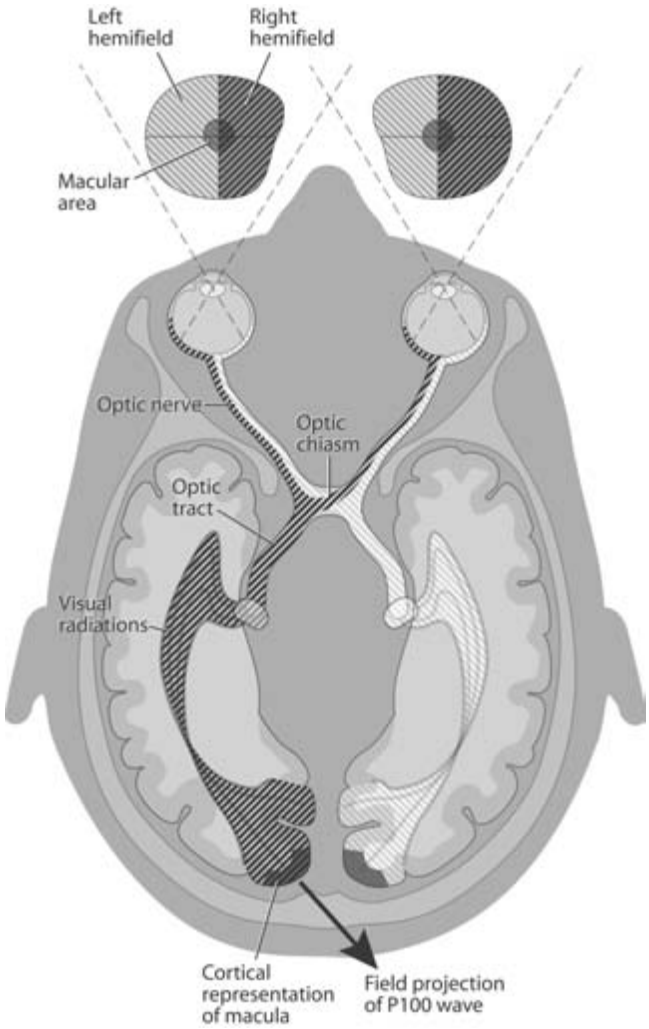

Fig. 5.20 Anatomy of the visual pathways, with ipsilateral projection of fibers from the temporal fields of the retina, and crossed projection of the nasal fields through the optic chiasm. The region of representation in the calcerine cortex for the macula is relatively enlarged in comparison to other areas of the retinal surface, and is located at the posterior occipital pole (heavy black line). The tangential field of the occipital VER is also represented.

is more commonly performed in young, encephalopathic, or otherwise uncooperative patients. Recording electrodes are placed over the occipital region. In our lab, this includes a midline occipital electrode, and two additional recording electrodes placed laterally from the midline to each side. These "active" electrodes are referenced to an electrode placed in the frontal midline.

Developmental changes

Unfortunately, there is a great deal of individual variation with regard to the latency and amplitude of flash VER. These are usually judged to be normal based upon the presence or absence of a consistent and symmetrical response to monocular stimulation (Baker 1995). The pattern-reversal VER shows higher amplitude responses with a tighter and more highly validated range of normal latency values. However, as noted above, pattern reversal study may not be possible in young or inattentive children.

Flash responses can be recorded as a long-latency, surface negative wave in pre-term infants as young as 24 weeks postconceptual age. A major surface positive waveform can be seen at 32 weeks, is consistently identifiable by 37 weeks postconceptual age, and is very well defined by term. The latency of this surface positive peak decreases rapidly until 5–6 months of age when it approximates adult values.

For high-risk newborns screened at 40 weeks postconceptual age with flash VER, an intact response is strongly associated with normal visual function at 1 year of age, while an abnormal response is associated with abnormal visual function at 1 year in approximately 50% of cases. Consequently, an abnormal VER during the newborn period should identify the child as "at risk" and requiring follow-up, but does not necessarily imply an abnormal outcome (Kurtzberg 1982).

Clinical aspects

VER results can be influenced by ocular pathology, such as opacifying lesions of the cornea, lens, or vitreous, and therefore should always be preceded by fundoscopic examination.

Attempts to demonstrate a tight correlation between visual acuity and findings on VER testing for young or uncooperative children have been made, but thus far these techniques are technically demanding, and unsatisfactory for practical use. Even so, the VER remains the best proxy for functional assessment of the visual system in these patients.

VER studies are most useful in detecting conduction defects in the anterior optic pathways (optic nerve and chiasm). Pattern-reversal VERs are highly sensitive to signal conduction changes of the optic nerve, particularly if the pathological process is unilateral or asymmetric. VERs can detect optic nerve lesions in the absence of obvious changes on MR imaging, such as with optic neuritis resulting from acute disseminated encephalomyelitis (ADEM), neuromyelitis optica (Devic disease), or the uncommon pediatric case of multiple sclerosis. VER can confirm or supplement the clinical exam in patients with optic nerve hypoplasia or atrophy. For patients with known structural abnormalities, such as a glioma of the optic nerve or chiasm, the VER can offer a powerful noninvasive method for serial studies, looking for progressive changes that may mandate a change in therapy.

VERs for diseases that affect the posterior optic pathways (posterior to the optic chiasm) are less useful. VERs have been studied as a modality for evaluating possible shunt

KEY CLINICAL QUESTIONS

VER studies are helpful for…

- Children with unexplained visual loss and/or nystagmus (often performed with ERG).
- Localizing a visual conduction deficit to the optic nerve or chiasm.
- Following visual function in young patient with known optic nerve glioma.
- Usually not helpful for evaluating children with cortical visual impairment.

dysfunction in shunted hydrocephalus, or for evaluating patients with childhood leukodystrophies. In each instance, they appear to have limited clinical utility for most patients. VER studies have also proven to have limited value in evaluating patients with cortical blindness (cortical visual impairment), as patients with intact responses may still demonstrate disabling visual impairment when old enough for behavioral testing of visual function. Conversely, patients with absent VERs may still demonstrate useful (though usually not normal) vision.

Brainstem auditory evoked responses

Clinical indications

Peripheral and central auditory conduction pathways can be evaluated with brainstem auditory evoked responses (BAERs). BAERs are used to evaluate two related functions. First, they can evaluate hearing in infants and children who are unable to cooperate for conventional auditory threshold testing. Secondly, they can assess the functional integrity of brainstem conduction in an effort to localize pathology to the brainstem or to a specific location within it. A normal BAER study is shown in Fig. 5.21.

Anatomic considerations

Auditory stimulation usually consists of clicks, delivered at the selected intensity via insert earphones. The responses are recorded by electrodes placed at the vertex and bilaterally on the earlobes or mastoid regions. Sound intensities up to 95 or 100 dBnHL can be used.

The most commonly used and validated modality, the short-latency BAER, demonstrates auditory signal transmission through peripheral and brainstem structures that occurs during the first 10 msec after click stimulation (see Fig. 5.21). Waves I, III, and V are the most consistent and easily identified. Lesion studies and microelectrode recordings in humans and animal models have established that wave I originates from the peripheral (most lateral) aspect of the VIIIth (auditory) cranial nerve, wave III from the lower pons (superior olivary nucleus and possibly cochlear nucleus), and wave V from the lower midbrain (inferior colliculus). Auditory pathways through the brainstem have bilateral representation, but lesions ipsilateral to the stimulus are more likely to attenuate or abolish BAER waveforms. Fig. 5.22 provides representation of waveform identification with respect to the anatomy of the auditory conduction system.

By making use of these relationships, the BAER may help to localize a neurological deficit. As an example, a tumor in the cerebellopontine angle will tend to increase the ipsilateral wave I–III interpeak latency, or may abolish all waves subsequent to wave I completely (to ipsilateral stimulation).

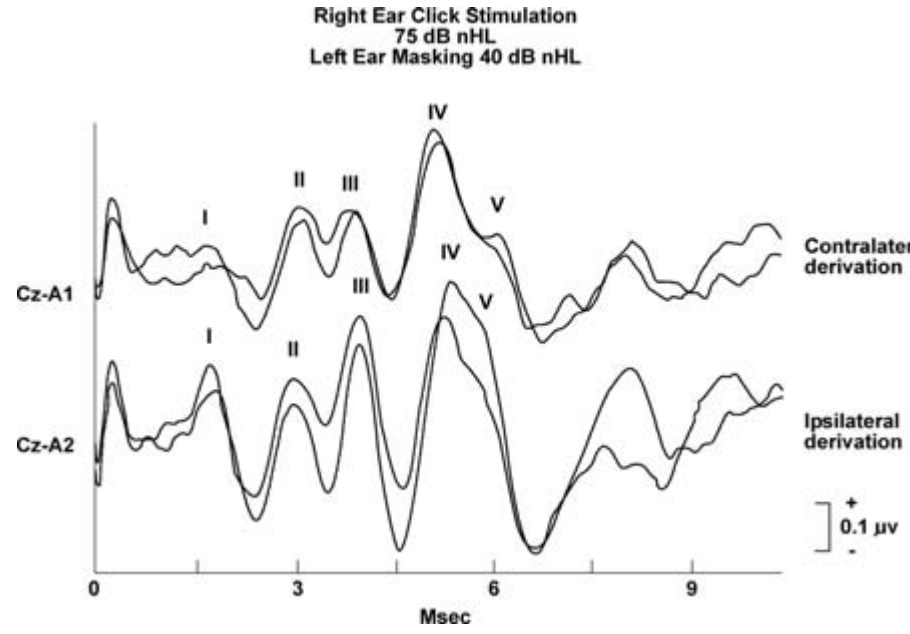

Fig. 5.21 Normal brainstem auditory evoked response (BAER). Waves I, III, and V are of the greatest clinical significance. A2 = R ear electrode, A1 = L ear electrode, Cz = vertex electrode.

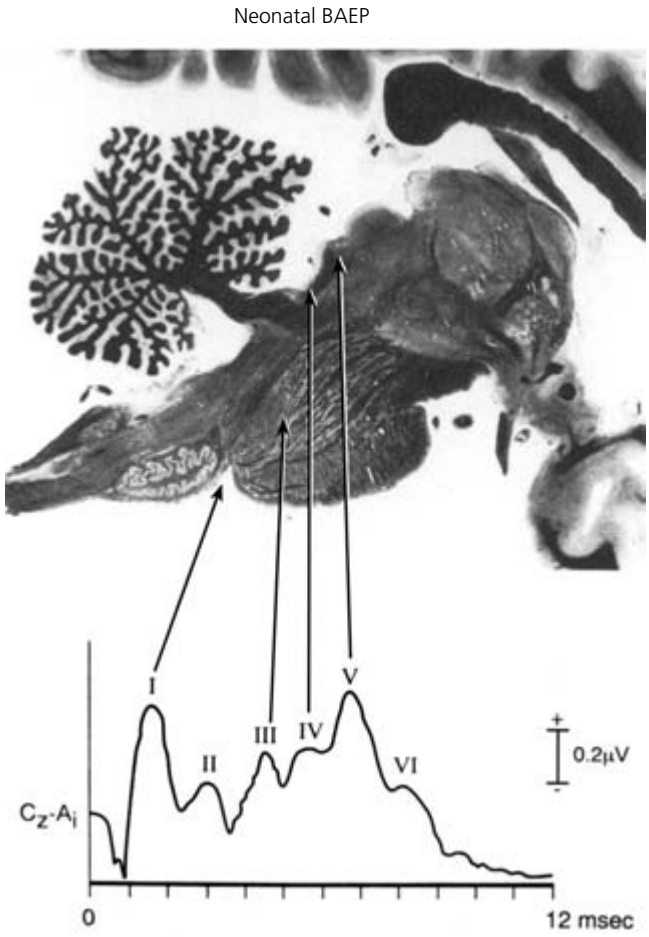

Fig. 5.22 Sagittal brain slice with anatomic localization of the principal BAER waveform generators. Some of the BAER waveforms are compound waveforms, with contributions from more than one structure. (With permission from Goodman MH, Beacham SG, Streletz LJ: Clinical neurophysiology. In: Duckett S (Ed.) Pediatric Neuropathology. Philadelphia: Williams & Wilkins 1995.)

As one may guess, the clinical utility of BAER studies in localizing neurological lesions has been largely superceded by current imaging techniques.

Mid-latency and long-latency BAER studies are recorded by some laboratories, but are more variable, and of limited clinical usefulness

Audiological assessment

For patients who are too young or too encephalopathic to cooperate with traditional behavioral-response audiology, the BAER provides a tool for assessing hearing. The sound intensity threshold at which wave V appears (generally the most robust and easily identified of the BAER waveforms) provides a clue as to the hearing threshold. A threshold of 15–20 dBnHL is considered normal. This threshold is affected by either conductive or sensorinerual disturbances, so correlation with the otological examination is required for abnormal results. Additionally, BAER waveform latencies decrease as the intensity of the sound stimulus increases. The detailed measurement of wave V latency against sound stimulation intensity yields a latency-intensity curve, the characteristics of which may help differentiate conductive versus sensorineural hearing loss (see Fig. 5.23).

BAER studies are commonly used to screen for hearing impairment in high-risk newborns. Factors that would include a newborn in this high-risk category include premature birth, low birth weight, possible intrauterine infection, hyperbilirubinemia, meningitis or sepsis, exposure to aminoglycoside or other ototoxic medications, the presence of a congenital syndrome associated with hearing impairment, or family history of deafness. The presence of other neurological problems, including neonatal seizures, hypoxic-ischemic encephalopathy, or intracerebral hemorrhage, also call for audiological screening. Alternative studies, more easily performed but still sensitive to the conductive or sensorineural (cochlear) deficits that are common in newborns, such as the otoacoustic emission (OAE), are also performed at some institutions. Automated auditory brainstem response studies (A-ABR) is a newer technology now used at a large number of institutions for screening purposes.

Developmental changes

BAER waveforms can be elicited in pre-term newborns, with wave V appearing as early as 27 weeks postconceptual age. There is a progressive decrease in waveform latency and an increase in waveform amplitude during maturation, so that normal adult values are approximated at 1–2 years of age. Changes occurring between 30 weeks and 40 weeks of postconceptual development are shown in Fig. 5.24.

Clinical aspects

Newborn screening is by far the most important and common use of the BAER modality in clinical use. Older but still uncooperative patients with some of the problems identi-

PEARLS & PERILS

Brainstem Auditory Evoked Responses (BAER)

- BAER (or another suitable auditory screening modality) should *always* be performed in high-risk newborns before hospital discharge.
- Alternative technologies for screening include otoacoustic emission (OAE) or automated auditory brainstem response (A-ABR).
- BAER abnormalities in children should *always* be correlated with physical examination of the external auditory canal and tympanic membrane to exclude obstructing problems or middle ear disease.

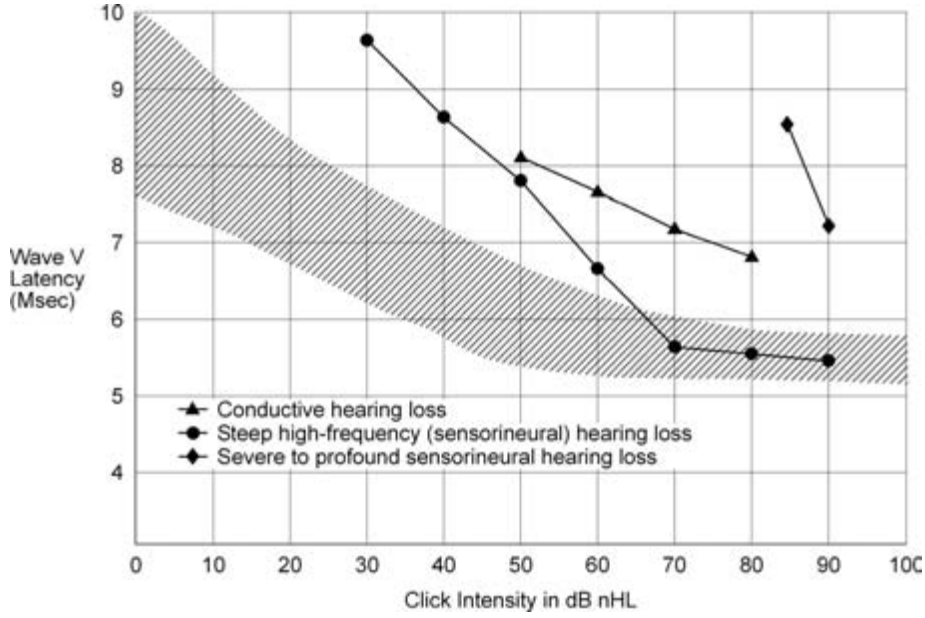

Fig. 5.23 Latency-intensity graph, with normal range and idealized representations of sensorineural and conductive hearing loss. Stippled area = range of normal for children, ●— = mild-moderate sensorineural hearing loss (example: history of hypoxic-ischemic injury at birth), ▲— = conductive hearing loss (example: chronic middle ear effusion), ◆— = profound sensorineural hearing loss (example: history of bacterial meningitis).

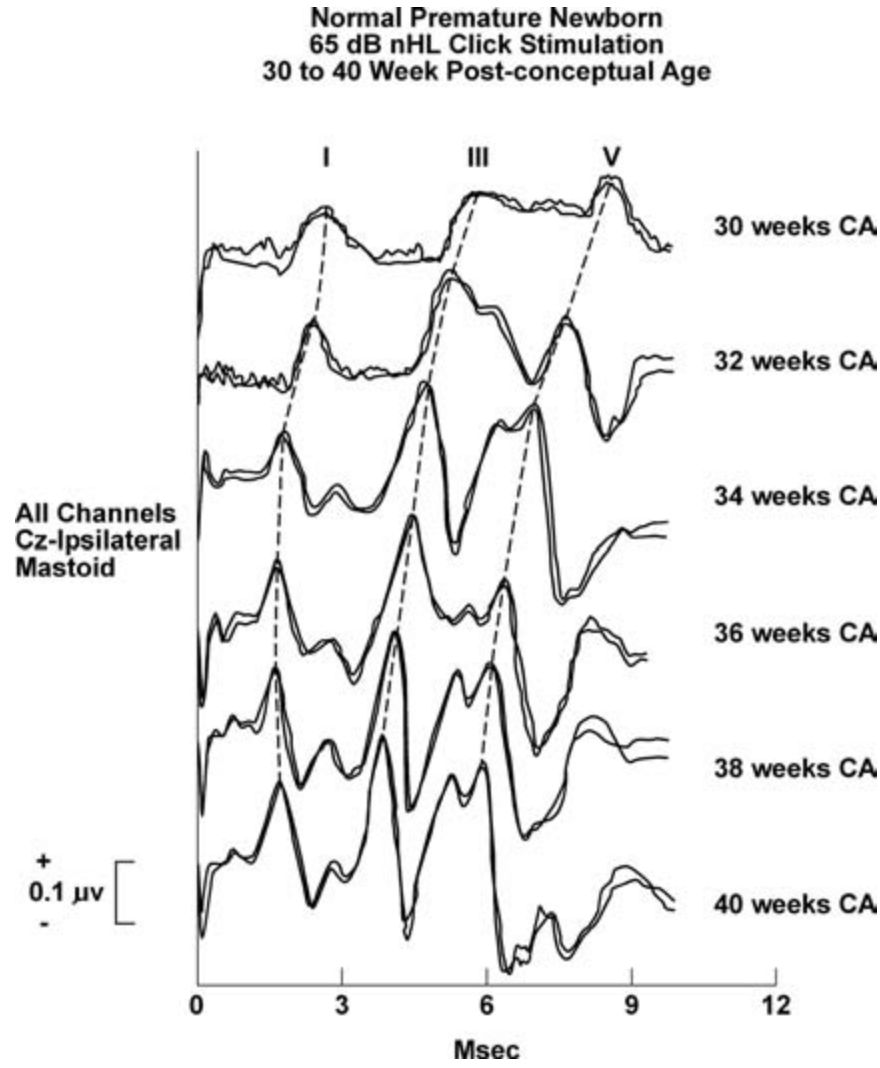

Fig. 5.24 Normal BAERs from 30 weeks to 40 weeks postconceptual age (CA). There is a progressive decrease in waveform latency, and increase in waveform amplitude and definition with increasing maturity. (With permission from Krumholz A, Felix JK, Goldstein PJ, McKenzie E: Maturation of the brain-stem auditory evoked potential in premature infants. *Electroencephalogr Clin Neurophysiol* 62:124–134, 1985.)

KEY CLINICAL QUESTIONS

BAER studies are helpful for…

- Children with suspected hearing loss who are younger or otherwise unable to cooperate.
- High-risk newborns with prematurity, intrauterine growth retardation, hyperbilirubinemia, possible intrauterine infection, meningitis or sepsis, exposure to ototoxic medications such as aminoglycosides, presence of a syndrome associated with hearing impairment, or family history of deafness.
- Infants or young children recovering from meningitis.

fied above as neonatal risk factors may also be studied in this way, such as infants and young children recovering from bacterial meningitis.

The latency of wave I may be delayed by conductive problems, such as an occluded external ear canal, or middle ear infection or effusion. However, in the absence of neurological disease, subsequent waveforms and interpeak latencies should be normal.

BAER studies are known to be abnormal in a number of different clinical conditions, and therefore may complement the clinical exam and other areas of testing in selected circumstances. BAER studies are sensitive to brainstem dysfunction but are nonspecific as to the underlying cause. Many of the neurodegenerative diseases, particularly the leukodystrophies, result in BAER abnormality. For some, most importantly Pelizaeus–Merzbacher disease, the BAER may be markedly abnormal early in the course of the illness, and therefore helpful with the initial diagnostic evaluation. (Definitive diagnosis for roughly 75% of such cases is now made by determining a mutation in the *PLP* gene, coding for proteolipid protein.) The degree of abnormality typically increases with disease progression, and therefore BAER findings may offer an objective way of following the clinical course of these diseases, and potentially the response to therapeutic interventions.

Somatosensory evoked potentials appear to be more specific than BAERs with regard to predicting poor outcome from hypoxic-ischemic injury in children (see below).

Unfortunately, BAER studies do not appear to be helpful with respect to identifying children or family members at-risk for sudden infant death syndrome (SIDS).

Somatosensory evoked potentials

Clinical indications

Somatosensory evoked potentials (SSEPs) allow for noninvasive and objective assessment of the peripheral, spinal, and cerebral somatosensory pathways. As with other evoked potential modalities, SSEPs complement the clinical exam and other diagnostic studies in selected circumstances. SSEPs can demonstrate the presence or absence of conduction deficits in the somatosensory pathways, and in the process can contribute to the localization of neurological lesions.

Technical features and anatomic considerations

Peripheral nerves are stimulated with very brief but repetitive application of alternating electrical current to the overlaying skin. The peripheral nerves utilized in common clinical practice are mixed sensory and motor nerves. Sensory conduction activated by electrical stimulation is mediated almost exclusively by large, myelinated nerve fibers. Activation of motor nerve fibers also results in orthodromic conduction to innervated muscles, resulting in a visible twitch, acting as an easily observed clinical confirmation of successful electrical activation. Antidromic (proximal) conduction through motor nerves also contributes to the recordable waveforms generated by peripheral structures such as brachial plexus at Erb's point, or other peripheral recording points.

Waveforms recorded from central (spinal or cerebral) electrode locations result from activity in sensory conduction pathways only. Common recording locations are the posterior cervical spinous process of C7, and the contralateral scalp for upper extremity (median or ulnar) stimulation. For lower extremity stimulation (posterior tibial or peroneal), a lumbar recording electrode, commonly at the L1 level, is also used.

The physiological generator of the peripheral waveforms, such as the Erb's point response, is the collective volley of action potentials traveling through the subjacent nerve structures. The central waveforms are more complex. Spinal responses are generated both by the volley of ascending action potentials in the posterior columns, as well as by postsynaptic activity in the dorsal gray matter of the cord.

PEARLS & PERILS

Somatosensory Evoked Potentials (SSEP)

- SSEPs provide information about both peripheral and central sensory conduction pathways. If a peripheral disturbance is suggested, results should be correlated with EMG and nerve conduction studies.
- SSEPs can detect focal conduction deficits that may escape detection with current imaging technologies, and can assist with the evaluation of multifocal or demyelinating disease processes.
- Peripheral nerves mature more quickly than central sensory pathways.
- Most of the signal for SSEPs travels through the posterior columns of the spinal cord. Accordingly, SSEPs are relatively insensitive to diseases that may affect the anterior portions of the cord exclusively.

It is important to be aware that SSEP signals are conducted primarily through the posterior columns. Therefore SSEP studies are typically not as sensitive to pathology that may affect the anterior portions of the spinal cord.

The scalp response, recorded by electrodes placed over the cortical sensory representation areas for either upper or lower extremities, consist of postsynaptic activity in the sensory nuclei of the thalamus, projected to the scalp as a far-field surface negative wave. This is followed shortly thereafter by a largely surface negative near-field wave generated by activation of sensory cortex in the parietal lobe, followed by an equally prominent surface positive peak. These findings are illustrated in Figs. 5.25a and 5.25b.

Developmental changes

Myelination, and therefore conduction velocity, matures more quickly in the peripheral nerves in comparison to the central sensory conduction pathways. Peripheral nerve conduction velocities reach adult values around 3–4 years of age, while interpeak latencies that reflect central conduction velocities appear to reach adult values around 6–8 years of age.

Because of this relative immaturity, SSEP waveform components, most commonly the cortical peaks, may not be present in all normal newborns. In one study, 33% of term newborns failed to demonstrate a cortical SSEP peak, with

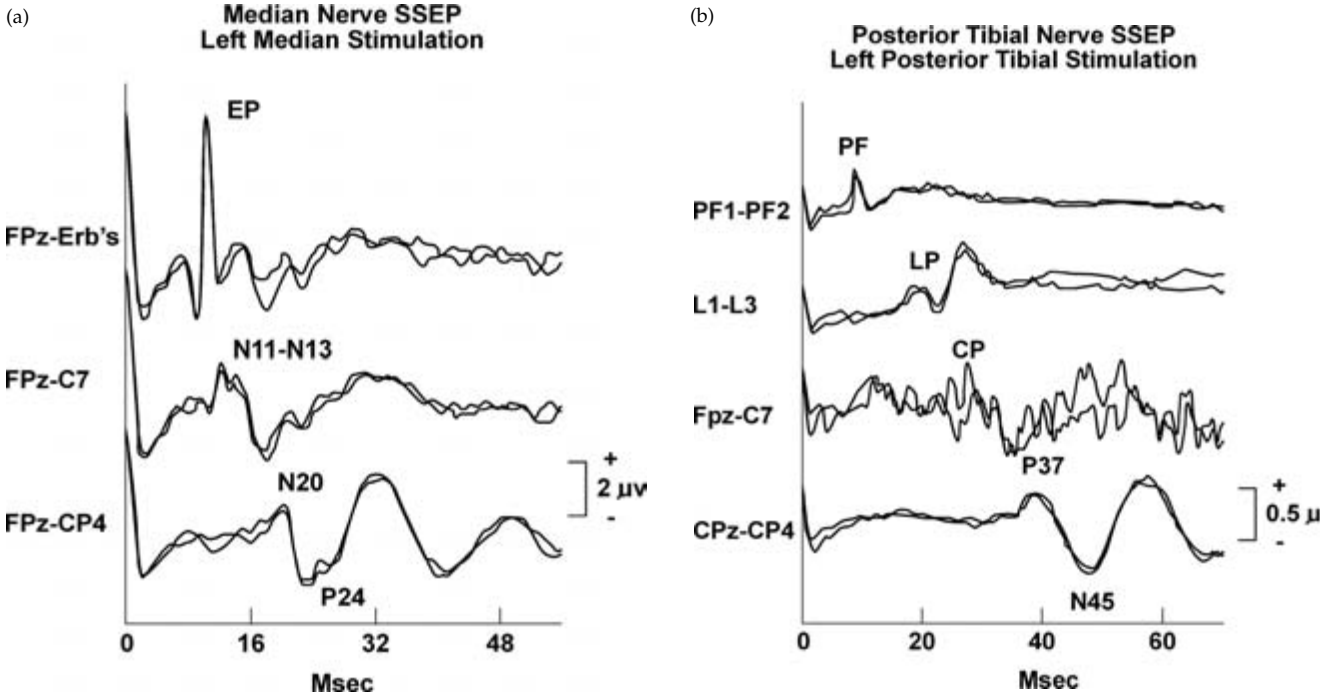

Fig. 5.25 (a) Representative SSEP waveforms in a normal 14-year-old boy. Median nerve stimulation results are shown in three channels. The top channel shows the peak at Erb's point, representing the volley of action potentials traveling through the brachial plexus. The second channel down shows the cervical peak, with bifid features. The first negative potential (N11 in this derivation) represents the volley of action potentials traveling through the underlying posterior columns, while the second of the two peaks (N13) is due to postsynaptic activity in dorsal gray matter of the cord. The bottom channel demonstrates the response at the contralateral scalp. CP4 is the "active" electrode over the arm/hand area, and the polarity convention reveals an initial upgoing, scalp negative peak (N20), followed by a downgoing, scalp positive peak (P24). The N20 is due to thalamic activation, projected out to the scalp electrodes, while the subsequent P24 is generated in parietal sensory cortex. (b) SSEP study of lower extremity in same normal 14-year-old boy. Responses to stimulation of posterior tibial nerve at the ankle are shown in four channels. The top channel shows the ascending volley of action potentials recorded at the popliteal fossa (PF). The second channel demonstrates the lumber peak (LP), recorded with a pair of electrodes at L1 and L3. Like the cervical peak to median nerve stimulation, this waveform is a combination of the ascending volley in posterior columns, as well as postsynaptic activity in dorsal gray matter of cord at the level of entry. The ascending volley traveling through cervical cord from the lower extremities is shown in the third channel. This waveform is difficult to record, and may be absent in normals. The bottom channel shows the response at the scalp. CPz is now the "active" electrode, as it is closer to the sensory cortex for leg near the sagittal midline. The surface negative peak due to thalamic activation is not well seen, and the major upgoing, scalp positive potential is due to activation of the primary sensory cortex (analogous to the P24 to median nerve stimulation). The polarity conventions used in our laboratory account for the P24 going downward in Fig. 5.25a and the P37 going upward in Fig. 5.25b. However, both are surface positive potentials generated by activation of somatotopic cortex.

all subjects demonstrating this peak at 2 months of age (Willis 1984). This highlights the need to avoid over-interpretation of abnormal SSEP studies in the newborn. Fig. 5.26 shows the evolution of median nerve SSEP features with age during infancy (Laureau 1988).

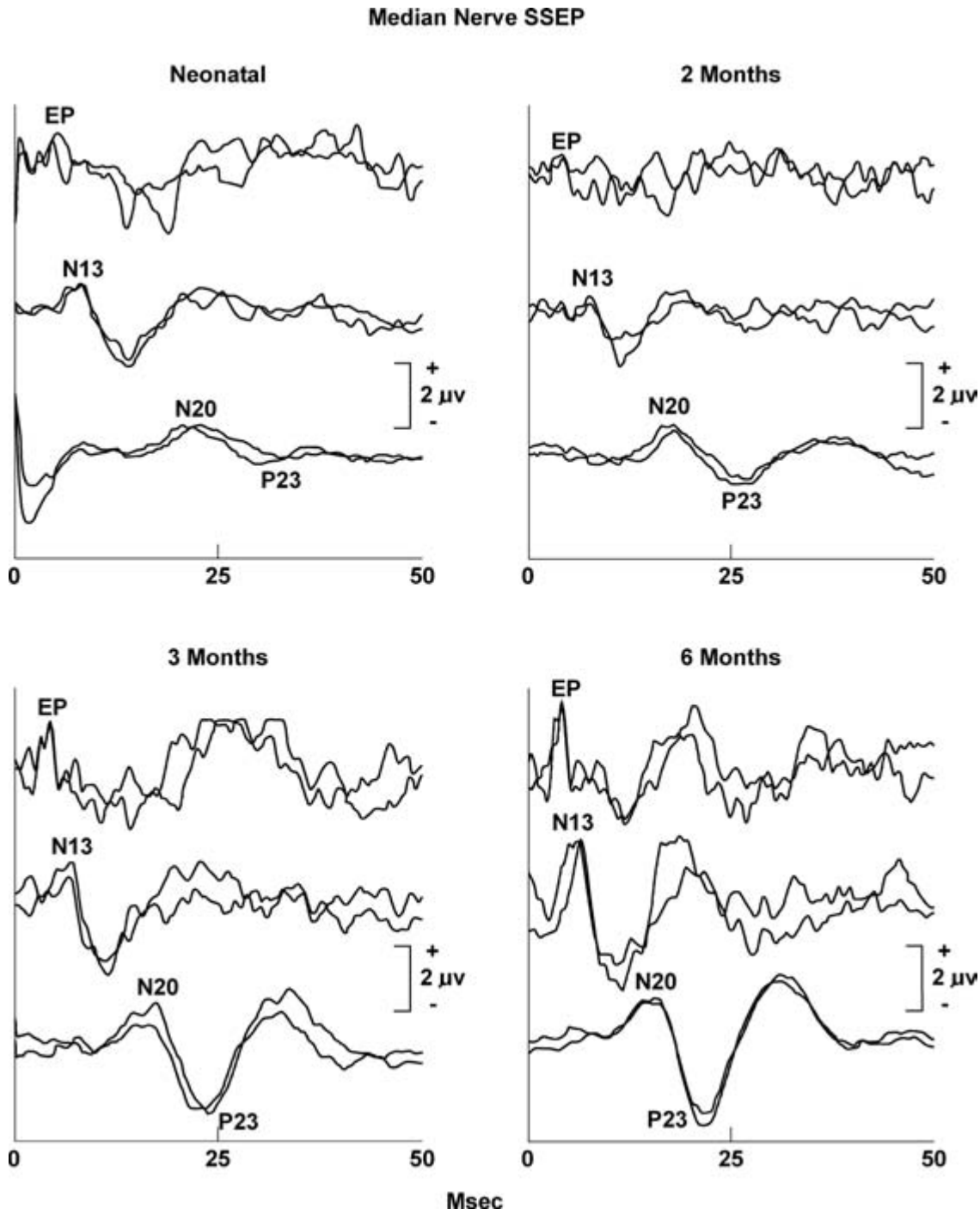

Fig. 5.26 Evolution of median nerve SSEP latencies and morphologies with increasing age during infancy. EP represents the peak at Erb's point (brachial plexus), N13 represents the main negative potential recorded from the posterior cervical region, and N20 and P24 represent the main negative and then positive potentials recorded from contralateral scalp. N13, N20, and P24 are the names of the peaks, reflecting the usual latencies seen in normal adult subjects. The actual latencies must be measured for each study and compared to age-related normal values. (With permission from Laureau E, Majnemer A, Rosenblatt B, Riley P: A longitudinal study of short latency somatosensory evoked responses in healthy newborns and infants. *Electroencephalogr Clin Neurophysiol* 71:100–108, 1988.)

Clinical aspects

SSEPs can help localize single lesions within the nervous system, although their anatomic specificity is poor. As an example, a lesion can be localized to the thoracic spinal cord (involving the posterior columns) with normal median nerve SSEP results, along with abnormal posterior tibial SSEPs that show normal peripheral nerve and lumbar peaks, but delayed or abolished cervical and cortical peaks. From time to time an SSEP study can supplement the clinical examination and other studies. However, as discussed in the introduction to this chapter, the development of current imaging techniques has largely eclipsed the role of EP studies in localizing solitary lesions (tumor, hemorrhage, stroke, etc.).

SSEPs continue to be useful in demonstrating the involvement of sensory pathways in multifocal neurological disorders. The classic example is the role of SSEPs to help establish multiple lesions in "space and time" that are the hallmark feature of multiple sclerosis (MS). While the lesions within cerebral white matter are usually clearly seen on MRI, demyelinating lesions affecting the optic nerves or the spinal cord may not. Accordingly, EP studies (most notably VER and SSEP modalities) are clinically useful for those relatively uncommon cases of MS presenting in children or adolescents. They are equally useful for establishing the multifocal nature of monophasic, acquired disorders with demyelination, such as acute disseminated encephalomyelitis (ADEM), seen more commonly in children.

Not unexpectedly, most of the leukodystrophies have been reported to show abnormalities of SSEPs, including adrenoleukodystrophy, metachromatic leukodystrophy (MLD), Krabbe's disease, Pelizaeus–Merzbacher disease, and others. SSEPs may help to demonstrate peripheral as well as central sensory conduction disturbances in diseases where these coexist, such as MLD, Krabbe's, and Friedreich's ataxia. However, it must be recognized that the more specific genetic and enzymatic studies available for many of these neurodegenerative processes relegate EP studies to a secondary role in establishing the diagnosis. This on-going shift in diagnostic utility will continue with the tremendous advances in molecular medicine.

Similar to EEG, the role of evoked potential studies in modern pediatric neurology practice will be as a noninvasive modality to assess neurophysiological function, rather than to provide neurological localization or diagnostic specificity. A clinically important example of this role is the evaluation of children with coma, specifically with respect to making predictions of outcome. The absence of scalp responses to SSEP study is highly correlated with poor outcome (death, vegetative state or severe disability) in children with coma due to hypoxic-ischemic injury or cerebral trauma (DeMeirleir 1987, and multiple others).

KEY CLINICAL QUESTIONS

SSEP studies are helpful for…

- Children with suspected multifocal or demyelinating disease processes.
- Evaluating patients with possible posterior column dysfunction, particularly if imaging studies are unrevealing.
- Evaluating prognosis in children (but not newborns) with acute coma, due to known hypoxic-ischemic injury or severe cerebral trauma. Absent SSEP waveforms bilaterally at the scalp electrodes correlates with a poor outcome.

Intraoperative evoked potentials

Intraoperative evoked potential studies are utilized by the surgical team to avoid injury or damage to neural tissue, at a time when the patient is under anesthesia and therefore unavailable for standard clinical examination. Ideally, the changes in sensory (or motor) conduction, if detected early in the course of injury, can identify interventions that avoid or reverse the injurious process.

The intraoperative monitoring modalities provide information to the surgeon and anesthesiologist that are real-time or nearly real-time in nature, and this information can be incorporated with other known factors to tailor the procedure to the circumstances at hand. As an example, the surgeon may utilize the feedback from serial SSEP waveforms to assist with decision-making during evacuation of an intracerebral hemorrhage (see Fig. 5.27).

Mechanisms of potential iatrogenic injury in the OR include physical traction, either peripherally (as with positioning of the limbs) or centrally (as with tissue retraction), ischemia, or direct injury with instrumentation or resection.

The individual modalities selected are determined by the specific procedure under consideration and the risks that are associated with it. BAER and SSEP modalities are com-

PEARLS & PERILS

Intraoperative Evoked Potentials

- Allows the surgical team to monitor for neurological injury, potentially with the opportunity to reverse the process and protect function.
- Includes SSEP and BAER and additional modalities such as cranial nerve monitoring, intraoperative EMG, and motor evoked potentials.
- Can pick up changes at any time during the surgical process, including positioning.
- Provides real-time or very nearly real-time feedback to the surgeon and anesthesiologist. Along with multiple other factors, can assist with intra-operative decision making.

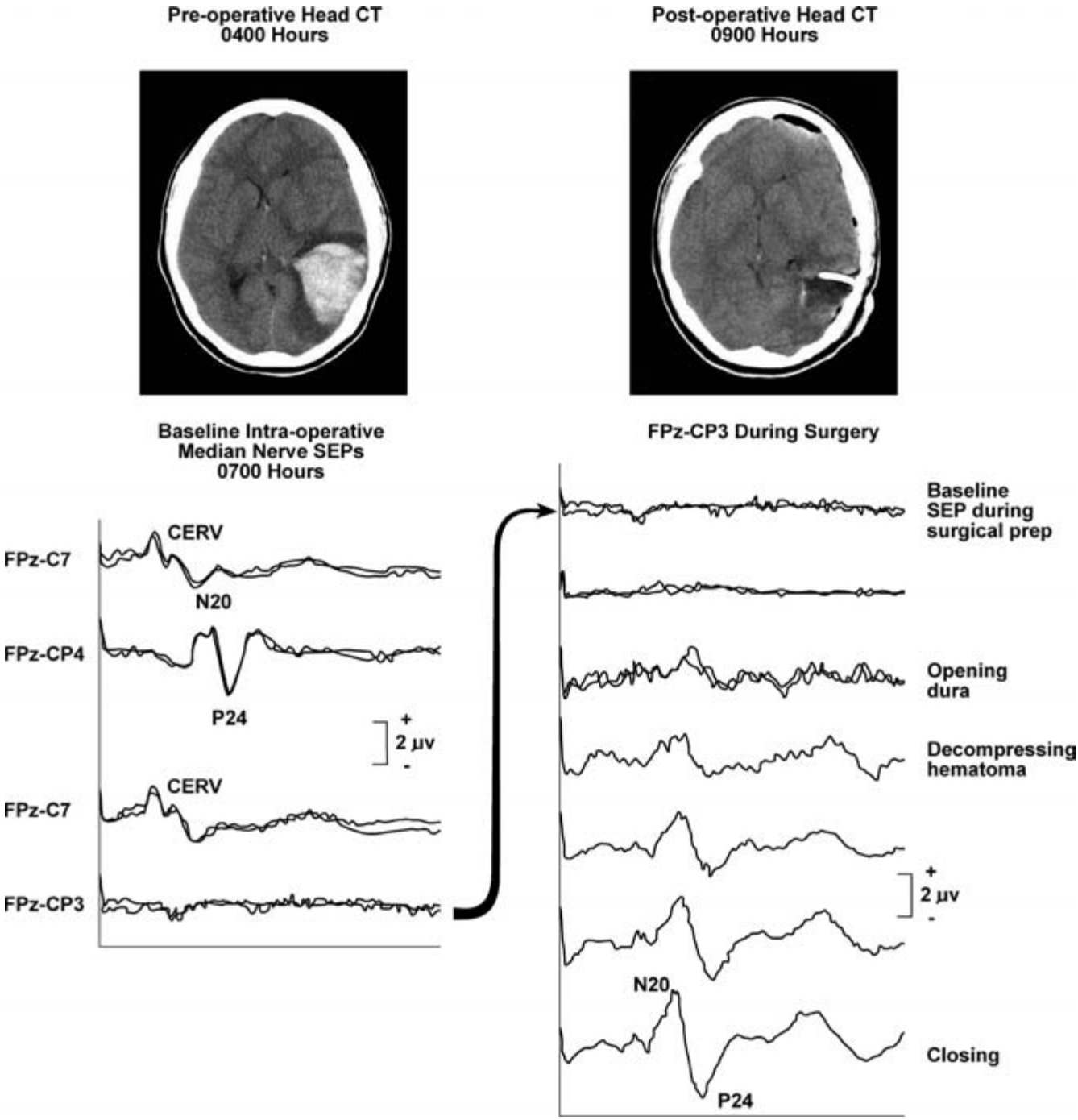

Fig. 5.27 Example of intraoperative evoked potential study showing changes in median nerve SSEP stimulation over the course of the surgical procedure. The patient is a 21-year-old woman who presented to the ER with coma and intracranial hemorrhage. The initial head CT is obtained at 0400 hours. Baseline median nerve SSEP responses in the OR are shown for both R and L sides. Subsequently the scalp response (FPz-CP3) to right median stimulation is shown at various time points during the surgical procedure to evacuate clot and resect an AVM. Recovery of the cortical response is observed. A postoperative head CT at 0900 hours is also shown.

KEY CLINICAL QUESTIONS

Intraoperative monitoring is helpful for…

- Many patients undergoing neurosurgical procedures, including craniotomy, skull base surgery, spinal surgery, or interventional neurovascular procedures such as embolization or stenting.
- Avoiding tissue injury during surgery due to traction, vascular compromise and ischemia, or tissue dissection and manipulation.
- Avoiding injury to peripheral nerves (or, in the presence of a mass lesion, the spinal cord) due to compression or stretch as a result of positioning and immobilization under anesthesia.

monly used, as are scalp EEG, motor evoked potentials, and surface or needle EMG monitoring of selected cranial or peripheral nerves. As an example, surgery within the posterior fossa can be monitored with BAERs, providing information relating primarily to the dorsum of the pons and midbrain, while more ventrally located ascending and descending tracts can be monitored with the use of SSEP or motor evoked responses. Skull base surgery can be assisted by additional monitoring of various cranial nerves by assessing compound muscle activity, occurring either spontaneously during the course of the procedure, or by electrically stimulating the nerves within the operative field, and monitoring conduction across a segment of concern.

Additionally, in conjunction with EEG, these modalities can be used to monitor levels of anesthesia and perfusion, as with recovery from hypothermic cardiac arrest procedures or other aggressive anesthetic techniques.

Conclusion

While the role of evoked potential studies has been reduced significantly in our current era of imaging and molecular diagnostics, they continue to provide an important tool for *functional* assessment of selected patients, particularly those who are too young or otherwise uncooperative for other means of testing. Newborn screening for hearing impairment and intraoperative monitoring are the most common use for these modalities in current clinical practice.

Acknowledgments

I wish to thank Dana L. Day, AuD, CCCA for her assistance with the preparation of this manuscript. I also wish to thank my son, Nicholas J. Kerrigan, for contributing his normal SSEP waveforms for Fig. 5.25. Lastly, I would like to acknowledge the technologists in the EEG and Evoked Potential Laboratory at the Barrow Neurological Institute for their expertise and support.

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CONSIDER CONSULTATION WHEN…

- Ophthalmological consultation should be obtained in all patients with visual complaints, or abnormal ERG or VER results, to exclude ocular disease and to provide a full examination of the retina.
- An audiologist should evaluate children with hearing complaints or abnormal BAER findings. An ear, nose and throat specialist should see patients with suspected middle ear disease, or abnormalities of the cochlea or vestibular structures.
- Further study with electromyography and nerve conduction studies should be considered for patients with SSEP findings that suggest a peripheral nerve disease process.

As the title states, a comprehensive textbook on clinical neurophysiology, including electromyography (EMG), electroencephalograph (EEG), and evoked potentials. An excellent single-text resource.

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Neuroimaging Techniques

Gary Hedlund, DO and James F. Bale Jr, MD

OUTLINE

Pediatric neuroimaging
Clinical applications

The past three decades have brought remarkable advances in the ability to image the nervous system of the young child. This era saw the development of cranial ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), as well as improved methods of catheter angiography. The clinician can image the central nervous system (CNS) of newborns, infants, young children, and adolescents safely, accurately, and in most instances, noninvasively. Although the new imaging modalities enhance greatly the clinician's ability to examine the structures of the CNS, the availability of these multiple techniques poses many new questions for the clinician. Should the clinician use US, CT, or MRI? Which MRI sequences should be obtained? Should the CT or MRI be enhanced? What are the relative sensitivities of magnetic resonance angiography, conventional catheter angiography, and CT angiography?

This section provides a technical summary of the available imaging modalities and presents a conceptual framework by which clinicians can make relevant decisions regarding the choice of modalities. The chapter focuses on common neurologic conditions, including the complications of the neonatal period, infections (congenital or acquired), cranial cerebral trauma, headaches, stroke, neurocutaneous disorders, and seizures. By collaborating with radiologists clinicians can make safe and cost-effective decisions regarding the optimum utilization of these new and sensitive techniques.

Pediatric neuroimaging

Imaging modalities

Imaging the pediatric neural axis has evolved rapidly in the last three decades. All of the imaging tools used to diagnose pediatric CNS disease, including sonography, CT/CTA, MRI and advanced MR techniques, nuclear medicine brain imaging (SPECT, PET), magnetoencephalography (MEG), and conventional angiography, have shown robust development. The purpose of this chapter is to emphasize the practical applications, strengths and weaknesses of currently available imaging techniques.

Patient preparation and sedation

The success of a pediatric neuroimaging study begins with consultation between the clinician and the neuroradiologist. The exchange of relevant clinical information allows selection of the best imaging tool to answer the clinical question at hand. The imaging process continues with further preparation of the patient, including sedation when necessary. In our pediatric imaging practice, the majority of cranial-spinal ultrasound, and CT/CTA are accomplished without sedation or with a short acting agent (midazolam and/or ketamine). When scheduling patients for longer imaging examinations,

such as MRI, conscious sedation with IV pentobarbital for patients less than 8 years of age is typically necessary. Anesthesia-directed sedation is considered for our pediatric patients less than 37 kg in weight, children with autism, severe developmental delay or movement disorders. Patients at any age with airway obstruction, achondroplasia, cardiovascular disease, pulmonary compromise, or other complex medical conditions require an anesthesiology consultation. Pediatric patients undergoing cerebral angiography may be studied with either conscious sedation or general anesthesia depending upon patient age, level of patient cooperation, and anticipated length of examination.

Ultrasonography

Ultrasound technology with the evolution of high-resolution variable mgHz probes, robust Doppler, and harmonic imaging has significantly improved clinical image quality, and expanded the applications of pediatric neurosonography. The portability of the ultrasound unit allows this advanced technology to come to the bedside. The most frequent indication for real-time pediatric neurosonography is the evaluation of the neonatal brain for intracranial hemorrhage (Fig. 5.28). The anterior and posterior fontanels and transmastoid foramen provide acoustic windows for the investigation of anatomic regions susceptible to hemorrhage.

Other important neonatal applications of cranial sonography include the evaluation of suspected periventricular leukomalacia (PVL), cerebral edema, congenital brain malformations, hydrocephalus, and destructive lesions. The robust color and pulse Doppler capabilities of current ultrasound equipment allow interrogation of central intracranial arteries and veins. In infants and children, transcranial Doppler (TCD) has been useful in the evaluation of vasculopathy, such as sickle cell disease.

Intraoperative cranial ultrasound applications include: localization of peripheral brain lesions, guidance of shunt catheters, and characterization of cerebellar tonsillar impaction in patients with Chiari I who are being considered for duroplasty. Spinal sonography is commonly used to evaluate the dorsal lumbosacral spine in newborns and infants with sacral dimples in an effort to detect occult spinal dysraphism and cord tethering. This is an efficient screening tool up to 6 months of age.

PEARLS & PERILS

Sonography

- The cranial fontanels are reliable acoustic windows up to 8–10 months of age.
- The major limitations of cranial sonography are the "blind spots" of the peripheral cerebral hemispheres.
- PVL is underestimated with cranial ultrasound. The gold standard for infants at risk is MRI.
- Spinal sonography for occult spinal dysraphism is most useful for patients less than 3 months of age, but diagnostic studies can be performed up to 6 months. Beyond this age MRI is advised due to increasing acoustic impedance of the posterior neural arch elements.
- In the evaluation of complex lumbosacral skin lesions (skin covered mass, verrucous hemangioma, dermal sinus, hypertrichosis or a combination of the above) MRI is recommended.

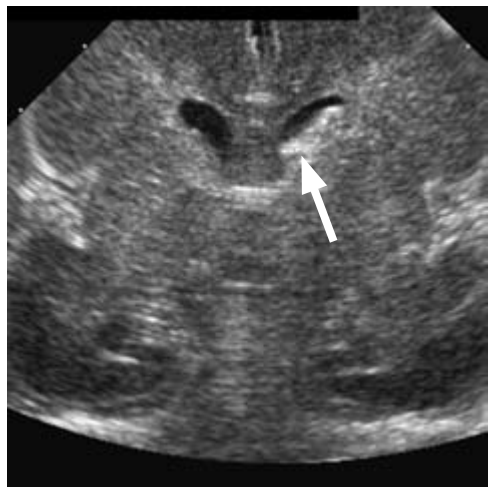

Fig. 5.28 Normal cranial ultrasound. Coronal ultrasound in a very low birth weight (VLBW) preterm newborn shows a smooth appearance of the cerebral hemispheres consistent with prematurity and a left Grade I, germinal matrix hemorrhage (arrow).

Computerized tomography

Godfrey Hounsfield developed the first clinical prototype CT scanners in the early 1970s. This revolutionary harnessing of x-ray technology earned him the Nobel Prize in 1979. The last three decades have brought engineering improvements culminating with the current multidetector CT scanner, which performs complex examinations with lightning speed. Continuous efforts have also been made to reduce radiation exposure with conventional as well as advanced CT technologies.

Conventional CT remains an important tool for the assessment of acute head injury, detection of intracranial hemorrhage, acute neurologic decline, status epilepticus, cranial facial malformations, investigation of lesions of the temporal bone and skull base, nasal obstruction in the newborn without evidence of intranasal mass and the follow-up of patients with intracranial shunts (Fig. 5.29).

Contrast enhanced CT contributes to the diagnostic evaluation of patients with cranial tumefactions, meningoencephalitis, suspected arteriovenous malformations, intracranial

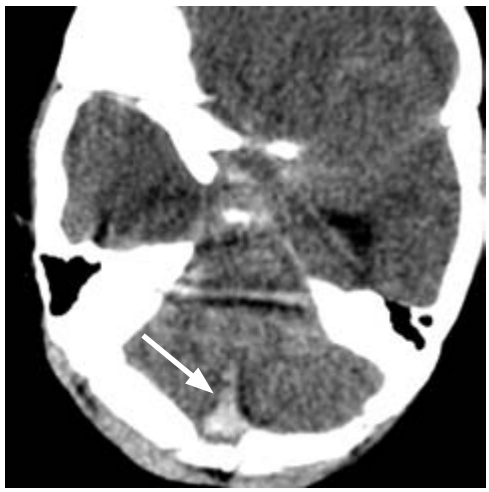

Fig. 5.29 Subarachnoid hemorrhage secondary to spinal vascular malformation. Axial noncontrast head CT (NCCT) demonstrates hemorrhage filling the cisterna magna (arrow).

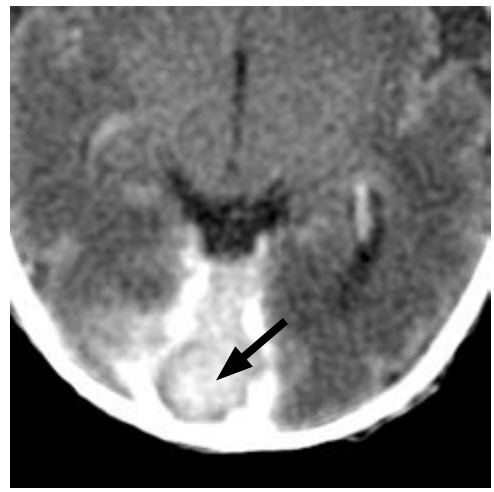

Fig. 5.30 Venous sinus thrombosis. Contrast enhanced CT (CECT) demonstrates thrombus within the torcular herophili (arrow).

venous thrombosis, and complicated sinonasal infections (Fig. 5.30).

CT angiography is a less invasive alternative to conventional catheter angiography. Multidetector scanners with improvements in image post processing speed have helped this technology to blossom. Indications for CTA in our pediatric population include: detection of intracranial aneurysms (screening patients at high risk and detection of low profile "blister" aneurysms), evaluating CNS and visceral vasculature in the work-up of suspected vasculitis, in the patient weighing less than 10 kg (where the risk of femoral artery injury is highest), penetrating neck injuries, and the evaluation of nonocclusive arterial dissection (Fig. 5.31). CTA used in the acute assessment of the unstable patient with cerebral hematoma secondary to ruptured arteriovenous malformation or aneurysm may provide valuable preoperative information to the neurosurgeon regarding the relationship of the malformation to the clot bed. Patients who are not good candidates for MRA (those with pacemakers, and surgical clips juxtaposed to vessels of interest) can often be successfully studied with CTA. We have found the spatial resolution of CTA to exceed MRA when studying the neck vasculature (Fig. 5.32). There is much more motion (swallowing and respiration) artifact to contend with when performing pediatric neck MRA.

Perfusion CT affords a quantitative measurement of regional cerebral blood flow. There is sequential acquisition of CT sections during IV contrast administration. Using the central volume principle, regional cerebral blood volume (CBV), blood mean transit time (MTT), and regional cerebral blood flow (rCBF) can be computed. The regional cerebral blood flow map deduced from perfusion CT leads to quantitative results, which closely approximate xenon CT. Some centers are also gaining experience with perfusion CT in the

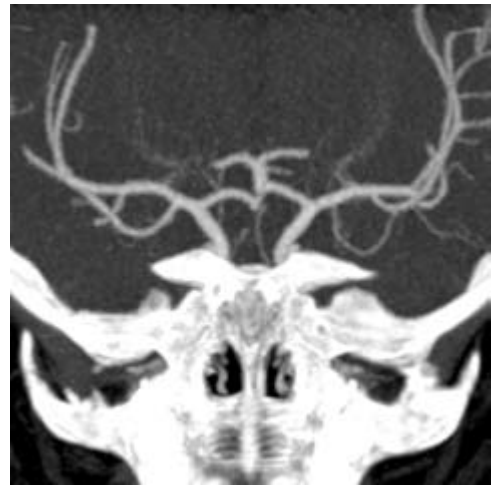

Fig. 5.31 Normal circle-of-Willis CTA.

emergency department setting after conventional CT in the assessment of acute stroke. This technology may find a future role with respect to inclusion criteria for thrombolysis protocols. Perfusion CT may also be utilized following cerebral synangiosis to evaluate for improved regional cerebral perfusion.

Magnetic resonance imaging

Perhaps nowhere in pediatric neuroimaging has there been more progress than in magnetic resonance (MR) imaging and advanced MR applications. The development of biologically safe high field strength MR systems, more powerful MR gradients, novel coil development, re-engineered image processing, and robust scan sequences has led to faster scan times and the capability to overlay functional MR informa-

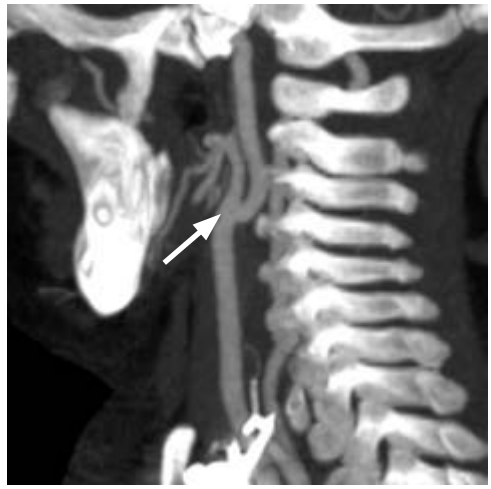

Fig. 5.32 CT angiography. Oblique neck CT angiography (CTA) showing a normal carotid bifurcation (arrow).

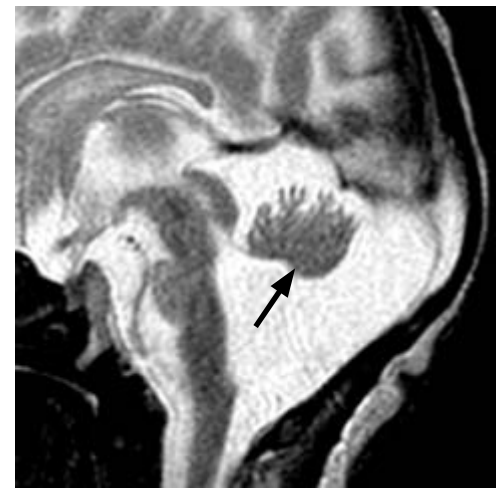

Fig. 5.33 Dandy Walker complex. Sagittal fast spin-echo T2 (FSE T2) image demonstrates upward rotation of the hypogenetic vermis (arrow). Note the prominent retrocerebellar CSF collection.

tion upon high resolution anatomic imaging. The ability to create multimodal MR acquisitions within practical scanning times has led to the rapid accumulation of clinically useful information. Advanced MRI techniques include diffusion weighted imaging (d-MRI), perfusion imaging (p-MRI), magnetic resonance spectroscopy (MRS), magnetic resonance angiography (MRA), magnetic resonance venography (MRV), functional MRI or cortical activation (f-MRI), and FAST scanning techniques for fetal MR imaging.

Conventional magnetic resonance imaging (MRI). This clinically useful modality represents the backbone for investigation of diseases of the pediatric CNS. Evaluation of cerebral malformations, assessment of traumatic neurologic injury, characterization of neoplastic and inflammatory disorders, and the diagnosis of early neurodegenerative disease are a few of the practical clinical applications of MRI (Fig. 5.33). Contrast administration becomes a helpful adjunct in the evaluation of neoplasms, demyelinating disease, suspected meningoencephalitis and its complications, and vascular malformations.

Diffusion weighted imaging (d-MRI). The signal intensity in a diffusion weighted MR image is a function of the random translational motion of water molecules (Brownian motion). Conditions that produce cell membrane depolarization such as acute ischemic stroke will result in cytotoxic edema, which is one underlying mechanism responsible for diffusion-weighted changes in the brain (Fig. 5.34). In cytotoxic edema, the apparent diffusion coefficient (ADC) of water in ischemic tissue is reduced relative to that of normal brain water and allows the ischemic territory to be visualized as a hyperintense region on trace diffusion images and a hypointense region on the ADC map. Other causes of restricted diffusion include: necrotizing infection (herpes encephalitis), mitochondrial cytopathies, toxic substances such as intermediary metabolites and organic acids, highly cellular tumors, empyema, abscess, and acute demyelination (Fig. 5.35).

Diffusion tensor imaging (DTI). Diffusion tensor brain imaging and tractography (DTI) exploit the concepts of water molecule motion properties in all directions (isotropy) and in prescribed paths (anisotropy). These techniques may be helpful in the evaluation of a structural lesion and its relationship to white matter tracts. Additionally, further investigation of developmental malformations, such as agenesis of the corpus callosum and holoprosencephaly, may be further understood by assessing the structural neural pathways with DTI. DTI may also bring insights to the investigation of cognitive abnormalities and developmental delay.

PEARLS & PERILS

Computed Tomography

- Requires exposure to ionizing radiation.
- Scan times are brief, rarely requiring sedation.
- Remains the method of choice for detecting acute hemorrhage and parenchymal calcifications.
- Lower anatomic resolution compared to MRI for the evaluation of temporal lobes, posterior fossa, and the cranial-cortical interface due to beam-hardening artifact.
- Underestimates acute ischemia.
- CTA is becoming a viable option to MRA and catheter angiography in many clinical settings.
- Remains a helpful adjunct in the evaluation of sinonasal diseases and their relationship to intracranial structures.

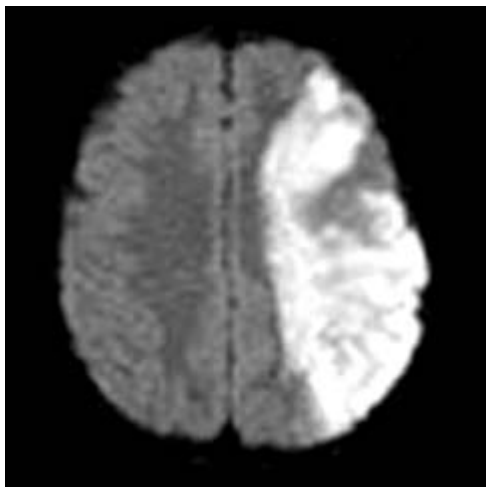

Fig. 5.34 Thromboembolic stroke secondary to carotid dissection. Diffusion weighted image shows a large left middle cerebral artery territory infarction.

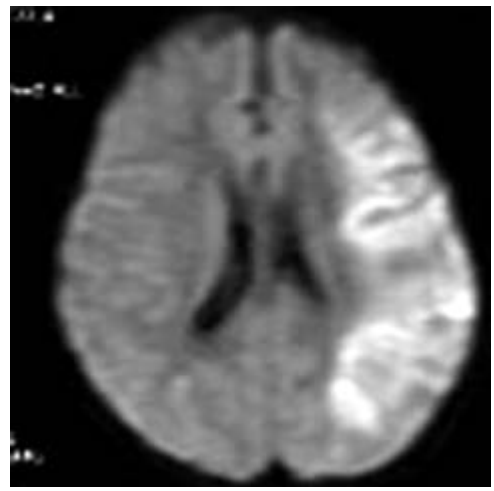

Fig. 5.35 Herpes encephalitis. This 16-month-old child with new onset seizures, fever, and confirmed HSV-1 infection demonstrates left MCA distribution diffusion restriction.

Noninvasive MRI vascular imaging (magnetic resonance angiography and venography [MRA, MRV]). These supplements to standard MR imaging provide valuable alternatives to catheter angiography and venography in the evaluation of intracranial vascular disease. MRA yields information regarding signal generated from protons in flowing blood (Fig. 5.36). Flow direction, volume and velocity of flow will affect signal and the apparent size of the vessel being studied. The MRA techniques most commonly utilized in the setting of pediatric neuroradiology are time of flight (TOF) MRA and phase contrast angiography (PCA). Time of flight techniques take advantage of the differences in signal amplitude between stationary tissue and flowing blood, whereas phase contrast angiography exploits the differences in signal phase between flowing and stationary spins (protons). Physiologic and anatomic factors influence the image quality and signal from vascular imaging studies. Relevant factors include blood flow direction relative to the imaging plane, geometry of the vessel being studied, velocity of blood flow, and complex flow patterns. The T1 relaxation of stationary tissue such as parenchymal hemorrhage may create a pitfall to TOF MRA image interpretation. In the setting of parenchymal bleed PCA is preferred.

Clinical applications of MRA include the investigation of developmental vascular anomalies or anatomic variations, such as embryonic basilar to carotid connections, evaluation of unusual vessel turns that may mimic an aneurysm or varix, relationship of tumors to vessels (displacement vs. encasement), vessel occlusion, dissection, and suspected arteriovenous malformations (Figs 5.37 and 5.38). Emphasizing venous flow (MRV) is helpful in children with intracranial venous thrombosis or pseudotumor cerebri and in the preoperative evaluation of tumors and encephaloceles juxtaposed to venous sinuses (Fig. 5.39).

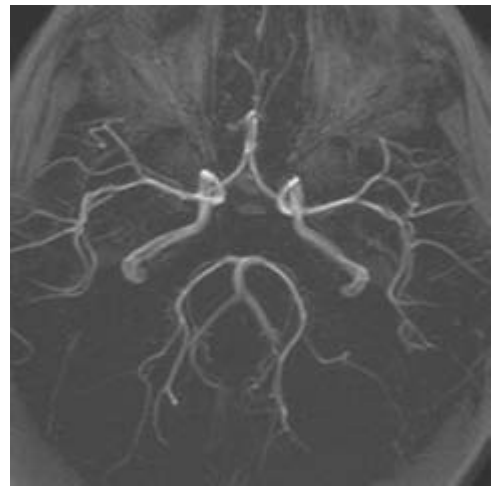

Fig. 5.36 Magnetic resonance angiography. Time of flight MRA demonstrates a normal circle of Willis.

Magnetic resonance spectroscopy (MRS). This clinically useful MRI technique allows the evaluation of brain metabolism in vivo. It has proven useful in the evaluation of pediatric brain tumors, metabolic afflictions, heritable disorders, epilepsy, chronic infection (HIV), demyelinating disease, hypoxic ischemic encephalopathy, head trauma, developmental delay and hypotonia (e.g. creatine deficiency) (Fig. 5.40). Technical limitations to acquiring diagnostic magnetic resonance spectroscopy include the presence of dental braces, intracranial hemorrhage, and patient motion, all of which create susceptibility artifacts.

Cortical activation (f- MRI). Functional cortical activation utilizes the blood oxygen level dependent (BOLD) technique to examine changes in the oxy/deoxy-hemoglobin ratio after

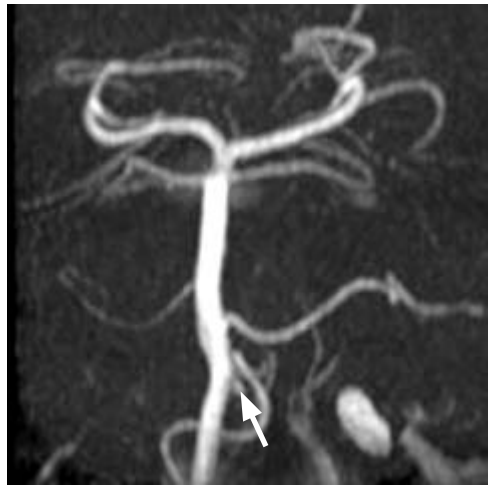

Fig. 5.37 Vertebral artery dissection. Time of flight MRA shows occlusion of the left vertebral artery (arrow).

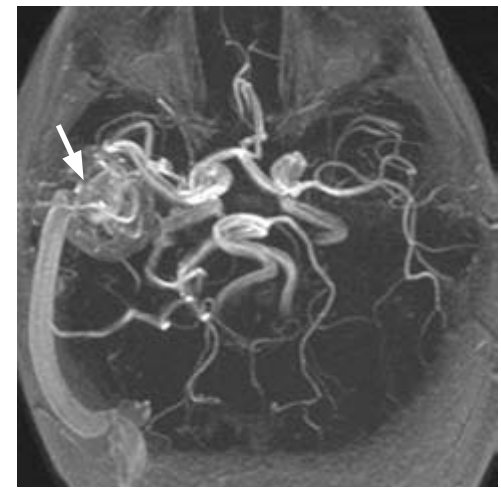

Fig. 5.38 Arteriovenous malformation (AVM). MRA shows prominent flow signal within a peripheral right middle cranial fossa arteriovenous malformation (arrow).

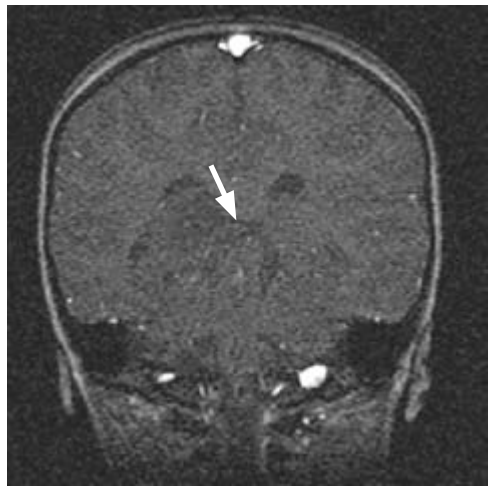

Fig. 5.39 Intracranial venous thrombosis. Coronal magnetic resonance venogram (MRV) shows loss of normal flow signal within the internal cerebral veins (arrow).

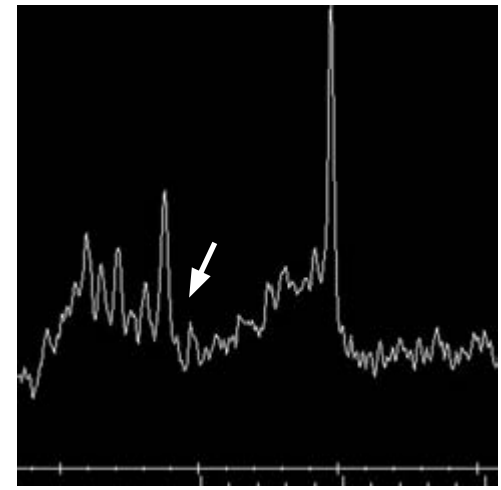

Fig. 5.40 Magnetic resonance spectroscopy (MRS). There is absence of the creatine peak (arrow) in a patient with guanidinoacetate methyltransferase deficiency (GAMT).

activities (paradigms) designed to stimulate a particular area of the brain. There are even novel techniques for the sedated pediatric patient. Functional MRI may be used to noninvasively map eloquent regions of the brain with respect to the presence of a structural mass. This noninvasive information is useful for surgical planning. Functional MRI paradigms may activate the motor and visual cortex, interrogate language, and query memory. In many centers f-MRI has replaced WADA testing.

Fetal MRI. The development of fast MRI sequences has opened the door for the evaluation of the fetal brain, head and neck, and body malformations. In many cases MRI provides significant supplemental information to fetal sonography. Certainly, before decisions are made to interrupt a pregnancy on the basis of sonographic observations, fetal MRI may provide additional clinically useful information.

Magnetoencephalography (MEG)

This is a noninvasive technique utilized for localizing and characterizing the electrical activity of the central nervous system by measuring the associated magnetic fields emanating from the brain. Every electrical current in the brain generates a small magnetic field according to the right hand rule of physics. This small magnetic field is detected via an instrument called a biomagnetometer. MEG provides information entirely different from that of CT or MRI. The latter two modalities provide structural and/or anatomic information. MEG provides functional mapping information.

Magnetic Resonance Imaging

PEARLS & PERILS

- With increases in MRI field strength anatomic resolution continues to improve.
- The peripheral cerebral cortex, temporal lobes, cerebellum, and brain stem are exquisitely visualized without osseous artifact that is typical for CT.
- Contrast agents (gadolinium) can enhance evaluation of the blood brain barrier, the CNS reticuloendothelial system and the extracellular spaces.
- Sensitivity is greater than CT for detecting structural lesions, developmental malformations, demyelinating foci and disruptions of the blood brain barrier.
- Magnetic resonance spectroscopy may aid in distinguishing tumefactions (neoplasm vs. tumefactive demyelination), inflammatory/infectious conditions, toxic/metabolic insults, and ischemia.
- MRI is insensitive to detect calcification.
- Sedation is required in almost all children less than 8 years of age.
- MRI and all advanced MR techniques such as MRA and MRV are susceptible to motion (swallowing, respiration, and vascular pulsation). Thus, we currently prefer CTA to MRA when evaluating cervical vasculature.
- MRV may overestimate the degree of venous sinus narrowing.

MEG information is often used along with data from other functional studies (SPECT, PET, and f-MRI).

Nuclear medicine brain imaging

These techniques derive images that reflect brain metabolism, and neural chemistry. The most developed techniques are single photon emission computerized tomography (SPECT) and positron-emission tomography (PET). For either SPECT or PET, knowledge of the type of seizure and its clinical localization is very useful information to the neuroradiologist allowing more accurate image interpretation. Currently SPECT, available in many centers, may offer the most widely available and widely applicable measure of neural behavior and offers spatial resolution similar to PET imaging. Many of the SPECT and PET tracers take advantage of the fact that cerebral perfusion and metabolism are tightly coupled. SPECT tracer such as technetium-99-m-hexamethylpropyleneamine (Tc-HMPAO), is extracted by brain tissue on the first arterial pass after intravenous injection, it is retained in the brain for several hours. This allows the patient to be imaged as soon the patient is stabilized following a seizure, or within hours after the seizure. SPECT imaging has been most useful in the ictal setting. The seizure focus shows increased ictal uptake (Fig. 5.41). During the interictal period the seizure focus is identified as a reduced region of perfusion or metabolism. The currently used PET radiopharmaceuticals include 18-FFDG PET 11-C-flumazenil PET (for temporal lobe epilepsy), and 11-C-alpha-methyltryptofane PET (identifies epileptogenic tubers in tuberous sclerosis).

Finally, subtracted SPECT and PET images may be coregistered with anatomic MR images to create multimodal overlap of functional and anatomic information.

Nuclear Medicine Brain Imaging

PEARLS & PERILS

- The choice of ictal or interictal studies is somewhat dependent upon institutional logistics.
- The availability of image integration software allows a fusion of SPECT and PET data with CT and MRI images.

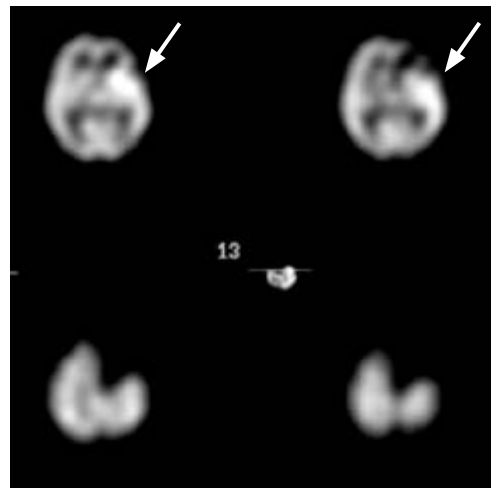

Fig. 5.41 SPECT nuclear medicine brain imaging. Axial ictal Tc-HMPAO SPECT image demonstrating increased radiotracer uptake adjacent to a region of brain injury (arrows).

Catheter angiography

In many clinical situations MRA, MRV, and CTA have supplanted catheter angiography. However, several important indications for catheter angiography remain. These include the initial characterization and follow-up of arteriovenous malformations or nonocclusive arterial dissections, preoperative evaluation of suspected meningothelial tumors, petrosal venous sampling in patients with Cushing's syndrome, and therapeutic applications, such as embolization of tumors, clot removal in the setting of venous thrombosis, and coil occlusion of congenital vascular abnormalities, such as vein of Galen malformations. In addition, the development of spiral (3D) angiographic techniques has diminished the contrast requirement and shortened examination time,

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Catheter Angiography

- There are growing applications of noninvasive vascular imaging (MRA, MRV, CTA).
- Risks of femoral artery occlusion rise with catheter angiography in patients less than 10 kg.
- General anesthesia is necessary in many pediatric patients requiring cerebral angiography.
- 3D and spiral catheter angiographic techniques reduce requirements for contrast and shorten examination time.
- Flow characteristics and associated stenoses within arteriovenous malformations are best evaluated with a catheter angiography.

which is critically important in the pediatric population (Fig. 5.42).

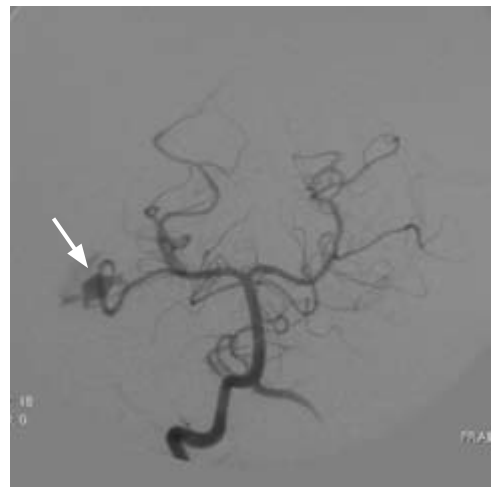

Fig. 5.42 Three-dimensional catheter angiography. In this patient with hereditary hemorrhagic telangiectasia (HHT), a right paratentorial arteriovenous fistula (arrow) is fed by the right posterior temporal artery.

Clinical applications

Disorders of the neonate

Full-term and premature infants commonly experience neurologic complications, including intracranial hemorrhage, seizures, post-hemorrhagic hydrocephalus, stroke, and infection. The choice of the neuroimaging modalities depends greatly upon the suspicions of the clinician and the ability of the infant to be transported safely to the imaging suite. Although cranial ultrasound, by virtue of its portable nature, has great utility in the unstable newborn infant with neurologic signs and symptoms, rapid acquisition CT and MRI can supplant ultrasound in certain disorders affecting the neonate.

Intracranial hemorrhage

Premature infants experience intracranial hemorrhage as a complication of germinal matrix hemorrhage and intraventricular hemorrhage (IVH). This condition directly relates to the degree of prematurity, but also reflects the integrity of the immature germinal matrix vasculature and alterations of cerebral blood flow that accompany prematurity and the complications of prematurity. The likelihood of IVH corresponds inversely with gestational age; approximately 20% of very low birth weight infants experience IVH, whereas the prevalence of IVH among infants >36 weeks is negligible. The severity of IVH is designated by grades I–IV (Table 5.2); infants with grades III and IV have increased risks of adverse outcomes, including developmental delay, seizures, and cerebral palsy (Fig. 5.43).

Infants with germinal matrix hemorrhage and severe IVH have increased risks of post-hemorrhagic hydrocephalus. This complication affects 25–35% of very low birth weight infants with IVH and reflects arachnoiditis and/or ventric-

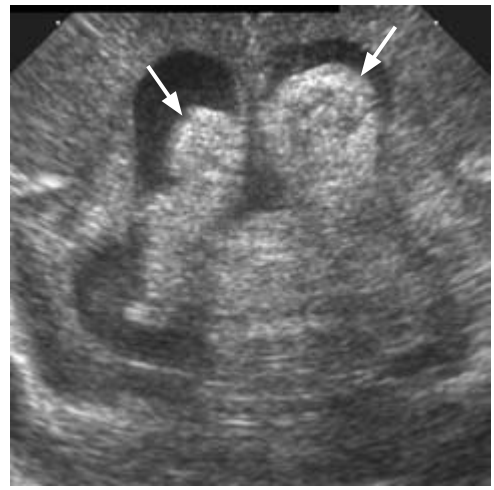

Fig. 5.43 Neonatal intracranial hemorrhage. Coronal cranial sonogram demonstrates intraventicular clot and ventricular dilation (arrows).

TABLE 5.2

Germinal Matrix and Intraventricular Hemorrhage

Grade I	Germinal matrix hemorrhage without intraventricular extension
Grade II	Germinal matrix hemorrhage with intraventricular extension filling <50% of the ventricular space
Grade III	Germinal matrix hemorrhage with intraventricular extension filling >50% of the ventricular space and causing ventricular dilation.
Grade IV	Germinal matrix hemorrhage with periventricular hemorrhagic infarction

ular outlet obstruction. Post-hemorrhagic hydrocephalus usually appears gradually during the first several weeks after birth and may be difficult to distinguish from passive ventriculomegaly during the early stages of evolution (Fig. 5.44).

In contrast to premature infants, term infants experience intracranial hemorrhage as a consequence of hypoxic ischemic encephalopathy, clotting disorders, or stroke. Term infants who sustain intracranial hemorrhagic with intraventricular extension are also at risk of post-hemorrhagic hydrocephalus. Cystic encephalomalacia, passive ventriculomegaly, or focal cerebral atrophy commonly develops in premature or term infants with stroke.

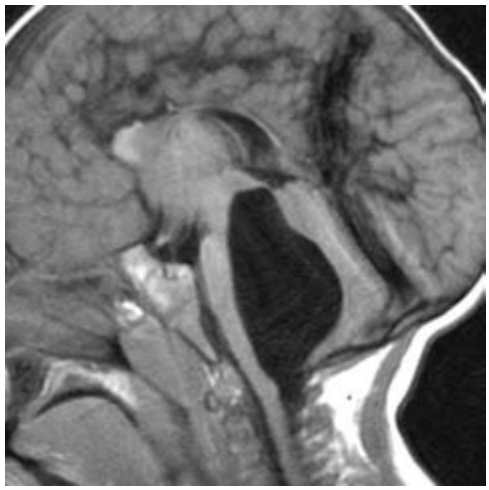

Fig. 5.44 Remote complication of intracranial hemorrhage of prematurity. Sagittal T1-weighted MRI demonstrates a trapped fourth ventricle as a complication of remote intracranial hemorrhage.

Cranial ultrasound remains an important screening study for the very low birth weight (VLBW) neonate. To detect hemorrhage we perform the first cranial ultrasound between 7 and 10 days of life. Serial sonograms track the evolution of intracranial hemorrhage and complications, such as hydrocephalus. Periventricular leukomalacia is manifest by early periventricular regions of hyperechogenicity followed by the development of periventricular cysts, and passive ventricular dilation (Fig. 5.45). Unfortunately, a significant number of neonates with PVL will have a normal initial and follow-up cranial sonogram. The subtle evolution of unexplained ventricular dilation suggests underlying PVL. It has become our policy to study VLBW neonates (<1200 g) with MRI nearing the time of discharge from the neonatal intensive care unit (30–50 days of life). This remains the gold standard for detecting PVL (Fig. 5.46).

Infection

Many different microorganisms, including bacteria, viruses, fungi, and protozoa, can infect the neonate as the result of intrauterine or postnatal acquisition. Congenital infections, historically designated as TORCH (*To*xoplasma gondii, *r*ubella, *c*ytomegalovirus, and *h*erpes) infections produce intracranial calcifications, hydrocephalus, or cortical dysplasia (Table 5.3, Fig. 5.47). Infections during the neonatal period, such as late onset neonatal meningitis or herpes encephalitis, can produce hydrocephalus, stroke-like lesions, and cystic encephalomalacia.

In the neonate suspected of having a congenital infection, cranial sonography may show regions of periventricular germinolysis (cysts) and scattered parenchymal foci of echogenicity (calcification). Additionally, sonography may show branching linear foci of hyperechogenicity within the thalami and basal ganglia indicative of mineralizing vasculopa-

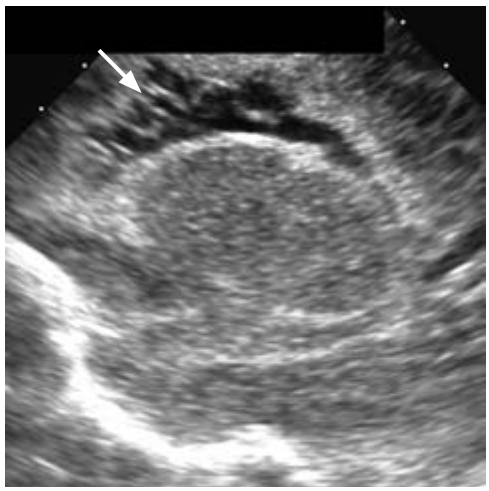

Fig. 5.45 Periventricular leukomalacia (PVL). Parasagittal cranial sonogram demonstrates numerous periventricular cysts (arrow).

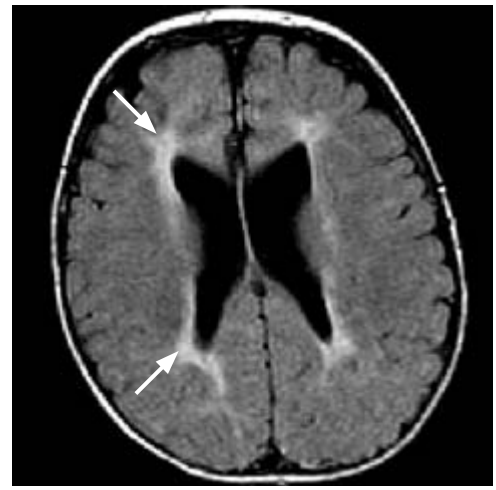

Fig. 5.46 Periventricular leukomalacia. Axial FLAIR MRI shows periventricular gliosis (arrows) and passive ventricular dilation.

TABLE 5.3

Congenital Infections and their Associated Imaging Abnormalities

Agent	Imaging features
Toxoplasma gondii	Hydrocephalus, scattered intracranial calcifications
Rubella	Microcephaly, periventricular calcifications
Cytomegalovirus	Microcephaly, periventricular calcifications, cortical dysplasia, cerebellar hypoplasia, porencephaly, schizencephaly, lissencephaly
Herpes simplex virus (congenital)	Cystic encephalomalacia, calcifications of the thalamus and basal ganglia
Lymphocytic choriomeningitis virus	Hydrocephalus, periventricular calcifications, cortical dysplasia
Varicella zoster virus (congenital)	Calcifications of the thalamus and basal ganglia, hydranencephaly, porencephaly
West Nile virus (congenital)	Cystic encephalomalacia, calcifications

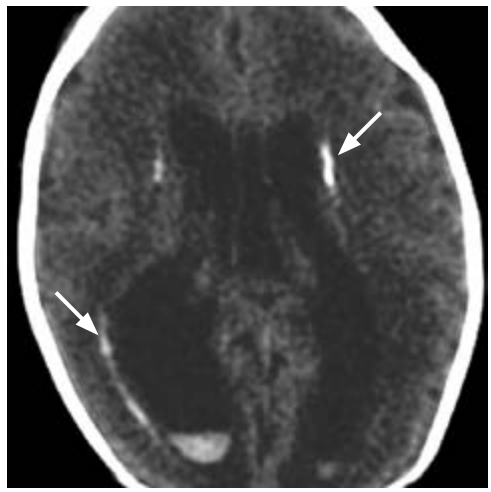

Fig. 5.47 Congenital cytomegalovirus infection (CMV). Noncontrast cranial CT shows extensive periventricular calcification (arrows).

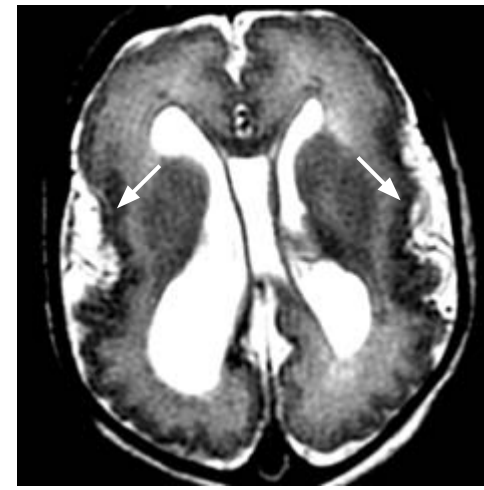

Fig. 5.48 CMV. Axial T2 MRI shows bilateral perisylvian polymicrogyria (arrows).

thy, which has been associated with a congenital infection, sepsis, and certain trisomies. Unfortunately, the peripheral cortex and regions of the posterior fossa are not completely characterized with sonography. MRI remains the most sensitive tool to evaluate the extent of injury with congenital infection detecting demyelination, germinolytic periventricular changes, encephalomalacia, ventriculomegaly, and associated cortical malformations (Fig. 5.48). Nonenhanced CT of the brain often is used as an adjunct to MRI given its greater sensitivity to detect calcification.

Hypoxic ischemic encephalopathy

Hypoxic ischemic encephalopathy (HIE) represents a common neurologic complication in both term and preterm infants. Coma, seizures, and stroke can be acute manifestations of HIE. Infants who survive HIE, like premature infants with IVH, have increased risks of epilepsy, cerebral palsy, and developmental delays. Cerebral palsy typically reflects periventricular leukomalacia (PVL), a lesion that commonly affects premature infants and can be a sequela of HIE or indicate a predisposing thrombophilic disorder such as factor V Leiden mutation.

The imaging abnormalities observed in the context of hypoxic ischemic insult relate to the patient age, profundity of the insult, and the physiologic milieu in which the injury occurs (hypoglycemia, hypotension, sepsis). In the acute and subacute setting of hypoxic ischemic encephalopathy MRI supplemented with diffusion weighted imaging and magnetic resonance spectroscopy are standard imaging techniques used to detect injury, characterize extent of abnormality, and when possible to prognosticate outcome (Fig. 5.49). In the late subacute and chronic setting following hypoxic ischemic injury, MRI remains a powerful tool to detect and characterize encephalomalacia, ventriculomegaly, cortical necrosis, gliosis, and extra-axial fluid accumulations (subdural hemorrhages).

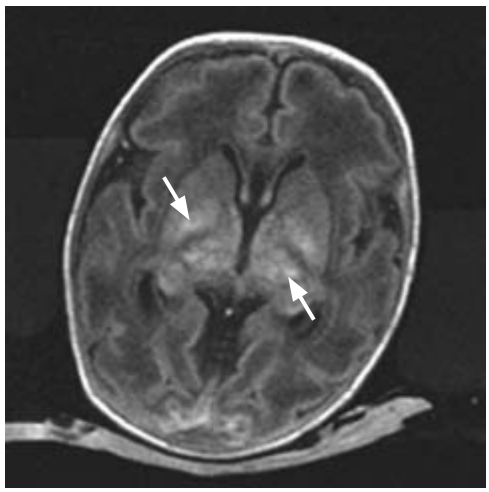

Fig. 5.49 Hypoxic ischemic encephalopathy in the pre-term newborn. Axial T1-weighted MRI shows basal ganglia and thalamic T1 shortening indicating profound pre-term hypoxic ischemic insult (arrows).

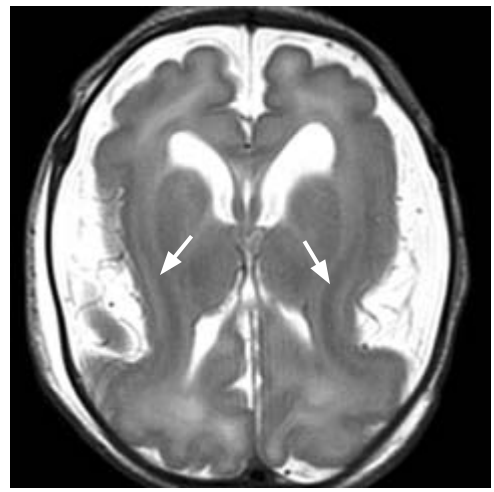

Fig. 5.50 Pachygyria. Axial T2-weighted MRI shows hourglass configuration of the brain, smooth cortex, and subcortical band heterotopia (arrows). Findings are consistent with incomplete lissencephaly-subcortical band heterotopia spectrum.

Central nervous system malformations, including lissencephaly, schizencephaly, chiari malformation, and cortical dysplasia

Infants with severe CNS malformations, such as lissencephaly, holoprosencephaly, schizencephaly, or diffuse cortical dysplasias, frequently become symptomatic in the neonatal period because of seizures, abnormalities of muscle tone, or dysmorphic features. Microcephaly or macrocephaly may also provide the initial clinical clue regarding a cerebral malformation. Chiari malformation, when recognized in the neonatal period, accompanies a meningomyelocele (Chiari type II) or occipital encephalocele (Chiari type III). Occasionally, Chiari type I is identified as an incidental finding during cranial imaging for other reasons.

The past decade has witnessed remarkable advances in understanding the genetic and environmental etiology of developmental CNS malformations. Holoprosencephaly can be associated with maternal diabetes, as well as mutations in several genes or gene loci, including Sonic Hedgehog, PATCHED, 2p, 7q, and 13q. Lissencephaly has been linked to congenital cytomegalovirus infection and to deletions in *LIS1.* Miller Dieker syndrome is the most commonly recognized disorder associated with lissencephaly. Schizencephaly has been associated with mutations of the homeobox gene EMX2.

Imaging the CNS of pediatric patients with disorders of cleavage, neuronal migration, and cortical organization is best accomplished with MRI (Fig. 5.50). With the advent of multichannel head coil technology and the ability to image at higher clinical field strengths, our sensitivity in detecting subtle cortical malformations has improved. There is promise that imaging at field strengths in the 3–7 Tesla range may yield near "histologic" images of some cerebral structures. The use of diffusion tensor imaging and tractography has already brought insights into the organization of the cortical spinal tracts in patients with holoprosencephaly.

Disorders of children and adolescents

Seizures and epilepsy

Each year several thousand children in the United States have their first unprovoked seizure, and many more children have seizures provoked by fever, illness, or trauma. Seizures have many distinct etiologies, ranging from life-threatening CNS infections to benign, inherited conditions, such as rolandic (centrotemporal) epilepsy. Epilepsy, affecting 0.5–1% of the pediatric population, can be symptomatic (reflecting remote or acute CNS pathology), idiopathic (indicating a genetic etiology), or cryptogenic (indicating an unknown etiology). Neuroimaging plays an essential role in evaluating children with seizures or epilepsy.

Practice parameters have examined in detail the role of neuroimaging in children with seizures or epilepsy. Children with uncomplicated febrile seizures do not routinely require neuroimaging. By contrast, imaging should be considered strongly in children with fever provoked seizures and signs suggesting meningitis or encephalitis, such as focal seizures, prolonged seizures, or prolonged postictal states. Children with seizures provoked by cranial trauma require neuroimaging emergently.

Neuroimaging studies in children with unprovoked seizures frequently reveal abnormalities, but the majority of these abnormalities do not affect urgent treatment decisions. Indications to obtain emergent neuroimaging include status epilepticus, focal seizures, postictal focal deficits, or prolonged postictal states. Young children (<1 year of age) or

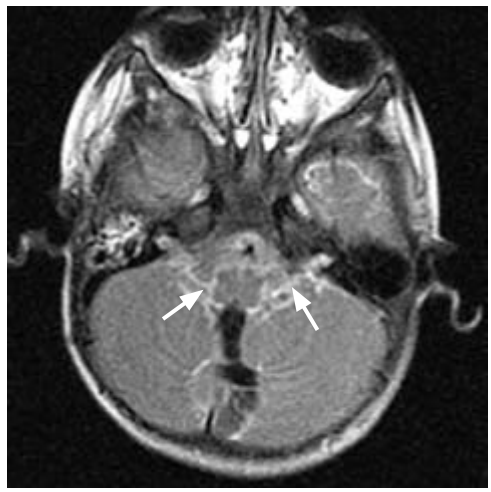

Fig. 5.51 *Hemophilus influenza meningitis*. Postenhanced axial FLAIR image demonstrates prominent basal cisternal and perimedullary enhancement (arrows).

children with unexplained cognitive or motor delays require nonurgent imaging. When nonurgent imaging is considered in children with seizures or epilepsy, MRI is the study of choice. MRI accurately detects cortical dysplasia, heterotopias, arteriovenous malformations, and other developmental or acquired disorders of the CNS that can be associated with seizures or epilepsy in children or adolescents.

When the health history and clinical evaluation indicates the necessity of urgent cranial imaging in the pediatric patient with seizure, nonenhanced cranial CT remains a front line imaging tool given its availability and scan times. Traumatic extra-axial hemorrhages, parenchymal hematomas, and tumors are quickly detected. For children with negative CT examinations and to further characterize CT abnormalities, MRI represents the next imaging step. Contrast administration in patients with seizures becomes important in CT and MRI to characterize suspected meningoencephalitis, cerebral tumefactions, extra-axial collections, venous thrombosis, and suspected vascular malformations (Fig. 5.51).

When nonurgent imaging is warranted in the evaluation of pediatric epilepsy, MRI is the technique of choice. MR offers high spatial resolution and sensitivity for detecting cortical malformations, cortical tumors, gliosis, tubers (tuberous sclerosis), hemorrhagic products, and atrophy (mesial temporal sclerosis) (Fig. 5.52). In the context of partial complex seizures and normal MRI examinations, ictal SPECT, interictal PET, or MEG may be employed to add additional useful information (Fig. 5.53).

Global developmental delay

Numerous conditions produce global developmental delay, and like children with epilepsy, a specific cause is often not identified. Neuroimaging has a major role in evaluating the children with developmental delay, especially when children have abnormal systemic or neurologic features. Imaging studies yield useful information in approximately one-third of children with global developmental delays. However, in certain disorders, such as the autistic spectrum disorder, Rett syndrome, and several genetic causes of global delay, imaging studies (including MRI and MRS) are nearly always normal.

Although CT can have utility in infants or children with microcephaly and suspected intrauterine infections, MRI should be considered in children with developmental delays, especially when accompanied by clinical features compatible with cerebral palsy. MRI may reveal abnormalities of white matter, severe developmental cortical anomalies, such as lissencephaly, porencephaly,

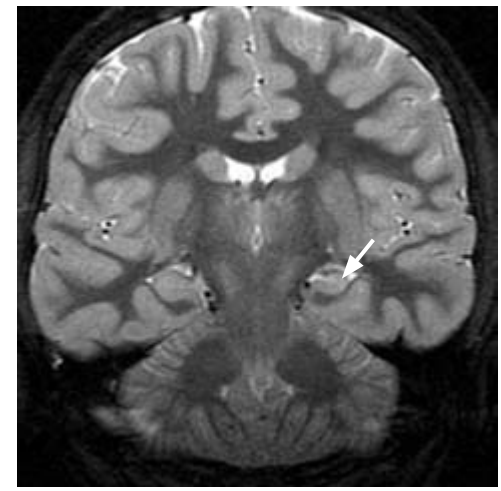

Fig. 5.52 Mesial temporal sclerosis (MTS). Coronal FSE T2 MRI demonstrates atrophy of the left hippocampus (arrow).

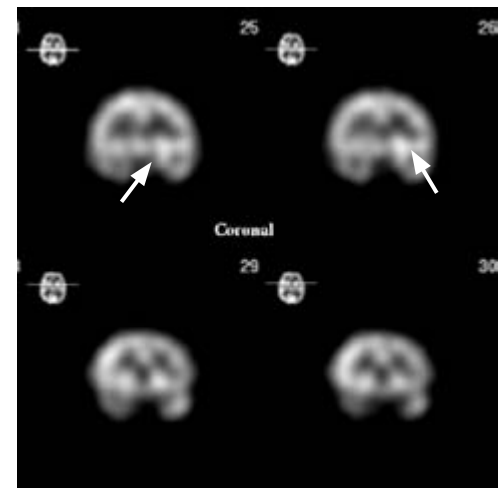

Fig. 5.53 Ictal Tc-HMPAO SPECT brain imaging. Coronal ictal SPECT demonstrates increased radiotracer uptake within the left mesial temporal lobe corresponding to the location of MTS (arrows).

or schizencephaly, or less obvious abnormalities such as periventricular nodular heterotopias, polymicrogryia, and cortical dysplasia. Periventricular leukomalacia, manifesting as white matter loss, passive ventriculomegaly, and T2 signal prolongation, especially evident on fluid attenuated inversion recovery (FLAIR) images, is commonly identified in children with global delays and cerebral palsy. Because of its relatively high yield, MRI is recommended as part of the diagnostic evaluation of children with global developmental delays.

Metabolic and neurodegenerative disorders

Neuroimaging has a useful role in evaluating children with suspected metabolic or neurodegenerative disorders, and certain findings, as summarized in Table 5.4, may lead to specific genetic and metabolic diagnoses. Children with suspected neurodegenerative disorders should undergo complete MRI studies as a routine part of their diagnostic evaluations; MR spectroscopy should be obtained when available, especially in children with suspected mitochondrial disorders.

Headaches

Like seizures and epilepsy, headaches can reflect many distinct disorders affecting the CNS of children and adolescents. Migraine, one of the most common causes of headaches in the pediatric population, consists of intermittent headaches that fulfill several clinical and historical criteria. Most importantly, children with migraine typically have family histories of the disorder. Imaging is not routinely indicated with children with migraines, normal neurologic examinations, and compatible family histories.

Chronic daily or nonprogressive headache of childhood and adolescence appears to be a multifactorial disorder with age- and gender-related vulnerabilities, provocative events, and personal and environmental factors that maintain the headaches. Cranial imaging will usually be normal in children or adolescents with chronic daily headaches and normal neurologic examinations, including fundoscopy. However, imaging should be considered strongly in children or adolescents with headaches of <6 months duration and features suggesting a space-occupying lesion, such as early morning headaches that awaken the patient from sleep, unexplained

TABLE 5.4 Imaging Features of Selected Metabolic and Degenerative Disorders of the Central Nervous System

Disorder	MRI or MRS feature(s)
Disorders of organic acid metabolism	
Glutaric acidemia	Extra-axial fluid collections, especially of the middle fossae and sylvian sulci; basal ganglia T2 prolongation and diffusion restriction
Proprionic acidemia	T2 prolongation in putamen and caudate nuclei
Methylmalonic acidemia	T2 prolongation within globi pallidi
Mevulonic acidemia	Progressive cerebellar atrophy
Mitochondrial disorders	
MELAS	Multifocal areas of T2 prolongation; elevated lactate peak in basal ganglia
Leigh's disease	T2 prolongation and lactate elevation of caudate nuclei and putamina
Leukodystrophies	
Metachromatic leukodystrophy	T2 prolongation in frontal and occipital white matter
Adrenoleukodystrophy	T2 prolongation prominent in peritrigonal white matter; gadolinium enhancement of the leading margin of demyelination
Vanishing white matter disease	Diffuse, near complete T2 prolongation of cerebral and cerebellar white matter; ± cysts
Peliazeus–Merzbacher disease	Profound delay in white matter maturation
Alexander disease	T2 prolongation of frontal white matter; macrocephaly
Miscellaneous	
Hallervorden–Spatz disease	Iron deposition in the globi pallidi leading to "eye of the tiger" sign
Gaunidinoacetate methyltransferase	Absent creatine peak on MRS; deficiency (creatine deficiency) T2 prolongation and diffusion restriction within globi pallidi
Wilson disease	Signal alteration of basal ganglia, thalami, brainstem; MRS shows decrease in NAA[1]/Cr[2], increased ml[3]/Cr[2], and increased iron/copper deposition
Huntington disease	T2 prolongation of caudate, globus pallidi; caudate and cortical atrophy
Subacute sclerosing panencephalitis	Focal periventricular demyelination, progressive cortical atrophy; reduced NAA peak and elevated myoinositol peak (MRS)

[1]NAA – N-acetyl aspartate; [2]Cr – creatine; [3]ml – myoinositol

vomiting, absence of a family history of migraine, or abnormalities on neurologic examination.

Children with other types of headaches should be assessed individually. When benign intracranial hypertension is suspected, children or adolescents require MRI, to exclude intracranial mass lesions, and MRV, to exclude sinovenous occlusion. Children with headaches and seizures also require CNS imaging, usually MRI. CNS imaging is always considered urgent whenever a CNS tumor is considered to be the cause of a child's headache or abnormal neurologic findings.

Intracranial infections

With the introduction of the vaccine for *Haemophilus influenzae* type b (HIB), the incidence of HIB meningitis declined dramatically in regions with compulsory immunization. Nonetheless, bacterial meningitis remains a potential threat to children of all ages. Children with suspected bacterial meningitis and papilledema, obtundation, seizures, or focal neurologic signs require cranial imaging prior to lumbar puncture. CT without contrast provides sufficient information regarding ventricular morphology and cerebral parenchyma to guide clinical management. Lumbar puncture should be deferred and empiric antimicrobial treatment provided to children with substantial hydrocephalus, mass lesions, cerebral edema, or compressed basal cisterns. Subsequent neuroimaging features in children with bacterial meningitis can include subdural effusions, cerebritis, abscess, communicating hydrocephalus, sinovenous thrombosis, or stroke.

Children or adolescents with viral meningitis do not typically have imaging abnormalities. By contrast, pediatric patients with viral encephalitis often have imaging findings that provide important clues to the etiologic diagnosis. Thus, neuroimaging studies, usually MRI, should be obtained in all patients with suspected viral encephalitis. Patients with herpes simplex virus type I (HSV-1) encephalitis display T2 prolongation and gadolinium enhancement of the mesial temporal lobe and insular cortex. Children or adolescents with encephalitis due to Epstein-Barr virus or Japanese encephalitis virus often have abnormalities of the basal ganglia or white matter. Patients with acute disseminated encephalomyelitis, a disorder that accounts for approximately 10–15% of encephalitis cases, have multifocal areas of T2 prolongation in the subcortical white matter, corpus callosum, cerebellum, brainstem, thalami, or basal ganglia.

Stroke

Stroke, either ischemic or hemorrhagic, occurs in approximately 6 per 100 000 children annually. Multiple conditions predispose to stroke, including trauma, congenital or acquired heart disease, thrombophilic disorders, infection, inflammatory disorders, and vascular anomalies. Many children or adolescents lack an identified predisposing factor despite extensive evaluations. Neuroimaging has a major role in the evaluation and management of stroke in the pediatric population.

The patient with an acute, focal neurologic deficit requires an urgent imaging evaluation that begins with a noncontrast CT to exclude hemorrhage or an intracranial mass lesion that requires neurosurgical intervention. If the CT is normal or detects a nonsurgical lesion, the evaluation should next proceed to MRI, using diffusion weighted, ADC maps, and as deemed necessary, MR angiography. If the MRI confirms ischemic stroke, the MRA is normal, and no systemic reason has been identified, many centers perform catheter angiography to detect vascular lesions, such as vasculitis or arterial dissection, since identifying such abnormalities influences clinical management. CT angiography through the circle of Willis may be useful when Moya-moya syndrome is suspected.

The precise sequence and timing of the neuroimaging evaluation should be tailored to the patient's condition and the potential for neurosurgical or medical intervention. Although the administration of thrombolytic agents has become the standard of care for adults with stroke, the role and benefit of thrombolytic agents or other medical interventions in pediatric stroke have not been studied rigorously.

Craniocerebral and spinal trauma

Traumatic brain and spinal cord injuries remain major sources of permanent disability among children and adolescents. Children with acute head injury require emergent CT to exclude lesions, such as an epidural or subdural hematoma, that require urgent neurosurgical evacuation. Associated spinal injury should not be overlooked in unconscious or obtunded patients, and the imaging evaluation of the injured child or adolescent should also include plain radiography of the spine. When cervical spine injury is suspected, radiographs should be obtained in the neutral position and cautiously in flexion and extension with neurosurgical assistance, as required. Depending upon these findings, thin section CT through the region(s) of interest may be necessary.

MRI displays greater sensitivity than CT for focal cerebral edema and shearing injuries to subcortical white matter; gradient echo MRI can be used to detect small intraparenchymal hemorrhages. MRI also readily detects post-traumatic lesions of the spinal cord. These may manifest as focal regions of cord swelling secondary to edema or intramedullary areas of T2 prolongation; peri-spinal hemorrhage, ligamentous tears, or disruption of tissue planes can be observed during spinal MRI. MRI during the convalescent stages of craniocerebral or spinal trauma can assist clinicians in making more accurate prognostications.

Neuroimaging with CT and MRI plays an essential role in evaluating infants and young children with suspected non-

accidental trauma (NAT). Detecting subdural hemorrhage and fluid accumulations of different ages strongly supports recurrent events as might occur with NAT. Identifying acute intrafalcine subdural hematomas and frontal lobe parenchymal lacerations also supports NAT as the likely mechanism for the child's injury. When the trauma is severe, follow-up imaging can show cystic encephalomalacia, chronic subdural hematoma, or stroke secondary to vascular injury.

Neoplasia

Children or adolescents with suspected intracranial tumors require urgent imaging evaluation, usually starting with CT. In general, MRI has superior sensitivity to CT, especially when imaging the posterior fossa, a common location for CNS tumors of childhood. However, CT can more readily detect intratumor calcifications, particularly when small. MRI should be obtained with and without gadolinium, because these modalities provide useful correlates to tumor histopathology. When primitive neuroectodermal tumors or other tumors that frequently disseminate throughout the neuroaxis are suspected, spinal MRI with gadolinium should be obtained.

Children and adolescents who undergo irradiation or chemotherapy for leukemia are at risk for post-therapy CNS injury. Because cranial irradiation under the age of 3 years commonly produces intracranial calcifications of the white matter and basal ganglia, cranial irradiation of young children is avoided whenever possible. Irradiation-related CNS effects can present acutely or chronically and be associated with atrophy or cystic degeneration. Methotrexate-related demyelination commonly presents with headache, focal deficits, and altered mental status. MRI usually detects focal areas of T2 prolongation.

Neurocutaneous disorders

Neurocutaneous disorders, including tuberous sclerosis, neurofibromatosis types I and II, and Sturge Weber syndrome, cause considerable neurologic disability among children and adolescents. Neuroimaging has a major role in identifying these disorders and monitoring children and adults for their associated complications. In addition, neuroimaging represents an essential component of the diagnostic evaluation of children with less common neurocutaneous disorders, such as incontinentia pigmenti, Bannayan–Riley–Ruvalcaba syndrome, von Hippel-Lindau disease, and the epidermal nevus syndrome. Table 5.5 summarizes the characteristic neuroimaging features of these disorders.

Patients with neurofibromatosis type I (NF1) present clinically with headache, macrocrania, developmental delay, learning disability, or visual dysfunction. Patients with suspected NF1 require MRIs at the time of diagnosis to establish the extent of their intracranial disease. Optic nerve pathway gliomas are a common finding and can be monitored by annual ophthalmologic examinations and periodic MRIs. Some authors have suggested that MRIs be obtained annually in patients with known optic nerve gliomas to guide therapeutic interventions. Because patients with NF1 are at risk of other intracranial lesions, brain MRIs should be considered when new symptoms, such as headache, seizures, or unexplained focal deficits occur. Spinal MRI is necessary in patients with NF1 and back pain, long track signs, or bladder dysfunction; nerve root neurofibromas are a common complication of NF1.

Young children with tuberous sclerosis (TS) complex often undergo CT when being evaluated for the new onset of seizures, especially infantile spasms. Characteristic CT features of TS complex include periventricular calcifications

TABLE 5.5

Imaging Features of Neurocutaneous Disorders

Disorder	Imaging feature (CT or MRI)
Neurofibromatosis type I	T2 prolongation in basal ganglia, brainstem, and cerebellum (MRI); optic pathway tumor (MRI); nerve root neurofibroma (MRI); intracranial tumors (CT or MRI)
Neurofibromatosis type II	Acoustic nerve schwannoma (CT or MRI); meningioma (CT or MRI); spinal cord ependymoma (MRI)
Tuberous sclerosis	Periventricular calcifications (CT); periventricular glial nodules (CT or MRI); cortical and subcortical tubers (MRI); radial and glial bands within white matter (MRI); hydrocephalus (CT or MRI) giant cell astrocytoma (CT or MRI)
Sturge Weber syndrome	Dural and parenchymal calcifications (CT); cortical atrophy (CT or MRI); accelerated myelination (early) and demyelination (late) (MRI)
von Hippel–Lindau syndrome	Vascular lesions of brain, cerebellum, and spinal cord (MRI with contrast) endolymphatic sac tumors (MRI)
Incontinentia pigmenti	Hemiatrophy (CT or MRI); heterotopia (MRI)
Epidermal nevus syndrome	Hemimegalencephaly (MRI); cortical dysplasia (MRI)
Bannayan–Riley–Ruvalcaba syndrome	Heterotopia (MRI)

and glial nodules; demonstrating symmetric bilateral calcific glial lesions near the foramina of Monro can be considered diagnostic of TS. These lesions can evolve to giant cell astrocytomas, obstruct cerebrospinal fluid pathways, and cause progressive hydrocephalus. Some authors suggest imaging studies be obtained annually to monitor such patients for tumors and hydrocephalus. Because MRI detects TS-associated cortical tubers more readily than CT, MRI should be considered at the time of diagnosis to establish the extent of intracranial disease and periodically thereafter based on the presence of new clinical symptoms and signs.

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SECTION 2

General Pediatric Neurologic Diseases and Disorders

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CHAPTER 6

Toxic and Metabolic Encephalopathies

Doris A. Trauner, MD

OUTLINE

Definitions and general features
Hypoxic ischemic encephalopathy
Disorders of fluid and electrolyte balance
Disorders of calcium homeostasis
Disorders of magnesium homeostasis
Disorders of glucose homeostasis
Nutritional disorders
Encephalopathies associated with systemic disease
Toxic encephalopathies

Definitions and general features

Encephalopathy refers to a generalized disturbance in neuronal or glial metabolism that results in alteration of consciousness, cognition or behavior.

Acute encephalopathy refers to a condition in which there is a sudden alteration in brain function induced by an alteration in normal metabolic homeostasis or exposure to a toxic substance. Typically the individual was functioning at a normal level prior to the onset of the encephalopathy, and a sudden observable change occurs over a few hours. A subacute change in consciousness or cognitive function evolves over several days.

Chronic encephalopathy evolves insidiously over days, weeks, or even months. Chronic or recurrent exposure to toxins, drugs, or metabolic derangements leads to progressive deterioration in cognitive function. The initial changes may be so subtle as to be missed for some time.

General symptoms of acute encephalopathy may include indifference, confusion, disorientation, other behavioral changes such as hyperactivity, irritability, or aggression, hallucinations, seizures, and alterations in the level of consciousness ranging from mild (lethargy) to severe (coma). The neurological examination of the encephalopathic child typically demonstrates evidence of diffuse dysfunction, including generalized hyperreflexia, positive Babinski signs, and preservation of cranial nerve function until late in the course. Focal findings are uncommon with metabolic or toxic encephalopathies (Table 6.1).

Chronic encephalopathies may have very subtle neurological changes over time. Symptoms often appear to be static or very slowly progressive. Some children may be misdiagnosed as having cerebral palsy, developmental delay, or attention deficit disorder. The neurological examination provides some information, but is nonspecific. Reflexes may be normal or increased, although occasionally they can be diminished, such as with certain mitochondrial disorders and with arsenic poisoning. Muscle tone may be normal or decreased, depending on the etiology of the disorder. Hyperactivity and behavioral symptoms are prominent features of some chronic encephalopathies. In assessing any child with developmental delay, hyperactivity, or behavior problems, it is very important to ask the parent or caretaker about loss of previously acquired skills by the child. Even subtle impairments in skills previously acquired may indicate the presence of a chronic encephalopathy and suggest that further studies are required.

Neuroimaging procedures such as computed tomography (CT) or magnetic resonance imaging (MRI), in acute encephalopathies generally demonstrate either no structural change, or evidence of diffuse cerebral edema. Such procedures are helpful in ruling out structural lesions such as tumors, bleeds, or cerebral infarcts. Electroencephalogra-

FEATURES

Table 6.1 Features of Metabolic Encephalopathy

Discriminating features

1. Generalized or multifocal brain dysfunction
2. Nonlocalizing findings on neurological examination
3. Laboratory evidence of metabolic derangement or organ dysfunction

Consistent features

1. Altered mental status
2. Diffuse slowing of background activity on EEG

Variable features

1. Hyperreflexia, clonus
2. Generalized or focal seizures
3. Epileptiform discharges on EEG

Metabolic Encephalopathy

PEARLS & PERILS

- Cerebral edema and increased intracranial pressure are major complications of most metabolic encephalopathies, and a frequent cause of death.
- Pupillary light reflexes are preserved until late in the course of acute metabolic encephalopathies, and can be helpful in differentiating metabolic from structural causes of coma.
- It is uncommon for children with metabolic encephalopathies to have focal abnormalities on neurological examination; however, focal findings do not rule out a metabolic etiology.
- The EEG in metabolic encephalopathy usually shows diffuse slowing of background activity; generalized or multifocal epileptiform activity is also common.

phy (EEG) reveals diffuse slowing of background electrical activity. Multifocal or generalized epileptiform abnormalities may also be seen on EEG. The EEG rarely has focal abnormalities, although shifting asymmetries may occur.

Hypoxic ischemic encephalopathy

One of the most common causes of acute neurological deterioration in infants and young children is hypoxic-ischemic encephalopathy (HIE). Acute hypoxia may result from severe respiratory distress (e.g. asthma, pneumonia), near-drowning, asphyxia, or respiratory arrest. Chronic hypoxia may be caused by cyanotic congenital heart disease or severe chronic pulmonary disease. Lack of sufficient oxygen to the brain adversely affects all cellular elements and all areas of the brain, although certain brain regions are particularly sensitive to the detrimental effects of hypoxia (e.g. hippocampus). Inadequate blood flow to the brain (ischemia) may also cause widespread damage, but the most severe insult occurs at the border zones or watershed areas of blood supply from major arteries such as anterior and middle cerebral arteries. In the case of ischemic brain damage, multiple infarcts of brain tissue may occur, resulting in a multifocal distribution of deficits.

Symptoms and signs of HIE are rapid in onset and progression. Agitation, followed quickly by depression in the level of consciousness, follows an acute hypoxic/ischemic insult. Cortical depression with obtundation and coma are followed by decorticate or decerebrate posturing, and in the young child in particular, opisthotonic posturing may persist for long periods. Generalized or multifocal seizures may be seen at any time during the course of the encephalopathy. The brain damage progresses in a rostral-caudal direction, so that brainstem dysfunction with involvement of cranial nerves develops late in the course of the encephalopathy, and respiratory arrest occurs as a result of involvement of the medulla.

After a hypoxic insult, the patient may appear to be improving in the first 24 hours, only to deteriorate over the next 48–72 hours as a result of severe cerebral edema. This second phase is often fatal, with tonsillar herniation causing cardio-respiratory arrest.

Recovery from a severe hypoxic or ischemic event is gradual, and return of function follows a caudal-rostral progression. Recovery is often incomplete with permanent neurological dysfunction, including seizure disorder, spastic quadriplegia, microcephaly, and mental retardation.

The EEG in HIE typically demonstrates diffuse slowing in the theta or delta range, at times with multifocal epileptiform discharges and even electrographic seizures. A burst-suppression pattern may be seen in severe cases.

A history of respiratory compromise (e.g. near-drowning) or an event that caused reduced cerebral blood flow (e.g. strangulation; severe hypotensive episode) suggests the probability of HIE. Arterial blood gas determinations soon after the event typically show a respiratory acidosis and increased CO_2 concentrations.

Intensive supportive therapy is required, including maintenance of adequate oxygenation and systemic arterial pressure, as well as careful fluid and electrolyte balance. Anticonvulsant therapy, such as intravenous fosphenytoin or benzodiazepines may be necessary to control seizures. Intracranial pressure (ICP) monitoring and control of ICP may be necessary in severe cases. Treatment of elevated ICP may include controlled hyperventilation, neuromuscular paralysis, elevation of the head of the bed, and osmotic diuretics. If the child is paralyzed or heavily sedated, continuous EEG monitoring is useful in detecting electrographic seizure activity.

Disorders of fluid and electrolyte balance

Water and electrolytes are constantly moving across capillary and cell membranes, maintaining equilibrium among all components of the organ. Fluid and electrolyte homeostasis are regulated by the interactions of the kidney, skin, lungs, adrenal glands, and brain. A malfunction in any one of these organs can cause disturbances in fluid or electrolyte balance. Persistent or severe diarrhea or vomiting, particularly when coupled with poor fluid intake, results in excessive depletion of body water, or dehydration. Other causes of dehydration include excessive sweating, polyuria, diabetes mellitus, and diabetes insipidus. Infants and young children are particularly prone to the detrimental effects of dehydration. Dehydration is often accompanied by electrolyte imbalances. Excessive loss of water over salt results in hypertonic dehydration; excessive loss of salt results in a

hypotonic state. Both of these conditions can be detrimental to the developing brain. With hypertonic dehydration, cell shrinkage occurs, and venous thromboses may develop. Rapid correction of a hypertonic state may result in cerebral edema. In the hypotonic state, excess water moves into brain cells, and cerebral edema with intracellular swelling may develop.

The clinical signs of dehydration depend on the rapidity of the fluid and electrolyte changes, as well as the degree of hypo- or hypernatremia. Lethargy and confusion occur in the presence of acute isotonic dehydration. If the condition persists, systemic hypotension may develop and lead to cerebral ischemia and coma. In addition to mental status changes, hypotonic dehydration may be accompanied by seizures. Acute hypertonic states present with irritability, increased muscle tone, hyperreflexia, seizures, and mental status changes. Overly rapid rehydration and reduction in serum sodium in this condition may result in intraparenchymal brain hemorrhages with worsening coma, multifocal abnormalities on examination, and seizures.

A history of vomiting and/or diarrhea, and poor fluid intake, combined with evidence of poor skin turgor, dried mucus membranes, sunken eyes, and lack of tear production, make the diagnosis of dehydration readily apparent. However, these findings may be less apparent in the presence of hypertonic dehydration, because extracellular fluid volume is relatively preserved.

Intravenous fluid replacement is the mainstay of treatment. Initial rapid replacement of fluid and electrolytes is required to establish or maintain adequate cardiovascular and renal function and organ perfusion. After that, slower replacement of fluids and electrolytes is needed to more fully replace what was lost and to maintain adequate fluid volume.

Specific parameters of fluid and electrolyte replacement must be determined on a case-by-case basis, using age, neurological and cardiovascular status, degree of electrolyte imbalance, and other factors in the decision-making. Monitoring of serum electrolytes and renal function is necessary to determine the course of therapy.

If severe acidosis is present, bicarbonate solutions may be useful. With hypernatremic dehydration, hypotonic solutions may be used for fluid replacement, but it is important to lower serum sodium levels gradually over about 72 hours in order to minimize the potential complications that occur with rapid correction.

Seizures usually respond to correction of the dehydration and electrolyte imbalance, and generally do not require anticonvulsant medication after the initial acute illness.

Outcome is generally favorable unless severe cerebral edema or intraparenchymal hemorrhages have occurred.

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Disorders of Fluid, Electrolyte, and Glycemic Balance

- When seizures occur as a consequence of electrolyte imbalance or hypoglycemia, treatment of the metabolic derangement generally results in seizure remission.
- Infants of diabetic mothers, premature infants, and those who are small for gestational age are most at risk for hypocalcemia, hypomagnesemia and hypoglycemia in the neonatal period.
- Myopathies are not associated with altered mental status, whereas metabolic causes of muscle weakness often have concomitant changes in alertness or cognition.
- Severe dehydration, hyperglycemia and hypernatremia may cause tearing of superficial cortical veins and bleeding or cerebral thromboses, leading to focal neurological deficits.
- Prolonged or recurrent episodes of symptomatic hypoglycemia may lead to irreversible brain damage.

Disorders of calcium homeostasis

Regulation of calcium homeostasis is the function of parathyroid hormone, vitamin D, and thyrocalcitonin; renal function and movement of calcium into and out of bone tissue also alter calcium concentration. Calcium has a number of important functions in the nervous system, including membrane stabilization and modulation of the excitable threshold of the cell. Thus, either hypo- or hypercalcemia may cause neurological symptoms.

Hypocalcemia occurs in the premature neonate, in infants of diabetic mothers, and in small for gestational age infants. In older children, hypocalcemia may be seen with vitamin D deficiency, hypoparathyroidism, pseudohypoparathyroidism, renal failure, acute pancreatitis, malabsorption syndromes, magnesium deficiency, as a complication of treatment with certain medications (e.g. phenytoin), and following infusion of large concentrations of citrate during blood transfusions.

Jitteriness, clonus, increased extensor tone, and hyperreflexia are the common findings on neurological examination of the hypocalcemic newborn. Seizures, either generalized or focal, may be the presenting symptom in some infants. In older children, muscle cramps, parasthesias, carpopedal spasms, and laryngospasm are typical manifestations of hypocalcemia. Lethargy, hyperreflexia, and focal or generalized seizures may also be found in older children. Positive Chvostek's and Trousseau's signs can be elicited in children with low calcium levels. Chvostek's sign is elicited by tapping the lateral aspect of the face over the facial nerve. A positive response is a brief contraction of the facial muscles on the side percussed. Trousseau's sign is elicited by applying pressure to the upper arm. Carpal pedal spasm is induced in the presence of low calcium levels.

Diagnosis is made by obtaining a serum calcium concentration below 7 mg/dL. The Q-T interval may be prolonged on electrocardiography. The EEG often shows diffuse slowing of background activity; multifocal epileptiform discharges may also be seen.

Treatment consists of intravenous infusion of calcium salt solutions. Seizures and other neurological manifestations typically disappear with this treatment. Long-term anticonvulsant medication is usually not necessary.

Hypercalcemia is found in conditions such as vitamin D or A toxicity, thyrotoxicosis, hyperparathyroidism, bony metastases, prolonged immobilization, hypophosphatasia, sarcoidosis, and Williams syndrome. High calcium levels adversely affect the nervous system by blocking synaptic transmission.

Infants with hypercalcemia have failure to thrive, weakness and hypotonia. In older children, symptoms are nonspecific, and include headache, constipation, anorexia, vomiting, irritability, lethargy, and weakness. Chronic hypercalcemia can predispose to renal stones and renal failure.

Since weakness and hypotonia are common features of hypercalcemia, this condition should be considered in any child who appears to have a neuromuscular disorder. Serum calcium concentrations make the diagnosis.

Treatment consists of administration of a chelating agent to bind excess calcium. Infants with hypercalcemia usually respond to lowering the vitamin D and calcium intake in the diet. If hyperparathyroidism is the cause, surgical removal of the parathyroid may be necessary.

Disorders of magnesium homeostasis

Hypermagnesemia is rare in healthy children. The usual cause is an overdose of magnesium-containing medications, although elevated magnesium levels may be found in association with uremia and adrenocortical insufficiency. Hypomagnesemia is seen in newborn infants of diabetic mothers, in infants who are small for gestational age, and after exchange transfusions. Hypocalcemia is usually present as well, but correction of the calcium level alone does not reverse the symptoms. In older children, prolonged vomiting or diarrhea, excessive use of diuretics, rickets, diabetic ketoacidosis, malabsorption syndromes, and hypoparathyroidism may result in hypomagnesemia.

Symptoms of hypermagnesemia include muscle weakness, hypotonia, and loss of reflexes. In extreme cases, alterations in consciousness may occur, as well as respiratory depression, hypotension, and flaccid paralysis. Symptoms of hypermagnesemia may resemble myasthenia gravis, infantile botulism, or toxin ingestions.

Hypomagnesemia produces symptoms that are similar to those of hypocalcemia, including tetany, irritability, increased muscle tone, and hyperreflexia.

Normal magnesium concentrations in the blood are 1.5–2.5 mg/dL. Levels under 1.0 mg/dL or over 4 mg/dL may produce symptoms. The diagnosis is based on serum calcium, phosphorus, and magnesium levels.

Treatment consists of intravenous infusion of magnesium sulfate in the case of hypomagnesemia. For elevated magnesium levels, intravenous hydration, administration of calcium gluconate, and at times diuretics, are the usual treatments.

Disorders of glucose homeostasis

Glucose is the primary energy substrate for the brain. Hypoglycemia produces seizures and altered mental status within 30–45 minutes after a severe drop in serum glucose concentration. If not treated rapidly, irreversible brain damage can result as early as 90 minutes following onset of severe hypoglycemia. Focal as well as generalized neurological abnormalities can be seen with hypoglycemic encephalopathy.

Hyperglycemia produces a hyperosmolar state with subsequent intracellular dehydration. CNS manifestations of this condition include seizures, hallucinations, tremor, lethargy and coma. Treatment consists of cautious hydration and exogenous insulin administration. Rapid rehydration may result in sudden fluid shifts that can lead to cerebral edema and worsening neurological dysfunction.

Nutritional disorders

Vitamins are necessary cofactors for many enzymatic reactions in the brain. Neurological dysfunction can occur in the face of vitamin deficiency states and in some cases in the presence of excess vitamin concentrations. In some cases, a dependency state exists in which the individual requires higher than usual levels of certain vitamins in order for the body to carry out normal enzymatic reactions. Vitamin deficiencies generally result from nutritional deprivation, malabsorption states, chronic infections, or malignancies.

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Nutritional Disorders

- The most common causes of vitamin deficiencies are malabsorption syndromes and inadequate nutrition.
- Deficiencies of the B-complex vitamins may result in cognitive delay or regression.
- Excessive intake of the fat-soluble vitamins A or D may cause pseudotumor cerebri with increased intracranial pressure.
- Vitamin E deficiency causes a neurological syndrome of ataxia and gait disturbance.
- Early recognition and treatment are key factors in reversing the neurological abnormalities caused by vitamin deficiencies.

Vitamin A deficiency

Deficiency of Vitamin A may lead to night-blindness, facial nerve palsy, and reduced sense of smell. Excess vitamin A ingestion in infants and children may cause seizures and cognitive slowing. Either a deficiency or an excess of vitamin A may cause pseudotumor cerebri. Symptoms and signs include headache, visual impairment, and papilledema. Although replacement of deficiency or reduction of excess intake may alleviate symptoms, often other treatment, such as acetazolamide administration or repeated lumbar punctures, may be necessary to reduce intracranial pressure and prevent permanent visual loss. In refractory cases, surgical intervention with lumbo-peritoneal shunt or optic nerve sheath fenestration may be necessary to protect vision.

Vitamin D deficiency

Vitamin D deficiency produces signs and symptoms associated with hypocalcemia. Excess vitamin D may cause pseudotumor cerebri.

Vitamin B deficiencies

Most of the B vitamins are cofactors for mitochondrial electron transport chain enzymes. Deficiencies in any of these are uncommon, but can lead to impaired energy production and serious neurological complications.

Vitamin B_1 (thiamine) deficiency interferes with cellular metabolism and may cause cerebral lactic acidosis. Thiamine deficiency is responsible for beriberi, a condition in which there is a mixed sensory and motor neuropathy, with weakness, absence of tendon reflexes, sensory loss, and ataxia. In severe cases altered mental status and increased intracranial pressure may occur. In adults, thiamine deficiency can also cause Wernicke's encephalopathy, but this condition is very rare in children. Symptoms include ophthalmoplegia, ataxia, and altered mental status (e.g. inattentiveness, lethargy, or dementia). Permanent neurological impairment may result from prolonged thiamine deficiency.

Vitamin B_2 (riboflavin) deficiency causes a chronic encephalopathy with mental retardation and slowing of the EEG.

Vitamin B_3 (niacin) deficiency is the cause of pellagra, consisting of dermatitis, diarrhea, and dementia.

Vitamin B_6 (pyridoxine) deficiency can be caused by certain drugs (e.g. isoniazide) as well as by malnutrition and malabsorption. Symptoms of pyridoxine deficiency include seizures and irritability. Infants with pyridoxine dependency syndrome present with intractable epilepsy, markedly abnormal EEGs, and developmental regression. Early treatment with large daily doses of pyridoxine may reverse or at least ameliorate these problems.

Vitamin B_{12} (cobalamin) is necessary for the synthesis of DNA during cell division. It also plays a role in the maintenance of myelin. Deficiency states are usually caused by malabsorption. Weakness, fatigue, and apathy may be the only CNS manifestations of cobalamin deficiency. Decreased reflexes, loss of balance, and sensory loss in the lower extremities (subacute combined degeneration) may be found in adults with chronic B_{12} deficiency.

KEY CLINICAL QUESTIONS

- What major features differentiate metabolic encephalopathy from intracranial hemorrhage or closed head injury?
  Answer: Typically there is an absence of focal findings in metabolic encephalopathy, though focal findings can occur (see Pearls & Perils); generalized slowing on the EEG; brain MRI either normal or diffuse cerebral edema.
- For how long is it necessary to treat a child who has hypoglycemic seizures with anticonvulsant therapy?
  Answer: In most cases, anticonvulsant medications can be discontinued once the acute metabolic problem has resolved.

Vitamin E deficiency

Vitamin E deficiency can occur in cystic fibrosis, chronic cholestasis, abetalipoproteinemia, and as a familial condition of isolated vitamin E deficiency. These conditions may result in a chronic encephalopathy that consists of cognitive slowing, progressive ataxia, muscle weakness, impaired position and vibratory sensations, and inability to walk. Measurement of serum vitamin E levels may not accurately reflect the degree of the deficiency state. The presence of any underlying condition that predisposes to vitamin E deficiency should raise suspicion of this condition in a child presenting with the typical clinical features. Administration of high daily doses of vitamin E will ameliorate the symptoms of this condition, especially if treated relatively early in the course.

Encephalopathies associated with systemic disease

Hepatic encephalopathy

Liver failure, regardless of etiology, is associated with multiple metabolic disturbances, including hyperammonemia, hyperbilirubinemia, and disturbances in carbohydrate and fatty acid metabolism. Both acute and chronic forms of hepatic encephalopathy (HE) may occur, depending in part on the rapidity and severity of the liver disease.

In acute HE, agitation, disorientation, and lethargy are the early symptoms. Asterixis can be demonstrated during the early stages. Asterixis is a loss of postural tone in the outstretched wrists that produces a flapping movement of the

hands. Obtundation and coma may follow in severe cases. The EEG in HE demonstrates diffuse slowing, and a pattern of triphasic waves may appear, though this is much less common in children than adults.

Treatment of HE involves multiple approaches, including intensive supportive care, correction of bleeding abnormalities, and reduction in ammonia levels using neomycin orally and/or rectally, or oral lactulose. Fulminant hepatic failure may require liver transplantation.

Cerebral edema complicates liver failure and treatment should include measures to reduce intracranial pressure, including osmotic diuretics, controlled hyperventilation, and elevation of the head.

Chronic HE occurs with liver damage that is prolonged and sufficient to cause metabolic derangements. Symptoms and signs include cognitive impairments, at times with frank dementia, and movement disorders such as choreoathetosis or dystonia. There is some evidence that liver transplant may improve cognitive function in these patients.

Inflammatory bowel disease (IBD)

Both ulcerative colitis and Crohn disease are associated with a number of complications, including a hypercoagulable state in which the patient is prone to develop thromboses. The etiology of this coagulopathy is unknown. Elevated levels of Factor VIII have been found in some patients with this condition, while thrombocytosis has also been reported in association with thrombo-embolic events in IBD. Arterial and venous cerebral thromboses have been reported in children with these disorders. Acute arterial thrombosis typically presents with a stroke-like picture of hemiplegia, aphasia, or other focal signs. Venous sinus thromboses cause acute alterations in mental status, with lethargy, headache, vomiting, seizures, and possibly coma. This complication can be fatal, although many patients survive with few or no sequelae. Treatment with steroids and anticoagulation may be warranted, but treatment must depend on the clinical severity as well as other factors including evidence of hemorrhagic infarct or other bleeding diathesis that might contraindicate the use of anticoagulation therapy.

Celiac disease

Celiac disease is a fairly common gastrointestinal disorder associated with gluten intolerance and malabsorption syndrome. Children with this condition have a history of chronic diarrhea, at times associated with short stature. Performing a small intestine biopsy and demonstrating villous atrophy and crypt hyperplasia makes the diagnosis. Circulating antigliadin, antireticulin, and antiendomysial antibodies are also diagnostic of this condition. Institution of a gluten-free diet and replacement of vitamins and other cofactors that were reduced because of malabsorption leads to a reduction or resolution of clinical symptoms.

Neurological complications of untreated celiac disease include a chronic encephalopathy in which there is cognitive decline, with psychomotor delay or retardation, or dementia with loss of previously acquired cognitive function. Behavioral disorders, depression, ataxia and seizures have all been reported in association with celiac disease. Dietary control generally improves the neurological condition.

Renal failure

Renal failure results in a number of metabolic derangements, including uremia, hypocalcemia, acidosis, and other abnormalities. Hypertension is also a complication of renal disease. The encephalopathy associated with renal failure may be caused by the metabolic derangements or by severe hypertension.

Acute uremic encephalopathy develops in the presence of sudden marked elevations of blood urea. Symptoms include lethargy, restlessness, agitation, and slurred speech. Muscle weakness with fasciculations may also be present, as well as tremors and other movement disorders. Progressive impairment in mental status may culminate in coma, with focal or generalized seizures, diffuse hyperreflexia, and rigidity.

Chronic renal failure is associated with a slowly progressive encephalopathy consisting of cognitive slowing (at times quite severe), and seizure disorders.

Hypertensive encephalopathy begins abruptly, in association with a sudden and severe rise in systemic arterial blood pressure, and typically presents with a sudden marked alteration in consciousness (usually coma) with generalized or focal seizures.

Encephalopathies Associated with Systemic Diseases

PEARLS & PERILS

- Bleeding tendencies are increased in patients with hepatic injury, and may lead to additional neurological complications. Correction of clotting disorders in patients with hepatic encephalopathy is difficult, and may require exchange transfusion or plasmapheresis.
- Systemic disorders such as liver and kidney disease can cause chronic, slowly progressive encephalopathy that may be difficult to recognize in the early stages.
- Asymptomatic peripheral neuropathy is found in many children with chronic uremia.
- Children with chronic liver or renal disease may decompensate and develop encephalopathic symptoms in the presence of acute infection or electrolyte imbalance, even when organ function has been fairly stable.

Diagnosis of uremic encephalopathy includes elevations of blood urea nitrogen, typically >90 mg, as well as elevations in serum creatinine. Diffuse slowing is seen on the EEG, at times with triphasic slow waves.

Treatment of the acute encephalopathy consists of dialysis to reduce the uremia. Long-term anticonvulsant therapy may be required, as seizures may persist beyond the acute stage. Chronic uremic encephalopathy is poorly responsive to dialysis, and tends to have a slowly progressive course despite treatment. Rapid control of systemic arterial pressure is necessary to treat hypertensive encephalopathy. Seizures may not recur once the acute episode is over. However, there may be long-term sequelae from hypertensive encephalopathy as a consequence of cerebral edema and petechial hemorrhages into the brain during the acute stages.

Thyroid dysfunction

Both hypo- and hyperthyroid states cause chronic encephalopathies with impairment in cognitive function and behavior. Hypothyroidism that begins after infancy produces a slow deterioration in cognitive function, with worsening school performance, inattentiveness, slurred speech, and general slowing. These children are occasionally misdiagnosed as having attention deficit disorder. Treatment with daily L-thyroxine replacement may reduce or reverse the neurological problems, but often some residual CNS dysfunction will remain despite adequate treatment.

Hyperthyroid conditions typically manifest neurologically as hyperactivity, restlessness, poor concentration, and occasionally mania or psychosis. Often, a fine tremor can be observed in the outstretched hands. Treatment with agents that suppress thyroid function usually reverses the encephalopathic symptoms.

Toxic encephalopathies

Lead

Lead exposure continues to be a common occurrence. Although lead paint is no longer used in homes, older buildings still may have some residual lead paint undercoats. Infants and toddlers can ingest chipped paint. Lead is also found in some china, pottery, and glassware products. Drinking water can be contaminated by lead pipes or by waste from industrial plants. Burned storage batteries emit fumes containing lead. Low-income, inner-city children are at highest risk for lead exposure, and African-American children have a higher incidence of lead exposure than other ethnic groups.

Acute lead intoxication causes a severe encephalopathy consisting of vomiting, ataxia, and seizures, followed by coma with increased intracranial pressure. Diffuse hyperreflexia and increased tone are found on examination, with few focal features. Seizures may accompany the acute encephalopathy.

Chronic lead intoxication has been associated with more subtle but also deleterious effects on the CNS. Behavior problems, hyperactivity, learning disabilities, and at times frank mental retardation have been attributed to chronic high levels of lead in the blood.

Diagnosis is made by blood lead-level determinations. Elevated free erythrocyte porphyrin levels and low hemoglobin are also found.

Treatment consists of chelation therapy, but the lead level at which chelation is warranted remains an area of controversy. In acute encephalopathic conditions, supportive care and treatment of elevated ICP are necessary. Anticonvulsant therapy may also be required. Toxic encephalopathies of lead and other metals are outlined in Table 6.2.

Cyclosporine

Newer immunosuppressive agents such as cyclosporine have contributed significantly to transplant survival and quality of life. Occasionally, however, cyclosporine toxicity may lead to encephalopathic problems. Acute cyclosporine toxicity is characterized by tremulousness and restlessness, as well as an acute confusional state at times with psychosis. Speech problems and myoclonus have also been reported in this condition. The neurological manifestations of cyclosporine toxicity are readily reversible if the drug is withheld

PEARLS & PERILS

Thyroid Dysfunction

- Thyroid dysfunction should be considered in a child with unexplained muscle weakness and hypertrophy.
- Children with thyroid dysfunction may have symptoms reminiscent of attention deficit disorder.

PEARLS & PERILS

Toxic Encephalopathies

- All children are at risk for lead exposure from many sources in the environment.
- Low levels of lead exposure over a long period of time have been associated with subtle cognitive and behavioral deficits.
- A serum salicylate level should be obtained in acute encephalopathy of unknown cause in young children, especially when hyperventilation and acidosis are present.
- Acetaminophen toxicity can cause acute hepatic failure and encephalopathy.

TABLE 6.2

Heavy Metal Toxicity

Heavy metal	Exposure source	Central nervous system symptoms	Diagnosis	Treatment
Thallium	Insecticides Rodenticides	Headaches Ataxia Seizures Somnolence Cranial nerve palsies	Urine thallium level	Bithizone KCl and charcoal Hemodialysis
Arsenic	Insecticides Herbicides	Headaches Irritability Seizures Sensory neuropathy	Urine and hair arsenic levels	British antilewisite Penicillamine
Mercury	Fungicides	Ataxia Movement disorders Tremor	Red blood cell mercury level	Chelation (?)
Manganese	Industrial exposure Impaired elimination of dietary Mn (from liver disease)	Mild cognitive impairment Tremor Parkinsonian symptoms	Blood manganese levels	Withdrawal of source of excess Mn

until blood levels return to the therapeutic range, and then reinstituted at a lower dose.

Salicylism

Although warnings on medications that contain salicylates have significantly reduced the administration of these drugs to children, accidental ingestion is still a concern in children, particularly those under the age of 5 years. Salicylate compounds are found in many over-the-counter medications. Salicylate overdose produces a number of metabolic derangements that lead to CNS compromise. These include metabolic acidosis, respiratory alkalosis, hypoglycemia, and lactic acidosis. Acute poisoning can also cause hepatocellular damage with additional metabolic problems including hyperammonemia.

Signs and symptoms of acute salicylate intoxication include vomiting, dizziness, hyperventilation, delirium and coma. Increased ICP with cerebral edema is a common complication, as is excessive bleeding.

Diagnosis is suspected from the history, and the laboratory findings of mixed metabolic acidosis and respiratory alkalosis, hypoglycemia, and elevated salicylate levels in the blood.

Treatment includes intensive cardiorespiratory support, correction of the metabolic derangements, treatment of elevated ICP, and administration of vitamin K to attempt to reduce the potential for bleeding.

CONSIDER CONSULTATION WHEN...

- An infant or child develops a sudden change in mental status that is not explained by fluid or electrolyte imbalance or hypoglycemia.
- A previously typically developing child begins to have difficulty with school performance, motor functions, or behavior.
- A previously healthy child complains of headache or has persistent vomiting and lethargy without clear gastrointestinal cause.
- Findings on neurological examination demonstrate hyperreflexia, positive Babinski signs, and/or papilledema.

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Each of these references provide additional information on this topic.

CHAPTER 7

Traumatic Encephalopathies

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OUTLINE

Severe acute traumatic brain injury
Mild traumatic brain injury
Deterioration following acute brain injury
Recovery from traumatic brain injury

Severe acute traumatic brain injury

The NIH Consensus Development Panel on Rehabilitation of persons with Traumatic Brain Injury reports that

> Traumatic brain injury results principally from vehicular incidents, falls, acts of violence, and sports injuries and is more than twice as likely to occur in men as in women … The highest incidence is among persons aged 15–24 years and 75 years or older, with a less striking incidence in children aged 5 years or younger.
>
> Ragnarsson *et al*. 1999

At Children's Hospital, Central California, a children's regional medical center, there were 73 416 children seen in the urgent care and emergency departments in a recent 12-month period. Of these, 2270 were diagnosed with traumatic brain injury. Only 61 required hospital admission. It has been estimated that head injuries are present in 75% of children with trauma, and that 70% of all traumatic deaths are due to head injury. Severe head injury is the leading cause of death and morbidity in children and in young adults. Nearly half of head injuries result from motor vehicle accidents. Most children with moderate to severe head injury suffer some disability lasting months or years.

Immediate loss of consciousness is a hallmark of severe brain injury that involves both hemispheres, or the brainstem. These injuries invariably involve shearing of axons referred to as diffuse axonal injury located in the cerebral white matter, or less frequently within the corpus callosum, brainstem or cerebellum. Persistent deep coma, often with gradual recovery, is a consistent feature of those patients whose brains at autopsy show diffuse axonal injury (Jennett & Teasdale 1981).

Pathology

Several mechanisms of injury occur simultaneously in severe traumatic brain injury (Marshall 2000). Direct contusion of the gray matter of the brain may occur at the site of impact, or opposite the point of impact (contre-coup) as a result of the brain being thrust against the inside of the cranium. More commonly the brain is contused on the undersurface of the temporal and frontal lobes, and on the anterior poles of the temporal lobes, whatever the site of impact. This pattern results from the brain striking against the bony prominences at the base of the cranial vault. Shearing forces are major contributors to the pathogenesis of the contusions (Adams *et al*. 1989). Rotational acceleration exaggerates these forces. A cascade of biochemical changes triggered by the mechanical disruption contributes to the pathogenesis of the injury.

Primary brainstem lesions in the absence of hemispheric diffuse axonal injury are rare. They often involve the reticular activating system, and may include hemorrhage, necrosis and axonal injury. They often occur by centroaxial injury with downward shift of the brain, and are exaggerated by rotational forces, or by flexion–extension of the cervical spine (Besenski 2002).

Contusions may be extensive without loss of consciousness, although they may become more significant secondary to the genesis of events such as hemorrhage and swelling. Laceration of the brain occurs with penetrating trauma, and may or may not include more extensive contusion or shearing forces depending on the velocity of the projectile. For example, gun shot wounds may result in direct injuries along the trajectory of the bullet as well as more diffuse injury owing to the shock wave produced by a high-speed projectile.

The predominantly white matter injury owing to shearing forces in brain trauma has been termed diffuse axonal injury (DAI). Electron microscopy very early after fatal injury

shows disruption of axon filaments. Later, axon retraction balls, and myelin blebs, may be seen in the light microscope. The histopathological classification of DAI includes three grades based on the extent of brain involvement. Grade 1 involves DAI in the white matter of the cerebral hemispheres, the corpus callosum, the brainstem, and sometimes the cerebellum. Grade 2 includes focal lesions in the corpus callosum. Grade 3 includes focal lesions in the dorsolateral quadrants of the rostral brainstem.

Animal studies have suggested that injuries of increasing severity involve first the cerebral hemispheres and then the diencephalon. Only the most severe injuries involve dysfunction of the mesencephalon directly. Direct brainstem contusion, without concomitant injury to the cerebral hemispheres, is rarely seen pathologically. However, several lines of evidence suggest that transient functional changes in the reticular activating system, without gross structural changes in the brainstem, may be involved in the initial loss of consciousness in traumatic brain injury.

Anoxic-ischemic injury complicates most severe traumatic brain injuries. Hypoventilation and hypotension, and unequal distribution of blood flow, are present to some degree with most head injuries. Multiple trauma increases the risk of anoxic-ischemic injury. The neurons of gray matter are particularly sensitive to anoxia, especially the amygdala, hippocampus and basal ganglia, although the cerebral cortex and cerebellum are also quite sensitive to such injury. In the most severe anoxic injuries the white matter is also damaged, with the outcome being poor.

Secondary brain damage occurring after the initial injury may be due to anoxic-ischemic events, or to transtentorial herniation. Herniation, in turn, may be due to diffuse brain swelling or to expanding intracranial masses. These secondary brain injuries may be more significant than the primary injury and are discussed in more detail later in this chapter.

Signs and symptoms

Loss of consciousness is characteristic of severe diffuse traumatic brain injury. The extent and duration of the loss of consciousness correlate with outcome. However, in an individual child, it is not possible to predict outcome reliably from length of coma. A few children present an alarming but short-lived picture of deep coma with unreactive pupils, followed by rapid recovery. Others may have a brief loss of consciousness followed by deterioration and a poor outcome. The presence of diffuse axonal injury, anoxic injury, and focal brain contusions or subcortical gray matter lesions, may account for some of this individual variability.

With the exception of primary brainstem injuries, the severity of loss of consciousness (or of coma) correlates with the severity of injury. Deeper levels of unconsciousness imply more severe injury. Plum and Posner (1980) have defined levels of consciousness corresponding to dysfunction of progressively more caudal structures in the brain. Recovery from loss of consciousness often follows this rostral-caudal progression in reverse order.

The diencephalic stage is the first of Plum and Posner's stages. At this level consciousness is altered, but not necessarily lost. Some children are agitated or combative. Others are somnolent, but may become agitated transiently with stimulation. Appropriate motor responses to noxious stim-

Acute Diffuse Traumatic Brain Injury

PEARLS & PERILS

- Worsening vital signs (blood pressure may be increased) owing to brain injury almost always occur after a decrease in the level of consciousness. Therefore, deteriorating mental status and level of consciousness is the most sensitive indicator of neurological deterioration. The Glasgow Coma Scale is widely used to monitor level of consciousness.
- Coma is defined as being present in those children who do not open their eyes, speak, or obey commands. Coma is present in babies who do not open their eyes or cry.
- People with GCS scores of less than 8 account for 30% of all head injury admissions, but more than 95% of deaths.
- CT is superior to plane skull radiography that does not image the intracranial contents.
- Maintenance of airway, breathing, and circulation are of the highest priority for the treatment of brain-injured children.
- Some severe or fatal brain injuries occur without external evidence of trauma.
- The presence of retinal hemorrhages in an infant suggests child abuse.
- Secondary brain damage may be preventable. The major causes of secondary brain damage are anoxic-ischemic injury and transtentorial herniation.
- In an individual child, it is not possible to predict outcome reliably from the length or severity of coma.
- Severe focal brain injuries, and cervical spinal cord injury, may be overlooked in comatose children because of the lack of responsiveness and motor signs associated with coma.
- The tendency to ascribe warning signs of other injury to brain dysfunction should be avoided. Hypotension rarely occurs as a result of acute brain injury. Hypertension is the usual response. Fever over 102°F rarely is due to brain dysfunction.
- A long bone series should be done in cases of child abuse.
- The most common conditions resulting from inadequate treatment include hypoxia, hypotension, sepsis, and seizures.
- Comatose children with traumatic brain injury usually require intubation, intravenous lines, and transfer to an appropriate intensive care unit.

ulation are present. Except babies in the newborn period, children can usually move their limbs toward the source of noxious stimulation. Children of all ages withdraw from pain. Oculocephalic and pupillary reflexes are intact.

The second, or late diencephalic, stage is marked by loss of consciousness and flexor (decorticate) posturing. Posturing occurs in response to stimulation, discomfort, or sometimes at rest. Oculocephalic and pupillary reflexes remain intact. Hypoventilation may occur and respirations are irregular.

The third stage correlates with dysfunction of the midbrain and upper pons. Responsiveness is deeply impaired. Extensor rigidity (decerebrate posturing) is the maximum motor response. Oculocephalic and pupillary reflexes are impaired because the brainstem nuclei controlling these reflexes are located in the damaged midbrain. Respiration is usually irregular, with hyper- or hypoventilation.

The fourth stage corresponds to dysfunction of the lower pons and upper medulla. The limbs are motionless and flaccid except possibly for some leg flexion to stimulation above the neck. Spontaneous breathing is present, but hypoventilation is the rule.

Periods of apnea commonly occur in more severely head-injured children. This, in part, accounts for the high incidence of anoxic damage complicating traumatic brain injury. Anoxic injury carries a worse prognosis than purely traumatic injury producing the same level of coma.

Sometimes symptoms do not fit a pattern of rostral-caudal progression. For example, a child may exhibit extensor rigidity with the eyes open and with conjugate eye movements. This suggests patchy compromise, and is often due to anoxic-ischemic injury to the brainstem, or to diffuse axonal injury, cortical contusions, or damage to subcortical gray matter. Careful examination may reveal other focal neurological deficits even in a comatose patient. Such deficits are more likely to occur with more severe injury, but are easily overlooked because of the motor signs and lack of responsiveness associated with coma. These signs are important because they may suggest severe focal brain injuries that are not reflected in the level of consciousness.

Diagnostic studies

Computed tomography (CT) has greatly aided the diagnosis and management of traumatic brain injury. This technique allows direct visualization of the brain and is particularly sensitive to the presence of intracranial bleeding. Although diffuse axonal shear injuries are often not evident on CT, the presence of petechial hemorrhages (small spots of blood), is a good sign that diffuse axonal injuries are also present. All imaging modalities underestimate the true extent of DAI. Skull fractures also may be seen on CT, although conventional plane skull films may be necessary to delineate the bony abnormalities. Other body areas, including the cervical spine, should also be examined radiographically, and a long bone series should be obtained in cases of suspected child abuse.

Magnetic resonance imaging (MRI) is superior to CT in resolution, but the problems of gaining access to a patient in a strong magnetic field, the longer times needed to acquire each image, and image degradation due to even small movements preclude its routine use in acute head trauma. MRI is particularly useful in the diagnosis of acute spinal cord injuries. It is also quite helpful in the evaluation of the patient who has not improved as rapidly as expected. MRI is superior to CT for all posttraumatic lesions other than skull fracture and subarachnoid hemorrhage (Besenski 2002).

Seizures may complicate the management of severely injured children. Often these children are sedated and given neuromuscular paralyzing agents. This may mask the physical signs of seizures, but does not ameliorate their deleterious effects. EEG is helpful in identifying seizures in these children. Continuous EEG, compressed EEG spectral array monitoring, and evoked potential monitoring are of great interest, but their usefulness in the management of individual patients is still being studied. EEG is of limited value for prognosis of the acutely injured child. If brain death is suspected, a formal protocol should be followed for the determination of death by neurological criteria (Ashwal 1997). EEG, by itself, is not a reliable determinant of death in children.

Although these diagnostic studies are useful, their utility is limited by their poor sensitivity to milder injuries, or those involving diffuse axonal shearing, which often does not show well on brain scans but can present as diffuse slowing on EEG. In these cases, the functioning of the child on bedside examination can be the most accurate measure of brain injury, with more subtle cognitive limitations only presenting on more sensitive neuropsychological assessment.

Treatment

The importance of adequate management of severe traumatically brain-injured children cannot be overemphasized (Mazzola & Adelson 2002). It has been estimated that, in as many as 70 or 80% of acutely comatose children and adults, gross errors in management are made when they are first seen. Errors in management occur in urban as well as in rural hospitals, and in teaching as well as private hospitals. Maintenance of airway, breathing, and circulation are the principles of basic life support and are of first priority. The most common conditions resulting from inadequate treatment include hypoxia, hypotension, sepsis, and seizures (van den Brink 2000). Iatrogenic complications include misplacement of endotracheal tubes, pneumothorax following subclavian puncture, and fractured ribs from overzealous resuscitation. Attention to details such as these has resulted in reduction in mortality from severe traumatic brain injury

for those who survive to the hospital from nearly 50% to about 25% over the past three decades (Zink 2001).

The taking of a history and examination for other injuries are essential. Life-threatening injuries of the chest, abdomen, spine, and limbs are easily overlooked in children with impaired consciousness. This is particularly true of abdominal injuries, in which tenderness, guarding, and rigidity may be absent despite severe bleeding or peritonitis. Stabilization of the neck and subsequent imaging studies of the spine, the chest, and, if indicated, the limbs are the next important steps. A history is often difficult to obtain but may be important. The details of the injury, information regarding the onset of symptoms, prodromal illness or the ingestion of poisons, and the use of drugs or alcohol must be sought. Scalp injuries or other signs of trauma are important in the assessment of brain injury. But some severe or fatal traumatic brain injuries occur with no external evidence of trauma. Retinal hemorrhages accompany severe deceleration or shaking injuries, but also occur with asphyxia. Marked retinal and preretinal hemorrhages, without a history of severe head trauma, strongly suggest child abuse (Johnson *et al*. 1993).

Severe brain injury rarely occurs in infants who fall from a height less than that of an adult (Chadwick *et al*. 1991). DAI has been reported in young infants who suffer traumatic brain injury, and in most infants who die from abuse. Gliding contusions (tears at the junction of gray and white matter) are more prominent in infants under 6 months of age compared to the callosal damage in older infants. Roughly half of abused children who die lack external evidence of trauma. It has been argued that simple shaking does not produce sufficient force to cause DAI (Alexander *et al*. 1990) whereas impact of the head against a cushioned surface generates forces up to 300 times gravity, more than enough to cause DAI (Prange *et al*. 2003). Thus the term Shaken-Impact Syndrome has been coined to suggest the role of forceful impact against a cushioned surface producing severe brain injury, but without external marks (Bruce 1992). An older term, coined by C. Henry Kempe, the "Battered Child Syndrome," is perhaps more descriptive. Additional autopsy findings include acute subdural hematomata, usually posterior and along the falx. Subarachnoid hemorrhage is frequent. Severe brain swelling usually occurs, often with ischemic neuronal damage and tentorial herniation. The swelling may be quite asymmetric, affecting one hemisphere more than the other, even lacking any other evidence of focal injury. Occasionally children who die of abuse show evidence of asphyxia, with traumatic damage absent or confined to the cervicomedullary junction.

Assessment of the level of consciousness should be carried out accurately. The Glasgow Coma Scale (GCS) is widely used for this purpose and is described in Table 7.1. One great advantage of this scale is that it may be applied quickly, repeatedly, and accurately by professionals with all levels of training. The scale records responses in terms of eye opening, movements, and vocalization. This information can be transmitted quickly and unambiguously to others involved in the care of the patient. It is not necessary to use, or remember, the numbers of the scale; words are sufficient and communicate more information.

According to the GCS, a child is in coma who fails to open his or her eyes, to speak, and to obey commands. Coma in babies is less well characterized but may be defined as existing in those babies with abnormal motor responses who fail to open their eyes or to cry. All children whose GCS is 7 or below are in coma by these definitions. Furthermore, many children with a GCS score of 8 will also be in coma. This is of great predictive importance. Patients with GCS scores of greater than 8 account for 70% of all head injury admissions but less than 5% of deaths. Those who die most often have severe injury to other organs, although brain swelling, and, less often, expanding intracranial hematomata contribute to their mortality. Conversely, those with GCS scores of less than 8 account for only 30% of admissions but more than 95% of deaths. A similar dichotomy exists for other causes of acute brain injury, including drowning and metabolic encephalopathy.

Once the initial assessment and stabilization have been accomplished, ongoing careful observation and management are essential to prevent secondary brain injury, and to treat injuries not involving the brain directly. This is often best accomplished in an intensive care unit. This further management will be discussed in the following section.

Clear and compassionate communication with the families of acutely injured children is an essential part of medical management (Jurkovich *et al*. 2000). A wealth of printed material is available that is designed to answer some of their questions (Hutchison & Hutchison 1983). When discussing a child's injury with parents, it is critical that the clinician understand the inherent difficulty in predicting outcome. Two children with grossly identical injuries, in respect to etiology, severity, symptom presentation, etc., may have vastly different outcomes, with one recovering to functional levels, and the other remaining significantly compromised. Due to the numerous factors influencing recovery of function following a brain injury, prognosis becomes an educated guess. Accordingly, when discussing prognosis with parents of a brain-injured child, often it is better to be vague, giving both a best-case scenario and a worst-case scenario, but without removing hope. Honesty is the best approach, but with the caveat that one cannot easily predict outcome of an individual patient (Table 7.2).

Mild traumatic brain injury

At one end of the spectrum of loss of consciousness are those children who have suffered no loss, or no more than a brief loss of consciousness, and who have no focal neurological

TABLE 7.1

Glasgow Coma Scale

Response	Value	Explanation
Eye opening		
Spontaneous	4	Eyes are open without stimulation
To speech	3	Eyes open to speech or sound. This does not imply obeying commands
To pain	2	Eyes open only to noxious stimuli
None	1	Do not score if eyes are swollen shut
Motor response		
Obeys commands	6	Follows commands like "stick out your tongue"
Localizes pain	5	Limb moves toward source of pain
Withdrawal	4	Normal response with abduction of the shoulder (this is the maximum response babies can generate)
Flexion	3	"Decorticate" posturing with adduction of the shoulder, elbows flexed, legs extended, rigid
Extension	2	"Decerebrate" posturing with elbows and legs extended, rigid
No response	1	Tone is flaccid
Verbal response		
Oriented	5	Knows time, place, person
Confused	4	Conversational speech but confused
Inappropriate	3	Words but no coherent speech – often swearing and combativeness
Incomprehensible	2	No recognizable words – moans and groans or crying in babies (this is the maximum response babies can generate)
No response	1	Makes no sounds – score of 1 is given for intubated patients

The maximum score generated with maximum stimulation is added in each section. Maximum possible is 15 (10 in babies). Remember that words are a perfectly adequate form of communication, and that description of what happens in each area is more useful than numbers alone. After Teasdale G, Jennett B: The Glasgow Coma Scale. *Lancet* 2:81, 1974.

deficits. These children are said to have suffered a minor or mild head injury. Concussion is another term with similar meaning. Although some of these injuries do not lead to negative consequences involving cognitive functioning, other injuries of this kind may not necessarily be minor or mild. Confusion and amnesia are the hallmarks of concussion and can last from minutes to days or even months depending on the severity. The confusional episode and amnesia may occur immediately after the blow or occur several minutes later. Some children with such an injury have persistent, subtle, but disabling symptoms of brain dysfunction lasting hours to months. Rarely, children who initially appear to have suffered a mild head injury show marked deterioration owing to brain swelling or, less often, to an expanding intracranial hematoma.

Pathology

Mild traumatic brain injury exists as a pathophysiologic entity along a spectrum of injury, ranging from mild concussion to severe, diffuse injuries (Dixon *et al*. 1993). The mechanisms of these injuries represent the lower end of the continuum discussed above in which pathological disturbances increase as the severity of the mechanical forces increase.

Signs and symptoms

The evaluation and management of injured children may be influenced by the local practice customs, settings where children are evaluated, the type and extent of financial coverage, and the availability of technology and medical staffing.

The Mild Traumatic Brain Injury Committee of the Head Injury Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM) (Kay *et al*. 1993; Barth & Macciocchi 1993) has defined mild traumatic brain injury (MTBI) as an injury with:

- Loss of consciousness not exceeding 30 minutes;
- After 30 minutes following the injury, the minimum Glasgow Score is 13–15;
- Post traumatic amnesia must not exceed 24 hours.

Physical examination is necessary. It is important to look carefully for signs of other injuries or illnesses, including cervical spine injuries, as these often are overlooked.

FEATURES

Table 7.2 Severe Acute Traumatic Brain Injury

Discriminating features

1. Loss of consciousness in all severe traumatic brain injuries, except purely focal injuries.
2. Deepening coma following a rostral-caudal progression from hemispheric dysfunction through diencephalic, midbrain, pontine, and medullary stages.
3. Trauma sufficient to produce the injury.

Consistent features

1. Contusion of the undersurfaces of the temporal and frontal lobes, and of the anterior poles of the temporal lobes, whatever the site of impact.
2. Brainstem dysfunction associated invariably with hemispheric dysfunction.
3. Deepening coma associated with the progressive appearance of flexor posturing, extensor posturing, and finally flaccidity.
4. Hypoventilation, or apnea, accompanying deeper levels of coma.
5. Some degree of anoxic-ischemic brain injury.

Variable features

1. Contusion of the brain on the side opposite the point of impact (contre-coup lesions).
2. In an individual child, the depth of coma is only roughly correlated with the severity of injury. Focal traumatic injury and anoxia account for some of this variability.

PEARLS & PERILS

Mild Traumatic Brain Injury

- Mild head injury, minor head injury, or concussion is not necessarily minor. Children who have experienced loss of consciousness, vomiting or seizures have been found to have a prevalence of intracranial injury ranging from 2 to 5%. A few percent of children are quite disabled by such seemingly trivial injuries, and the organic deficits may persist for months.
- Confusion and amnesia are the hallmarks of mild traumatic brain injury, also called concussion. However, normal people also sometimes endorse these symptoms.
- Rarely, children who initially appear to have suffered a mild head injury show marked deterioration.
- Most symptoms of MTBI resolve entirely within 2 or 3 months. Depending on the situation, up to a third of children with MTBI continue to have some complaint at 3 months. Headache is the most frequent complaint.
- History may not always determine the severity of the injury. Some children over report the symptoms, and others may minimize the injury.
- When evaluating a child with mild traumatic brain injury, it is important to consider the child's condition before the injury.

The physical signs of MTBI include nausea, vomiting, dizziness, headache, blurred vision, sleep disturbance, quickness to fatigue and lethargy.

Cognitive and behavioral symptoms of MTBI initially include deficits in memory, thinking, attention and concentration, behavioral and mood lability, and lethargy. In a few patients, these symptoms persist longer than 2–3 months. The diagnosis and management of cognitive and behavior deficits is discussed later in the section on Recovery from Traumatic Brain Injury.

Unfortunately, the history may not always determine the severity of the injury (Barth & Macciocchi 1993). Children with personality traits such as somatoform, affective and histrionic tendencies may over report symptoms. Malingering, pretending or exaggerating illness for some secondary gain, leads to over reporting in a minority of children. On the other hand, other children may under report symptoms, especially if they wish to avoid restrictions involving athletic participation or physical play activities such as riding bikes or skateboarding.

It is important to note that headaches, dizziness, memory deficits, confusion, concentration difficulties, irritability and moodiness, and the like may be signs of many different disorders, both organic and emotional, and they also may be present in normal individuals. In one survey (Iverson & Lange 2003), between 35.9% and 75.7% of normal adults endorse postconcussion-like symptoms related to any experience in the past 2 weeks. From 2.9 to 15.5% endorse more severe symptoms. These complaints are highly correlated with depressive symptoms.

Another study (Lees-Hayley *et al.* 2001) found similar rates of endorsement of postconcussive symptoms among adults with MTBI and with orthopedic injuries. Thus it is important to establish whether the MTBI is the proximate cause of the symptoms.

The American Academies of Pediatrics and of Family Physicians (AAP/AAFP) have prepared a practice parameter for the management of minor closed head injury in children (Coombs 1999). This useful document discusses the management of children between 2 and 20 years with no loss of consciousness, or brief loss of consciousness no longer than 1 minute in duration. Younger children, and all children who meet certain exclusion criteria, exit the algorithm to appropriate individualized patient management. These excluded children are considered to be at higher risk for undetected injuries, and for delayed deterioration, that may lead to more serious morbidity and mortality. They are transferred to a higher level of care that may include refer-

ral to a pediatric trauma service at an institution with fully staffed and equipped pediatric intensive care unit and operating rooms.

The definition of MTBI by the AAP/AAFP is much more stringent than that by the ACRM and includes:

- Loss of consciousness less than 1 minute;
- Normal mental status at initial exam;
- No abnormal or focal neurological findings;
- Normal fundoscopic examination;
- No physical evidence of skull fracture;
- May have had seizure immediately after injury;
- May have vomited;
- May have had lethargy or headache.

It is proposed that these children may be observed at home if the physician believes that this is appropriate and that the parent(s) is competent to observe the child at home. Any signs/symptoms of intracranial problems warrant emergency CT head scan or transfer to a facility with definitive neurosurgical care facilities. If the CT reveals a lesion in the absence of signs/symptoms of intracranial problems, then the physician should arrange consultation with appropriate specialists. The value of this screening tool is debated as some studies report nearly similar rates of complications of MTBI whether or not the child has a history of brief loss of consciousness. The diagnostic studies supporting these arguments are briefly discussed below.

Lately, much interest has been given to the issue of sports-related brain injuries. The American Academy of Neurology (AAN) (Greenberg 1997) has developed a practice parameter for the management of concussion in sports. Among the difficulties encountered with such research is the estimation of the number and extent of head injuries due to reliance on self-report, and the differences in the interpretation of "injury." Brain injury may occur in any sport. At least 60 000 American high school football players suffer concussion every year (Daniel 1999). Usually, the injury is witnessed by several people. The athlete may feel considerable pressure, internal or external, to be released to return to play. This may lead the child, and those attending to him or her, to minimize the injury.

Several approaches to sideline evaluation of the injured athlete have been proposed to provide a rapid and reliable evaluation of the risks of further injury and the athlete's ability to return to play (Greenberg 1997; Cantu 2001). This evaluation should include evaluation of level of consciousness, steadiness of gait, orientation and post-traumatic amnesia. Bailes and Hudson (2001) nicely summarize no fewer than eight guidelines for return to play, including the AAN practice parameter, as noted in Table 7.3.

Very rarely, athletes suffer diffuse cerebral swelling following a seemingly minor injury. This rapidly developing swelling leads to delayed catastrophic deterioration in these children and adolescents resulting in death or persistent vegetative state. Cantu (2001) and others argue that this syndrome is related to a "second-impact" or the result of a second concussion on a brain that has not yet recovered from the first. This is part of the rationale for limiting athletes from return to play until their symptoms are clear. McCrory (2001) argues that there is little evidence to support a "second-impact" rather than just "diffuse cerebral swelling," a well-recognized complication of traumatic brain injury. He estimates that this catastrophic condition occurs in about 1 in 11 million player-games among registered athletes in Australian football, a sport with a very high injury rate.

Another postulated source of brain injury is repeated "sub-concussive" blows. Soccer players may suffer hun-

TABLE 7.3

Summary of Guidelines for Evaluation of Injured Athletes

Grade 1: Mild concussion with confusion

This includes athletes who have had no loss of consciousness observed by team mates, coaches or spectators. Confusion lasting less than 15–30 minutes is the hallmark sign of mild concussion These players sometimes are referred to as having been "dinged." They may be able to function unnoticed during the course of the athletic contest. This is a common condition that occurs at least once in most American football games. After 20–30 minutes, if the athlete is absolutely symptom-free, and has no headache dizziness or confusion, then he or she may return to play. Most of the published guidelines include a sideline mental status examination so that more subtle confusion and lack of coordination is not overlooked.

Grade 2: Moderate concussion with amnesia

There is no observed loss of consciousness, or loss of consciousness less than 5 minutes in duration. There is loss of memory of the events surrounding the blow. The athlete may have retrograde amnesia for some of the events preceding the injury, and anterograde amnesia for some events that have occurred after the injury. This anterograde or posttraumatic amnesia must not exceed 30 minutes. Evaluation of such memory deficits is included in the sideline mental status examination. The athlete is removed from play and not permitted to return the same day. If he or she still is symptomatic the following day, then urgent medical evaluation is indicated.

Grade 3: Severe concussion

Athletes who have loss of consciousness longer than 5 minutes (or post-traumatic amnesia longer than 24 hours) should be transported to a medical facility equipped to handle traumatic brain injury. Care should be exercised to protect the cervical spine and the airway. Consideration should be given to prohibiting play for the remainder of the season.

Adapted from Bailes JE, Hudson V: *J Athl Train* 36:236–243, 2001.

dreds or thousands of such blows over a period of years. There is a large variation in rates of MTBI reported for soccer players probably due to differences in willingness of soccer players and other athletes to report concussions, different methods of reporting, and different criteria used to identify a concussion. In most studies that compare soccer and American football the concussion rates are slightly higher for American football than for soccer. These rates generally are less than one concussion per 1000 player-hours. Rutherford *et al.* (2003) reviewed the available research into the effects of head injuries in soccer, and concluded that although there is some exploratory evidence of subclinical neuropsychological impairment as a consequence of soccer-related concussions, there is no reliable evidence, and certainly no definitive evidence, that such impairment occurs as a result of general soccer play including heading the ball. The extent to which younger versus older athletes are at risk for soccer-related cognitive impairment is unclear (Downs & Abwender 2002). Certainly, concussion does occur in soccer as a result of collisions with other players and with the goal posts. In contrast to soccer, repeated blows to the head in boxing may lead to permanent dementia, or the "punch drunk" syndrome.

Diagnostic studies

Estimates of the likelihood of intracranial injury in children with no loss of consciousness are varied. Simon *et al.* (2001) report that 35 (16%) of 215 children seen at a Level 1 trauma center, but with normal neurological examination, and without history of loss of consciousness, had signs of intracranial injury on CT scan. Among these children, five required neurosurgical intervention or intubation. They urge a liberal policy of CT scanning of children with MTBI. On the other hand, Palchak *et al.* (2003) found that of 304 children undergoing CT with normal mental status, and who lacked clinical signs of skull fracture, vomiting, scalp hematoma, or headache, only one had CT evidence of intracranial injury. That child was discharged from the ED without complication.

Hoffman *et al.* (2001) report a very high rate of intracranial injury in patients who presented to the emergency department in Maastricht in the Netherlands with MBTI defined as Glasgow coma score 14 or 15, loss of consciousness less than 20 minutes, and posttraumatic amnesia less than 6 hours. Using sensitive MRI and SPECT techniques, they were able to demonstrate, by at least one technique, intracranial lesions in 77% of patients with MTBI. On follow-up, all patients with abnormal imaging studies developed mild brain atrophy as determined by volumetric analysis.

Of the patients of Hoffman *et al.* (2001), one-third had persistent cognitive complaints 6 months after the injury. Neurocognitive testing demonstrated that those patients with intracranial injury scored worse those those with normal imaging studies in the acute phase, and at 2 months after injury. No difference overall was detected at 6 months after injury, but a reaction time task remained lower in the group with intracranial injury.

It is generally agreed that MRI is more sensitive than CT for MTBI (Hoffman *et al*. 2001). Currently, however, there is no appreciable difference between CT and MRI in the diagnosis of clinically significant acute intracranial injury and bleeding that requires neurosurgical intervention (Coombs 1999). CT offers substantial advantages because of ease of obtaining the study, and lower cost. It is important to keep in mind that the CT findings after brain injury may evolve over hours to days. Therefore repeat CT should be considered in view of changing neurological condition.

Treatment

In spite of the publication of the AAP/AAFP practice parameter (Coombs 1999), Blostein and Jones (2003) found no standard practice for defining, evaluating, or managing MTBI at Level I trauma centers. It is clear that a detailed physical examination is essential to evaluate properly a child's need for further treatment and observation. An essential feature is the mental status examination. The examiner must be aware of the appropriate expectations for the child's age and preinjury developmental level. If there is any persisting abnormality in the mental status examination, then further evaluation, and/or treatment, is indicated. Signs of intracranial pressure also are important. The Cushing reflex, associated with intracranial hypertension, involves increasing arterial hypertension and bradycardia. Arterial hypertension and tachycardia also are often seen together, but this combination of symptoms more likely is a nonspecific sign due to catecholamine release.

When there is a clear history of no loss of consciousness, and the circumstances or mechanism of injury are consistent with this history, then observation in the clinic, office, emergency department, or at home under the care of a competent caregiver may be safe (Coombs 1999). The risk of delayed deterioration in these children is small, but still may not be zero. Imaging ordinarily is not necessary. However, even some children who initially are neurologically normal and asymptomatic may have significant injuries that require intervention. More worrisome signs may appear, and then the child should return immediately for repeat examination, including CT of the head. Several investigators urge a liberal policy of CT scanning in seemingly normal children following MTBI because on the order of 1% will require some invasive intervention for complications that threaten survival and good recovery.

Children with brief loss of consciousness, or who demonstrate amnesia at the time of evaluation, or who have headache or vomiting at the time of evaluation, have a prevalence of intracranial injury detectable on CT that ranges from

FEATURES

Table 7.4 Mild Traumatic Brain Injury

Discriminating features

1. Confusion and amnesia are the hallmarks of MTBI.
2. Trauma sufficient to explain the complaints.

Consistent features

1. Loss of consciousness less than 30 minutes.
2. Posttraumatic amnesia less than 24 hours.
3. Nausea, vomiting, dizziness, headache, blurred vision, sleep disturbance, quickness of fatigue, lethargy.
4. Impairments in memory, thinking, attention and concentration, behavioral and mood lability.
5. CT and other imaging studies may show contusion or epidural, subdural or subarachnoid bleeding.

Variable features

1. Children with mild or minor head injury, or concussion, who have experienced loss of consciousness, vomiting or seizures have been found to have a prevalence of intracranial injury ranging from 2 to 5%.
2. Catastrophic deterioration of children following seemingly mild injury leading to permanent severe sequelae is described in a few case reports (Coombs 1999).
3. Some children over-report and others under-report symptoms.
4. Most symptoms of MTBI resolve entirely within 2 or 3 months. Depending on the situation, up to a third of children with MTBI continue to have some complaint at 3 months. Headache is the most frequent complaint.
5. Symptoms of MTBI often are endorsed by uninjured children.
6. Sideline examination of children with sports-related injuries may help to identify those at greater risk when returning to play.
7. A small number of children with loss of consciousness and amnesia should be transported to a center prepared to diagnose and treat severe traumatic brain injury.

PEARLS & PERILS

Deterioration Following Acute Brain Injury

- Fever of any source aggravates brain swelling.
- Nutrition is critically important in head-injured children. Orogastric feeding or parenteral nutrition should begin early.
- The Cushing reflex associated with intracranial hypertension involves arterial hypertension and bradycardia. Arterial hypertension and tachycardia are also often seen together, but this combination of symptoms is due to catecholamine release rather than intracranial hypertension.
- Lumbar puncture is relatively contraindicated in the presence of diffuse brain swelling because of the risk of herniation.
- Paralyzing drugs mask the clinical signs of seizures, but the brain hypoxia and acidosis caused by seizures may continue.
- Early post-traumatic seizures occur more often, and late seizures less often, in children than in adults.
- The outcome in patients with intracranial hematomata has more to do with the underlying brain injury than with the presence of blood.
- Most children with gradually deteriorating mental status and consciousness do not have an intracerebral hematoma.
- CT (or MRI) scanning is an essential part of the diagnosis of intracerebral hematomata.
- Prompt drainage (within 4 hours) may yield dramatic improvement with subdural hematomata.
- Prompt drainage of epidural hematomata may be lifesaving.
- The appearance of a third-nerve palsy is often more useful as a sign of impending herniation than as an early sign of an intracranial hematoma.
- Life-threatening intracranial hematomata may follow mild head trauma.
- New bleeding may occur for a week or more after head trauma.
- Brain edema associated with a hematoma may be more dangerous to the child than the bleeding.

0 to 7%. A substantial portion of children, between 2% and 5% of those with minor head injury and loss of consciousness, may require neurosurgical intervention (Coombs 1999). In children where the circumstances of the injury, or the length of loss of consciousness, are unknown, CT of the head, and close observation, should be done (Table 7.4).

Deterioration following acute brain injury

Immediate loss of consciousness is the rule is most cases of severe traumatic brain injury. There are some exceptions to this rule. About 4% of adults with severe diffuse brain injury have a lucid interval during which they are able to talk before lapsing into deeper coma. Up to a third of children may have some lucid interval (Bruce 1992). Most children with secondary deterioration have a benign course with a spontaneous and full recovery. A few children may go on to more prolonged and deeper coma, or even death.

Neurological deterioration following acute traumatic brain injury often warns of life-threatening complications. Many of these complications are treatable, and most are preventable. The most sensitive indicator of neurological deterioration is a progressive decrease in mental status and ultimately the level of consciousness. Brain damage secondary to events occurring after the initial injury is often more severe than the primary traumatic damage. Two mechanisms underlie these secondary injuries (Marshall 2000). First, there is a high risk of ongoing anoxic-ischemic injury in severely injured children. Other metabolic derangements, such as electrolyte imbalance, hypoglycemia, hyperosmolar

states, are also common. The effects of alterations involving excess excitatory amino acids, free radicals, cytokines, apoptosis, calpain proteolysis and axonal stretch are under active investigation (Marshall 2000). The second major process, increased volume within the cranial vault due to diffuse brain swelling and/or an expanding intracranial hemorrhage, may lead to herniation of the brain through the tentorium, compression of the brainstem as it is pushed caudally, or to global ischemic injury through lack of blood perfusion to brain tissue. Infection and fever may aggravate diffuse swelling.

Seizures occur in more than one in five patients during the first week after moderate-to-severe brain injury (early posttraumatic seizures) and may be associated with a worse outcome (Vespa *et al*. 1999). Seizures may be even more problematic in victims of child abuse (Gilles & Nelson 1998; Barlow *et al*. 2000).

In recovering patients, seizures may cause a temporary loss of consciousness with a period of postictal depression. Status epilepticus may lead to prolonged worsening, and to hypoxic-ischemic injury and more severe brain edema (Jennett & Teasdale 1981; Vespa *et al*. 1999). Seizures may be more important as a cause of secondary deterioration in children than in adults. Late onset posttraumatic epilepsy adversely affects the outcome of brain injury (Jennett & Teasdale 1981; Asikainen *et al*. 1999).

Subacute diffuse brain swelling is more likely to cause secondary neurological deterioration in children than in adults (Bruce 1992). In young children this swelling is sometimes so dramatic that it has been called the syndrome of "malignant brain edema." This condition is often treatable with good outcome if herniation and brain ischemia are prevented. On the other hand, diffuse brain swelling may cause death owing to increased intracranial pressure or transtentorial herniation. The pressure in the head may become so high that it exceeds the arterial pressure generated by the heart, making it incapable of perfusing the brain. This results in diffuse ischemic death of brain tissue. Once blood flow to the whole brain, or to portions of the brain, has ceased entirely for more than a period of time of minutes to hours, reperfusion and recovery do not occur (see Ashwal 1997 for discussion of the relationship between absent cerebral blood flow and brain death).

Intracranial hematomata occur in a minority of children with deteriorating neurological signs (Aoki & Masuzawa 1984; Dhellemmes *et al*. 1985; Stein *et al*. 1993; Oertel *et al*. 2002). Focal deficits, such as hemiparesis or eye deviation may warn of bleeding in the head. This is especially so when these signs appear gradually after an injury. Similarly, a gradual deterioration of mental status and ultimately consciousness may warn of bleeding, causing increasing intracranial pressure or pressure on the brainstem. Seizures commonly are associated with hematomata, and at times may contribute to clinical deterioration. If the child survives the initial deterioration, the outcome often has more to do with the underlying brain injury than with the presence of intracranial blood.

CONSIDER CONSULTATION WHEN...

- There is a decreasing level of consciousness detected by history, on examination, or on the Glagow Coma Scale.
- Focal neurological signs, or hemiparesis, are noted on neurological examination.
- Pupillary and eye movement abnormalities are detected. A gradually developing third-nerve palsy is most worrisome.
- A child has any prolonged seizures (more than about 1 minute) or if seizures occur after the first 24 hours, especially after the first week.
- Fever or other symptoms suggest a complicating systemic illness.
- There is a persistent hypermetabolic state with arterial hypertension and tachycardia. Even more worrisome is arterial hypertension and bradycardia.
- Electrolyte abnormalities suggest diabetes insipidus or the syndrome of inappropriate antidiuretic hormone secretion.
- Imaging studies suggest collections of free blood in the epidural space, in the subdural space, in the ventricles, or within the brain parenchyma.
- Imaging studies present a picture of small ventricles and lucent brain with blurring of the gray-white borders.
- Radiographs show a fracture of the skull that might be associated with rupture of an artery lying near the skull.

Pathology

Traumatic brain injury often disrupts the blood–brain barrier. Tight junctions between the endothelial cells of brain capillaries form this barrier and prevent passage of larger molecules out of the capillaries. The capillary barrier is susceptible to traumatic damage permitting a transudate to fill the extracellular spaces in the brain. This vascular compromise (termed vasogenic edema) involves biochemical mediators and is not due to direct mechanical disruption of the vessels. It affects the white matter preferentially. Cytotoxic edema, on the other hand, affects all parts of the brain and involves swelling of the neuronal and glial cells without an increase in extracellular fluid. Anoxic-ischemic injury, and injury resulting from most metabolic causes, is the major contributor to cytotoxic edema. Hyperemia also increases the volume of the brain, and is the major contributor to brain swelling in children during the first 24 hours or so following injury (Bruce 1992). The cerebrospinal fluid may be trapped within the ventricles, or it may fail to be absorbed into the venous system.

Intracranial hematomata may arise from bleeding in the epidural space, in the subdural space, in the ventricles, or

within the parenchyma of the brain. The clinical and pathological findings and the mechanisms of injury differ among these sites of bleeding.

Epidural hematomata (Dhellemmes *et al*. 1985) often are associated with a fracture of the skull and the subsequent rupture of an artery lying next to the skull. The middle meningeal artery often is injured, leading to a temporal fossa clot. However, epidural hematomata may also occur in the posterior fossa. The bleeding may be brisk, accounting for rapid neurological deterioration (over minutes), especially if the main branches of the middle meningeal artery are involved. Damage to smaller branches of the artery can result in less rapid (over several hours) deterioration of neurologic functioning. The clot of blood often forms a lens-shaped mass as it dissects the dura away from the skull. This mass then deforms the underlying brain that may herniate if the bleeding continues. Except for this mass effect and the pressure it exerts, the underlying brain may be relatively uninjured.

Subdural hematomata (Aoki & Masuzawa 1984), on the other hand, more often are associated with underlying brain injury. They appear to result from tearing of the veins bridging the subdural space. The bleeding is venous and therefore often slower and under less pressure than epidural arterial bleeding. Strong shearing forces appear to mediate the formation of subdural hematomata. These shearing forces are particularly disruptive to cortical nerve fibers. Microscopic evidence of axonal disruption (DAI) (Tomita *et al*. 1997; Hoskote *et al*. 2002) frequently is found in the brain underlying a subdural hematoma. This underlying brain may become quite edematous. As has been discussed above, such shearing does not occur in trivial injuries.

Intracerebral blood often is associated with focal contusions or lacerations of the brain. Contusions alone, though they may be extensive, rarely are large enough to account for loss of consciousness. However, they frequently are accompanied by focal or diffuse brain edema and axonal injury, which accentuates their clinical importance. Petechial hemorrhages, and small hemorrhages in the hemispheres, corpus callosum or brainstem, suggest DAI. Persistent evidence on MRI of contusion, or of DAI, suggests a worse prognosis.

Collections of blood occasionally are found within the ventricular system, usually when subdural, epidural, or intraparenchymal hematomata are also present. Intraventricular hemorrhage often is correlated with more severe injury and with a worse outcome.

Occasionally intraparenchymal bleeding is delayed by hours or days following the injury (Givner *et al*. 2002; Oertel *et al*. 2002). The mechanism of this curious circumstance is unknown but may be related to local or diffuse clotting abnormalities induced by the trauma. Evidence of intravascular fibrinolysis is frequently obtained. The tendency to form delayed hematomata may be related to the severity of the underlying brain injury.

Signs and symptoms

Brain swelling causes clinically significant signs and symptoms by two mechanisms: increased intracranial pressure and transtentorial herniation. The most sensitive indicator of progressive compromise owing to brain swelling is a deterioration of mental status and ultimately a decreasing level of consciousness. The GCS monitors the rostral-caudal progression of symptoms caused by downward herniation of the brain and brainstem (Jennett & Teasdale 1981). The GCS score reflects the sequential compromise of the diencephalon, midbrain, pons, and medulla. The symptoms associated with compromise at each of these levels were discussed previously. Brain swelling can also exert pressure on the third cranial nerves resulting in dilated and unresponsive pupils bilaterally for diffuse swelling, and unilaterally when swelling is restricted to one hemisphere.

Inadequate ventilation with hypoxia and hypercarbia is the most common condition aggravating brain swelling and leading to neurological compromise following head trauma. Hypoventilation, with its attendant deleterious effects, sometimes occurs in association with acute brain injury before medical assistance arrives. Further hypoventilation is then often preventable. Primary pulmonary complications cause hypoventilation and may include pneumonia or pneumonitis from aspiration of gastric contents, or of water as in drowning. Intubation, or sometimes tracheostomy, may be necessary to maintain an open airway. Almost every seriously head-injured child has difficulty swallowing and handling secretions, a problem that may lead to airway obstruction or pneumonia. Infection and fever from any source may aggravate brain swelling.

The adult respiratory distress syndrome occurs in children and may make ventilation difficult. Rigid posturing also may interfere with ventilation and require management with neuromuscular paralysis. Pulmonary edema caused by injudicious fluid management is a preventable complication. On the other hand, hypotension owing to inadequate fluid administration may further damage the brain and other organs. Good hemodynamic balance is essential (Marshall 2000).

The hallmark of clinically significant intracranial bleeding is gradual neurological deterioration with the appearance of focal neurological signs, deterioration of mental status, and a decreasing level of consciousness. Seizures frequently are associated with hematomata, and may suggest their presence. While these signs and symptoms are consistent with an expanding hematoma, only a minority of children with these symptoms has clinically significant intracranial bleeding (Stein *et al*. 1993). More often, these symptoms are the result of progressive brain swelling. Similarly, not all intracranial hematomata are symptomatic. Furthermore, the symptoms of the various kinds of intracranial bleeding often overlap. Thus the clinical evaluation of intracranial he-

matomata is not entirely reliable. CT scanning (see below) adds greatly to the clinical characterization of intracranial bleeding and is of obvious therapeutic importance. MRI is more sensitive for small extra-axial bleeding and contusions close to bone, but usually MRI is not clinically necessary in the acute setting.

A hemiparesis sometimes is associated with an intracranial hematoma. This condition may be difficult to evaluate in a comatose child, but careful observation of spontaneous movements, and movements in response to stimulation, may reveal the deficit. Reflex asymmetry, or the Babinski sign, sometimes is helpful. Conjugate eye deviation, or a gaze preference, sometimes correlates with a hemispheric hematoma. As a rule, the eyes look toward the side of the lesion. In a few per cent of cases, this sign may be "false-localizing" and the eyes look toward the side opposite the lesion (Tijssen 1994). Fortunately, CT provides a rapid and direct determination of the location of a hematoma of clinically significant size (Givner *et al*. 2002).

Unilateral pupil dilation, with ptosis and failure of adduction of the affected eye, suggests third-nerve palsy. When this sign appears after an injury, it suggests an expanding intracranial mass and incipient uncal herniation. Except in a minority of cases, the affected eye is on the same side as the mass (Lawrence *et al*. 2001). This third-nerve sign is not a part of the previously discussed central herniation syndrome. Unfortunately, this clinical sign occurs late and is more important as a herald of impending uncal herniation than as an early sign of intracranial bleeding.

Retinal and preretinal hemorrhages may be associated with traumatic hematomata, especially when they involve acceleration/deceleration injury. Extensive retinal and preretinal hemorrhages and retinal tears, without a history of trauma adequate to explain the injury, strongly suggest nonaccidental injury (see the first section of this article).

Hematomata may occur in the posterior fossa after mild or severe head injuries. Rapid deterioration accompanying larger hematomata may produce apnea and deep coma. Brainstem compression may be quickly fatal. Pupillary movement, eye movement, and motor signs often, but not always, accompany larger posterior fossa hematomata. Small hematomata in the parenchyma of the brainstem may produce devastating symptoms that belie their size. Headache, papilledema, nystagmus, and ataxia suggest less severe hematomata.

Epidural bleeding often is brisk. Neurological deterioration may occur from a matter of minutes to several hours after the injury (Dhellemmes *et al*. 1985). Untreated, the deterioration associated with epidural hematomata may be profound. However, because the underlying brain may be relatively uninjured, prompt evacuation may result in a gratifying outcome.

Seizures complicate the hospital course of about one in five children with traumatic brain injury. Roughly 50% of children with penetrating injury or intracranial hematoma have seizures (Jennett & Teasdale 1981; Vespa *et al*. 1999). In about 60% of cases, seizures occur within the first 24 hours after injury. Seizures further aggravate the effects of brain injury by increasing brain metabolism and producing acidosis. Hypoxia, systemic acidosis, increased intracranial pressure, and fever may accompany the muscle contractions of seizures. These movements may worsen other injuries. Furthermore, seizures may not be detected clinically in patients being treated with paralytic agents, and may not be prevented by prophylactic administration of phenytoin. Recently, continuous EEG recording has been shown to be useful for detection of seizures under these conditions (Vespa *et al*. 1999). Paralyzing the child does not reverse the central effects of seizures. Local brain tissue hypoxia and acidosis may continue to damage the brain even though paralyzing drugs mask the clinical signs of seizures.

Late post-traumatic epilepsy (seizures occurring more than 1 week after the injury) is more likely to occur if there is penetrating brain injury or hematoma, or if early seizures have occurred. Early post-traumatic seizures occur more often, and late seizures less often, in children than in adults (Jennett & Teasdale 1981; Asikainen *et al*. 1999).

Electrolyte abnormalities are common following severe head trauma. Inattention to electrolyte balance may add to the problems caused by diabetes insipidus or inappropriate antidiuretic hormone secretion. These latter abnormalities may occur at different times in the same patient. Poor temperature regulation accompanies severe brain injury. However, as already noted, hypothermia rather than fever is the rule.

A hypermetabolic state occurs in many children with traumatic or metabolic brain injury. Increased catecholamine secretion into the peripheral circulation, triggered by the injured brain, causes arterial hypertension and tachycardia. Direct cardiac injury and cerebral perfusion disturbances may result when this condition is severe. Although the arterial blood pressure is high, the intracranial pressure also may be high and the cerebral blood flow compromised. Excessive catecholamine release is to be distinguished from the Cushing reflex that comprises arterial hypertension and bradycardia, rather than tachycardia, in response to increased intracranial pressure. The hypermetabolic state caused by excess catecholamine secretion may be treated with beta-adrenergic blockade. As the arterial blood pressure is reduced the intracranial pressure often follows, without further compromise of the cerebral perfusion pressure (for a more complete discussion see Marshall 2000).

Nutrition is compromised by the need for fluid restriction and the relative inability to provide oral feedings. Hypermetabolism complicates this nutritional deficiency. Some children lose 20% of their body weight in the first 2 weeks in the hospital. This condition can be alleviated partly by early institution of nasogastric feedings or parenteral hyperalimentation.

Penetrating head trauma is a special problem because of the risks of infection and the need for surgical intervention to debride the wound. If the penetration is by a low-velocity object, the signs and symptoms are those of purely focal brain injury, with any swelling being restricted to the damaged tissue. Unless there is involvement of both hemispheres, or of the brainstem, there is no, or only brief, loss of consciousness, with the sequelae being related to the injured portion of the brain.

Diagnostic studies

CT is the major diagnostic tool for the evaluation of brain swelling (Givner *et al*. 2002; Oertel *et al*. 2002), but it is limited because it cannot measure intracranial pressure. Thus clinically significant swelling may accompany a normal CT, and marked swelling on CT may accompany normal intracranial pressure. CT in acute head injury often shows small ventricles, and reduced size of the perimesencephalic cistern, which is immediately posterior to the mesencephalic structures of the superior and inferior colliculi (quadrageminal plate). The parenchyma may be lucent with blurring of the border between the gray matter and the white matter appearing as reduced gray-white differentiation. In children these changes may be difficult to distinguish from normal. Acute or incipient herniation of the brainstem may be suspected if there is obliteration of the perimesencephalic cistern. The lateral recesses of this cistern separate the midbrain from the unci of the temporal lobes. Although CT is most often used, MRI also is sometimes useful in detecting early edema.

CT provides a rapid and reliable, and noninvasive means of diagnosing and following intracranial bleeding (Stein *et al*. 1993; Tomita *et al*. 1997). A CT scanner is mandatory for any center treating head injuries. CT frequently allows the diagnosis of intracranial bleeding before symptoms associated with the hematoma appear or are recognized. This allows the physician to follow the course of the hematoma and to be forewarned of possible problems relating to acute management and to rehabilitation.

MRI may detect some hematomata not seen on CT. However, the small increase in yield rarely justifies the extra time required and risk of placing an acutely ill patient in a device with which monitoring is difficult and all magnetic materials must be removed from the room.

Since the coming of CT, angiography rarely is used to identify hematomata. However, this procedure may be of value to the surgeon in defining vascular supply. Blindly placed skull trephine or burr holes without CT are dangerous and frequently miss significant hematomata easily identified by CT. Subdural taps in an infant with an open fontanel are less dangerous, but still much less sensitive than CT.

Plain skull X-rays may be helpful in identifying fractures associated with epidural or subdural hematomata. These fractures are usually, but not always, visible on CT images as well.

Intracranial pressure monitoring (see below) is an indirect measure of cerebral blood flow. The ability directly to measure cerebral blood flow, or tissue oxygenation, rarely is available, but may demonstrate hyperemia or ischemia. Such techniques are promising additions to future management of brain injury (Marshall 2000; van den Brink *et al*. 2000). Similarly, continuous EEG monitoring may become an indispensable tool in monitoring children with traumatic brain injury (Vespa *et al*. 1999).

Lumbar puncture is relatively contraindicated in the presence of increased intracranial pressure because of the risk of herniation, and usually is unnecessary.

Treatment

Intubation and hyperventilation are the most rapid and effective ways of treating progressive brain and brainstem compromise owing to increased intracranial pressure. This procedure is not without risk because hyperventilation sometimes exacerbates cerebral ischemia (van den Brink *et al*. 2000). Injudicious use of hyperventilation will reduce cerebral blood flow, may cause loss of autoregulation, but will not consistently cause a reduction of intracranial pressure (see Marshall 2000 for a more complete discussion).

For severe brain injury, it is standard practice to paralyze the patient to prevent "fighting" the ventilator, and to reduce intrathoracic pressure that is transmitted to the brain. Hyperosmolar agents, such as mannitol or sodium, may be helpful to reduce brain water. However, early in the course in children, brain swelling may result from hyperemia with little increase in brain water. Therefore these agents may worsen the problem initially by increasing blood volume, and also may contribute to hyperosmolar damage and electrolyte imbalance. Their use should be limited to an intensive care unit, and to medical and nursing personnel who are familiar with their effects (Marshall 2000; van den Brink *et al*. 2000).

Monitoring of intracranial pressure is a standard of care in the management of brain swelling (Marshall 2000). Ventricular catheterization is the most invasive of the monitoring procedures. Furthermore, the catheter cannot always successfully be placed because of small ventricular size owing to brain swelling. On the other hand ventricular catheterization allows for the most direct measurement of intracranial pressure and permits some reduction of intracranial hypertension by venting cerebrospinal fluid. A fiberoptic pressure monitor in the subarachnoid space threaded through a screw in the skull provides reliable readings and is less invasive than the ventricular catheter.

There is little evidence that intracranial hypertension per se causes secondary brain injury. Rather the increased pressure is transmitted to the intracranial vascular tree and may

compromise cerebral blood flow. The maintenance of brain cellular oxygenation is of fundamental importance, and is the subject of current research. Brain tissue hypoxia occurs frequently during the treatment of severely brain-injured patients and is significantly related to poor outcome (Marshall 2000; van den Brink *et al*. 2000).

Prompt evacuation of larger extra-axial hematomata is often lifesaving. In spite of the underlying brain injury associated with subdural hematomata, evacuation within 4 hours greatly improves survival. With large epidural hematomata, survival is dramatically better with prompt drainage. Thus the early diagnosis of intracranial hematomata is essential. CT scans should be obtained initially in all children with severe traumatic brain injuries, and should be done whenever evidence of neurological deterioration appears (Stein *et al*. 1993; Givner *et al*. 2002; Oertel *et al*. 2002).

Smaller clots that do not produce clinically significant mass effects need not be evacuated acutely. Debridement of contused and lacerated brain may be necessary because of increasing intracranial pressure and local mass effect. Delayed intraparenchymal hematomata usually do not require drainage. Furthermore, the location of these hematomata within the brain parenchyma, and the coagulopathy associated with them, make surgical removal more difficult.

The brain edema associated especially with subdural and intracerebral hematomata may pose important therapeutic problems. Craniectomy, and removal of portions of the damaged brain, may be of benefit in the treatment of expanding masses aggravated by focal brain edema. The amelioration of the effects of brain edema by bilateral craniectomy, barbiturate coma, glucocorticoids, and hypothermia are subjects of ongoing study (Marshall 2000; van den Brink *et al*. 2000).

Children who are comatose (GCS of 8 or less), or whose deteriorating level of consciousness suggests they may become comatose, should be treated in an appropriate intensive care unit. The presence of other injuries, or systemic illness, increases the risk of deterioration and complicates the management of brain injury.

The most important feature of an appropriate intensive care unit is nurses who are familiar and comfortable with the management of acutely brain-injured children. Round-the-clock availability of neurosurgical care committed to the management of traumatic brain injury also is important. CT capability must be immediately available.

Transport to an appropriate facility should involve initial stabilization, which usually includes intubation. Many units now have transport teams to ensure against secondary brain damage in transit (Table 7.5).

FEATURES

Table 7.5 Deterioration Following Acute Brain Injury

Discriminating features

1. Subacute decreasing level of consciousness is the most sensitive indicator of progressive brain and brainstem compromise.
2. Increased brain volume is due to greater quantities of extracellular fluid (vasogenic edema), intracellular fluid (cytotoxic edema), or blood (hyperemia).
3. Collections of free blood in the epidural space, in the subdural space, in the ventricles, or within the brain parenchyma.

Consistent features

1. Increased intracranial pressure.
2. CT picture of small ventricles and lucent brain with blurring of the gray-white borders.
3. Focal neurological signs.
4. Hemiparesis with a supratentorial hematoma.
5. Pupillary and eye movement abnormalities and motor signs suggest a posterior fossa hematoma.
6. Seizures.
7. Gradually developing third-nerve palsy suggests an intracerebral hematoma and may herald impending uncal herniation.

Variable features

1. Obliteration of the perimesencephalic cisterns may be seen in incipient or actual herniation.
2. Seizures worsen brain swelling, but are more likely to occur if there is some focal injury to the brain.
3. Electrolyte abnormalities may be due to diabetes insipidus or to the syndrome of inappropriate antidiuretic hormone secretion.
4. A hypermetabolic state with arterial hypertension and tachycardia.
5. Epidural hematomata often are associated with fracture of the skull and rupture of an artery lying near the skull.
6. Subdural hematomata often are associated with marked underlying brain injury owing to the shearing forces involved in the formation of the hematoma.
7. Intracerebral bleeding often complicates focal contusion and lacerations and may be delayed by hours or days following the injury.
8. Retinal and preretinal hemorrhages may accompany intracerebral hematomata, especially those involving acceleration/deceleration injuries.
9. Retinal and preretinal hemorrhages suggest nonaccidental trauma.

Recovery from traumatic brain injury

Recovery from a traumatic brain injury in childhood is variable. Those children with the worst injuries die or remain in a coma or persistent minimally conscious or vegetative state. Surviving children show transient or permanent neurological deficits. Less obvious lasting deficits become evident as difficulties in school, or as findings on more detailed neuropsychological evaluation. The rate and extent of recovery from traumatic brain injury follows a characteristic course when one looks at many patients (Levin 1982; Jaffe

1995; Levin 1997; Catroppa & Anderson 2002; Ewing-Cobbs *et al*. 2003). No two children have identical deficits involving motor, cognition or behavioral functioning. The pattern of recovery similarly is variable. Yet the similarities in the patterns of impairment and recovery tend to outweigh the individual differences. Early in the course, it is hardly possible to predict reliably the outcome of any particular patient. For those children who have not recovered fully within the first year after injury, the rate of recovery slows. Those children with greater severity of injury improve less over the 2 years following the injury than do children with less severe injuries (Jaffe 1995). It is clear, however, that in a population of brain-injured children, significant recovery continues for several years following a traumatic brain injury (Jaffe 1995; Ewing-Cobbs *et al*. 2003; Johnson *et al*. 2003). Traumatic brain injury differs from severe anoxic-ischemic injury (Kriel *et al*. 1994) in that good recovery from prolonged coma is the rule, and not the exception. More than half of children who have been in coma for 3 months eventually walk, talk and go to school (Brink *et al*. 1980). Among former students who had suffered traumatic brain injury, 62% had returned to school by 6 months after injury (Ruff *et al*. 1993) Recovery from coma lasting longer than 3–6 months is unusual

At first glance, the prognosis for recovery from traumatic brain injury in children might seem better than that for adults. This is true for older children and adolescents. In contrast, the immature brains of young children are particularly vulnerable to diffuse damage, and they are more likely to show residual neuropsychological deficits. Because injury takes place during sensitive developmental periods, some deficits may not present until several years later in a child's life, when the functions were expected to mature naturally. Later deficits frequently include difficulties with executive functions such as foresight, hindsight, planning, organization and the conceptualization of abstract concepts (Levin 2002; Hanten *et al*. 2002; Ewing-Cobbs *et al*. 2003; Johnson *et al*. 2003).

Injuries in primary cortical areas that produce specific deficits such as visual field scotomata or anopias, motor paralysis, and tactile deficits typically show rapid and compete recovery. However, recovery from problems persisting for more than a few months is likely to be incomplete.

Lesions in the posterior cortical association areas of the parietal lobe involve more complex functions such as constructional abilities, visual-motor coordination, higher order language and visual processing, and one's ability to allocate attention appropriately. These problems show more gradual improvement that continues beyond the first year after injury (Lezak 1995; Ewing-Cobbs *et al*. 2003).

Patterns of behavior involving the prefrontal and anterior temporal cortical areas, or that are symptomatic of more diffuse injury, portend prolonged impairment (Levin 1982; Schwartz *et al*. 2003). Even if a brain-injured child returns to fully independent and functional living, subtle deficits that reflect the child's injury may be apparent to the experienced eye. Problems in memory, organization, speed of thinking, attention and concentration, affective control and irritability, motivation, judgment and socialization are the hallmarks of traumatic brain injury (Hutchison 1992). Children with mild head trauma, involving brief or no loss of consciousness, transiently show some of these typical sequelae. Such impairments usually disappear completely within hours. As discussed in a previous section of this chapter, depending on the situation, about a third of children with mild traumatic brain injury have persistent cognitive complaints 6 months after the injury.

PEARLS & PERILS

Recovery from Traumatic Brain Injury

- Transient blindness following a mild head injury often resolves without sequelae.
- A few children will have an alarming but transient picture of deep coma with unreactive pupils, but with rapid and complete recovery.
- An extended period of mutism lasting a few days to several months, followed by complete resolution, occurs in about 3% of adult brain-injured patients. The frequency of occurrence in brain-injured children is unknown, but certainly higher than in adults.
- Gaze palsies and visual tracking problems usually are transient, but may persist for more than 6 months in a third of brain-injured patients.
- The brains of young children appear to be more vulnerable to lasting damage than those of older children and adolescents.
- It is not possible to predict reliably, for most individual children, the rate and extent of recovery.
- Children with severe cognitive disability owing to traumatic brain injury do not necessarily score in the abnormal range on standardized tests.
- The normal emergence of continuing developmental skills may limit the recognition of residual deficits of traumatic brain injury until the deficient skill would be expected to appear.

Pathology

The pathology of traumatic brain injury has been discussed in previous sections of this article. Injury to the brain resulting in focal neurological deficits may occur by direct contusion at the point of impact, or opposite the blow in contre-coup injuries. Injuries involving more force, or those characterized by significant rotational acceleration, frequently produce direct contusion of the brain against the bony prominences of the calvarium. This pattern accounts for the almost universal signs and symptoms of frontal and anterior temporal lobe dysfunction seen in traumatic brain injury (Levin 1982; Baddeley & Wilson 1988; Garth *et al*. 1997; Hanten *et al*. 2002; Schwartz *et al*. 2003).

Intracerebral hematomata account for a major portion of focal symptoms. Encephalomalacia (loss of brain substance due to necrosis) almost always can be detected in the area of the hematoma. Penetrating trauma produces similar focal injuries. Compared to diffuse brain injury, focal injuries are more frequently associated with post-traumatic epilepsy.

More diffusely distributed but multifocal gray matter contusions and lacerations may be reflected in global symptoms involving reasoning and judgment. Diffuse white matter injury (DAI) sometimes results in prolonged coma or in a persistent minimally conscious or vegetative state. White matter injury contributes to the marked slowing and inefficiency of motor and cognitive processes encountered during recovery from severe injury.

Some measure of anoxia or ischemia accompanies most severe traumatic brain injuries. Anoxia affects the gray matter preferentially; the hippocampus and basal ganglia are the most sensitive areas. More severe anoxic-ischemic injury affects the gray matter globally, usually with severe sequelae (Kriel *et al*. 1994). Diffuse white matter destruction is typical following very severe anoxic-ischemic injuries.

Memory consolidation, subserved by the limbic system and thalamus, is impaired after traumatic brain injury because the hippocampus, in particular, is exquisitely susceptible to anoxia, and also to direct mechanical contusion of the temporal poles (Levin 1982; Catroppa & Anderson 2002).

Signs and symptoms

The relationships of brain injury to observed deficits have been discussed in great detail (Levin 1982; Lezak 1995; Kolb & Wilshaw 1996; Heilman & Valenstein 2003). Receptive deficits following traumatic brain injury may include signs and symptoms related to primary cortical sensory areas. Visual field deficits are common after severe hemispheric injury. Tactile sensory deficits are subserved by redundant systems and therefore pain and touch are rarely lost completely. The residual sensory deficits are easily overlooked in children. Discriminatory touch including stereognosis is more susceptible to injury, but may be quite difficult to test in children. Hearing loss is more easily tested but also easily overlooked. Hearing loss accounts for some delays in the acquisition or reacquisition of language. Loss of smell owing to shearing off of the small olfactory fibers as they traverse the cribriform plate prevents the awareness of danger signified by such odors as smoke and spoiled food. The vestibular system is easily damaged leading to dizziness and eye movement problems (Jennett & Teasdale 1981).

More complex receptive deficits involving the perception of language from auditory or visual material suggest damage to the posterior association cortex. Deficits in visual-spatial perception may be more subtle, but still quite debilitating. Constructional deficits, and poor drawing or writing skills, suggest disruption of the integration of sensory information with motor functions

Spastic paralysis results from injury anywhere along the length of the pyramidal tracts. More subtle limitations involving motor efficiency suggest disruption of secondary and tertiary motor cortices. Abnormalities of tone and posture, inaccuracy and poor coordination of movements, and movement disorders such as tremor, ataxia, choreoathetosis, dystonia and ballism, suggest injury to the extrapyramidal motor system. Slow, irregular, robot-like movements and gait are characteristic of children with severe brain injury and may persist in spite of otherwise excellent functional recovery. These deficits interfere with normal psychosocial development and preclude recreational activities requiring grace of movement. It is important to remember that extrapyramidal abnormalities may be quite delayed in onset, a year or more after injury (Krauss & Jankovic 2002).

Focal motor and sensory signs may reflect circumscribed injury anywhere in the brain or brainstem. The localization of these lesions benefits from the rich heritage of the study of vascular lesions in neurology. Brainstem signs, particularly gaze palsies, and visual tracking problems owing to frontal lobe dysfunction, usually are transient, but may persist for more than 6 months in a third of brain-injured patients (Jennett 1981). Unilateral frontal lobe damage close to the eye-gaze center can result in a period of eye deviation to one side or the other, making it important to interact with the child from the side that allows for easier visual contact. Rarely, transient blindness is present initially with complete resolution over time.

Problems in the planning and execution of complex coordinated movements suggest more anterior cortical injury. Some motor aphasic symptoms are in this category. The understanding and use of complex sentences, stories, and humorous material also suffers from frontal damage. The American Speech-Language-Hearing Association uses the term cognitive-communicative disorder to describe these deficits that are the predominant type of language disturbance related to TBI (Blosser & DePompei 1994). Such deficits undoubtedly account for peculiarities of language, and limitations involving verbal exchanges, that are recurrent attributes of brain-injured children.

More global brain injuries affect attention, concentration, and the ability to track complex concepts and reasoning. Slow and inefficient cognitive processing demands more time for the child to complete assignments. Deficient multitasking, or ability to track various components of a task, makes processing complex material or assignments more difficult. School and social functioning are impaired even when primary cognitive skills such as reading and computation are intact. Impulsivity, distractibility, and motor hyperactivity are frequent attributes of brain-injured children, as are states of apathy and inactivity. These deficits are particularly difficult to rehabilitate in part because they lead to

poor participation in a therapy regimen. Children who are fastidious in other ways may become erratic and careless in dress and hygiene. Children with impaired ability to start and stop activities, or to shift activities, may appear rigid and apparently uncooperative. Explosive behavior, catastrophic anxiety, and intractable indifference are exasperating to parents, teachers, and peers. These problems seriously may hamper goal-directed behavior in children who otherwise have shown excellent cognitive recovery.

The opportunity for the development of secondary emotional and behavioral problems is obvious. Preinjury family and child functioning play major roles in outcome (Rivara *et al*. 1994; Yeates *et al*. 1997; Schwartz *et al*. 2003). The family's ability to cope with the child's injury also is important, and family environment has been shown to influence postinjury progress (Rivara *et al*. 1994; Taylor *et al*. 2002). Unfortunately, the prejudices of parents and siblings, as well as of teachers and peers (Hawley *et al*. 2004), may have forceful negative impact on the brain-injured child. There is no substitute for an appropriately supportive and structured home environment in the rehabilitation of the child with traumatic brain injury.

Memory is a highly complex brain function that depends on several structures and processes. Thus it is not surprising that memory difficulties are virtually universal in traumatic brain injury (Catroppa & Anderson 2002; Levin 2002). Immediate memory recovers quickly in patients who regain consciousness. Thus they can grasp and remember the events around them for some seconds. However, recovery of the next process, short-term memory is more likely to be prolonged. Conscious children with short-term memory deficits are unable to lay down any lasting new memories, and may remain confused and disoriented even though they can recognize faces, speak, and converse on a perfunctory level. After further recovery, children have little or no memory of this period of disorientation following their injury, a phenomenon called *post-traumatic amnesia*. In addition to the extent of recovery, the length of post-traumatic amnesia commonly is used as a measure of the severity of injury (Levin 1982). The hippocampus plays an important role in short-term memory. It is quite sensitive to anoxia, and also may be injured directly by contusion of the temporal poles.

Confabulations are more prominent in children with posttraumatic amnesia who also have a frontally based dysexecutive syndrome (Baddeley & Wilson 1988; Fischer *et al*. 1995).

Retrograde amnesia (loss of memory for events preceding the trauma) commonly occurs with any degree of traumatic brain injury. An injury sufficient to produce posttraumatic amnesia also disrupts those memories that, at the time of the accident, had not yet been consolidated into long-term memory. This period rarely exceeds 30 minutes before the injury. In another phenomenon, called shrinking retrograde amnesia, memories of events several months before the accident are lost, but gradually return. Their loss reflects abnormalities in memory retrieval. Older and often-rehearsed memories are the most easily retrieved, but these represent only a small part of the stored experiences of a normal child (Levin 1982).

Deficits in speech and language are present in about a third of brain-injured adults and children at 6 months post injury (Levin 1982). Naming errors and word-finding difficulties routinely persist in brain-injured children. These deficits contribute to the use of inappropriate words, paraphasias (production of unintended syllables, words or phrases), verbal approximations and circumlocution where the child uses inefficient means to communicate verbally. Whereas naming involves memory, dysnomia following brain injury is more related to disruption of the language association areas of the posterior temporal cortex (Kolb & Wilshaw 1996). Aphasias are complex and involve a spectrum of deficits from subtle word-finding problems and agrammatism (disrupted sentence structure), to more severe deficits involving impaired comprehension and expression of the most basic

CONSIDER CONSULTATION WHEN...

- A child remains in coma for more than a day or so following brain injury, and when a team approach to rehabilitation seems essential because several overlapping areas of expertise are needed.
- It is anticipated that a structured and supportive environment is essential for a child (and family) with impaired executive functions and whose performance deteriorates with extraneous stimulation.
- Memory is lost of the events of the accident and immediately afterward.
- Motor deficits persist including spasticity, disorders of tone and posture, movement disorders, ataxia, and deficits in the planning and execution of complex coordinated movements.
- Language problems persist including comprehension, visual perceptual, naming, expressive difficulties and nonaphasic speech disturbances.
- Hearing loss is present.
- A child demonstrates the hallmarks of traumatic brain injury that include impairments in:
  - memory
  - organization
  - speed of thinking
  - attention and concentration
  - affective control and irritability
  - motivation
  - judgment
  - socialization.
- School performance remains below that expected from standardized testing given in a one-on-one setting.
- During the normal emergence of developmental skills, deficiencies become apparent that were not previously noted.

language functions. In a minority of children, these problems may continue to improve for years after a severe head injury (Chapman *et al*. 2001). Nonaphasic speech disturbances – including dysarthria, mutism, echolalia, palilalia, stuttering, difficulty with intonation and prosody, and nonaphasic misnaming – also occur in brain-injured children. Mutism lasting a few days to several months, followed by complete resolution, occurs in about 3% of adult brain-injured patients. The frequency of occurrence in brain-injured children is unknown, but certainly higher than in adults (Levin 1982; Dayer *et al*. 1998). The prognosis for recovery of speech and language generally is better in children than in adults.

Younger children with focal left-brain injuries may show excellent recovery of language with time. This is apparently because there is bihemispheric language potential, particularly in younger children. This recovery of language is in contrast to the greater susceptibility of the immature brain to the effects of diffuse injury.

Diagnostic studies

Neuropsychological testing is useful for assessing the functional consequences of brain injury (Levin 1982; Lezak 1995). Prediction of the course of recovery from brain injury is hampered by the relative paucity of studies in children, and by the variability from case to case. Furthermore, deficits from brain injury are superimposed on normally emerging and continuing developmental skills. Younger children have a limited ability to cooperate with testing, and many skills that one would like to measure have not yet appeared (Ewing-Cobbs *et al*. 2003). Thus different test instruments, each with age-adjusted norms, must be used. However, care should be taken when using normative values with a heterogeneous TBI population, as they can be misleading (Jaffe 1993). Even so, discovery of motor, cognitive, and behavior deficits resulting from brain injury may not be possible for years after the injury (Blosser & DePompei 1994). By then the myriad factors influencing normal development and adjustment to disability confound the test results. Normal school performance, and normal performance on intellectual tests, does not guarantee a good long-term outcome (Koskimiemi *et al*. 1995; Chapman *et al*. 2001; Hawley *et al*. 2004). With continuing difficulties involving social functioning and executive skills (Slomine *et al*. 2002), navigating a post school environment can be a daunting task for a survivor of childhood TBI.

Detailed assessment of a head-injured child is a complex process that includes formal testing and also the integration of the child's premorbid functioning and personal-social history. Because of the child's limitations in arousal and attention, and in motor and language skills, informal assessment of a child's abilities during therapy sessions, play activities and other less structured times can be very helpful in evaluating functioning. The major purpose of an assessment is to guide rational therapy in an inpatient or outpatient rehabilitation setting, or in school (Hawley *et al*. 2004). Sometimes an assessment is done for legal reasons, or better to inform the parents about the child's condition. There is no simple test battery that reliably will identify all the areas of residual injury. Many head-injured children are severely debilitated by their injuries and yet score within the normal range of standardized tests. This paradox is particularly true in ordinary school evaluations, when only simple reading, word recognition, and computational skills are tested (Jaffe 1993; Chapman *et al*. 2001; Hawley *et al*. 2004). When the test situation is highly structured within a one-on-one setting, and with minimal if any distractions, subtle but disabling difficulties experienced by these children may go unnoticed. The caution that, "absence of evidence is not evidence of absence" should be well considered when assessing TBI children. Thus the organic deficits preventing the child's success in the classroom are ascribed to "behavioral problems" and the child may be denied appropriate special education services. Recently, tests of selective learning, and of working memory and prospective memory, show promise of sensitivity to some of the higher cognitive functions that so limit the participation of brain-injured children in school and community (Hanten *et al*. 2002; Levin 2002). Tests of executive functioning have also shown promise in clarifying subtle deficits that significantly impact school functioning, but do not show up on basic tests of cognition. Interestingly, although skills involved with executive functioning are not generally considered important in younger children, a younger age at injury has been shown to place children at greater risk of impairment on measures of executive functioning (Garth *et al*. 1997; Levin 1997; Slomine *et al*. 2002). In contrast, because many children perform inconsistently in the classroom due to variations in attention, fatigue, and executive functioning, any poor performance may be attributed to behavior or effort, and not due to brain-related limitations (Hawley *et al*. 2004). Furthermore, the standard categories of special education – "learning disabled," "emotionally disabled," "mildly mentally retarded," and so on – do not address the patterns of deficits seen in traumatically brain-injured children, where variability of functioning is the rule, not the exception. Thus knowledge of the special patterns of recovery, special needs and problems, and use of more sophisticated neuropsychological testing, are of great importance to the brain-injured child, especially at the time of return to school (Hawley *et al*. 2004).

In the acute period following a traumatic brain injury, the child's abilities may change daily. Thus the team involved in his or her treatment best does the assessment of the child's deficits regularly. The team may be directed by a child neurologist, physiatrist, or pediatrician and includes therapists from several disciplines. Individuals involved in assessments should be trained and skilled in working with hard-to-test children, as formal testing techniques may not

be applicable to a particular patient due to motor and language processing limitations, or by the executive dysfunctions described above.

CT, MRI, EEG and evoked response testing provide important information about the structure and function of the brain. However these tests do not directly measure performance, and therefore they are of limited usefulness in planning appropriate rehabilitation therapy. In contrast, measures of functional ability, such as the FRESNO (Roberts *et al*. 1999), are sensitive to daily or weekly changes in performance in the areas of mobility, self-care, language, cognition and socialization. The FRESNO has proven to be useful in the acute rehabilitation setting, and after discharge.

Rehabilitation

The more severely brain-injured child requires acute inpatient rehabilitation, which should begin even while the child is in coma. A team approach to rehabilitation is essential because several overlapping areas of expertise are needed to address a child with multiple problems (Esselman & Dillman-Long 2002; Ragnarsson *et al*. 1999). Furthermore, a structured and supportive environment is essential for children with impaired executive functions and whose performance deteriorates with extraneous stimulation. The family is an essential part of the rehabilitation team, and appropriate social and family interactions are fostered by the team approach (Esselman & Dillman-Long 2002). The rehabilitation nurse typically spends the most time with the child and acts as liaison between the team and the family. The speech and language pathologist assesses and treats language problems and deficits in cognitive functioning, including learning style as it relates to academic skills. The occupational therapist is concerned with the functional use of limbs, motor planning and visual-spatial or perceptual skills related to activities of daily living. A feeding team is assembled for children who are not able to take adequate nutrition by mouth. The physical therapist is concerned with tone and posture, seating and positioning, and ambulation. The psychologist addresses problems in the control of emotions, anxiety and aggressiveness, and family issues. Formal psychological and neuropsychological testing is done when appropriate to assist other team members in understanding neurocognitive limitations, and how they impact therapy. In addition, the neuropsychologist is important in educating the family about the functional effects of the brain injury, and how that may influence transition to home or to an educational environment. The child life specialist acts as an advocate for the child as a whole person, integrating play and recreation into the child's therapeutic regimen. Patient education and play activities are designed to reduce stress and to foster the integration of the child with family and community. The schoolteacher involves the child in educational activities and begins the reintegration of the child into an appropriate school upon discharge. The social worker is involved in maintaining and supporting the family, and in coordinating community resources for the child's benefit. The discharge planner or case manager provides a smooth and timely transition to home and community, and secures needed equipment and funding to continue the child's rehabilitation outside the hospital.

Some children benefit from a post acute rehabilitation setting, which may involve residential care. These are children who have recovered some measure of independent mobility and cognition and need additional intensive help in achieving successful reintegration in home and community (Ragnarsson *et al*. 1999).

Less severely injured children do not require a full team approach to rehabilitation. But an awareness of the problems unique to traumatic brain-injured children is essential to assess and treat them adequately.

School is the major occupational activity of children beyond 5 or 6 years of age. Reintegration into an appropriate school situation is essential for children with injuries of all degrees. When children require assistance in school, the federal law IDEA (Individuals with Disabilities Education Act), mandates that schools provide special education services and/or accommodations to students that qualify because of special needs that result from a brain injury. Importantly, children with brain injury typically require different services than children with impairments that are developmental in origin. One major difference is that characteristically, brain injury leads to inconsistencies in cognitive functioning with some retained old learning. Thus, it is difficult to understand why a child can do well in some areas, and yet have so much difficulty with other skills (Chapman *et al*. 2001; Hawley *et al*. 2004). Too often this results in the attribution of, "not trying" or "lazy," to the child. Brain-injured children with limitations involving attention and problem-solving strategies have difficulty utilizing trial and error techniques to solve problems. Therefore, mentoring and small group tutoring is much more helpful as the child learns by repeated successes, and techniques of problem-solving and organization of work can be taught directly. Children who have poor understanding or awareness of cognitive problems, and who fail to understand the need for external assistance, should be monitored, and not just asked whether they need assistance (Hawley *et al*. 2004).

Brain-injured children with reduced cognitive processing speed and deficits in sustained attention have difficulty completing assignments in the expected time. Motor limitations that impact writing and drawing skills exacerbate these cognitive problems. Provision of additional time for assignments and tests becomes necessary to facilitate functioning for these children within a school environment.

Within school and at home, it is important to accentuate the positive in a child with brain injury. Decreased confidence and self-esteem follows from overemphasis on the

remediation of deficits, especially within an educational environment. It also is important for family members, friends and teachers to normalize their interactions with the child, and not treat the child differently. Treating the child as disabled or damaged becomes a self-fulfilling prophecy (Hawley *et al*. 2004; Yeates *et al*. 1997).

The protection and safety of the brain-injured child require caution upon re-entering the community following discharge from the hospital. The child's intellectual ability is likely to be overestimated because physical impairments typically improve faster than cognitive impairments. Thus, following recovery from physical injuries, the child may appear to be functioning normally in spite of subtle deficits in thinking ability. One must anticipate that the brain-injured child will not exercise the same degree of concern for the safety of himself or herself, or for others, as would be expected in another child of the same age. In addition, the child may be impulsive owing to reduced ability to self-monitor and regulate his or her actions. Impaired or diminished judgment may result in the child inadvertently doing things that are dangerous, or the child failing to recognize when he or she is in a dangerous situation. This imposes upon those who care for a child with a traumatic brain injury the duty to exercise a high degree of vigilance and caution, and to provide more stringent structure and boundaries for safety (Table 7.6).

FEATURES

Table 7.6 Recovery from Traumatic Brain Injury

Discriminating features

1. The hallmarks of traumatic brain injury include impairments in memory, organization, speed of thinking, attention and concentration, affective control and irritability, motivation, judgment, and socialization.
2. To establish that a specific event caused the signs and symptoms of traumatic encephalopathy, it is necessary to document that the signs and symptoms appeared following the specific injury.
3. Memory of the events of the accident and immediately after is lost in all but the mildest injuries.

Consistent features

1. Motor deficits including spasticity, disorders of tone and posture, movement disorders, ataxia, and deficits in the planning and execution of complex coordinated movements.
2. Attention and concentration problems, impulsivity, distractibility, and motor hyperactivity.
3. Difficulties with reasoning, and tracking complex concepts, and multi-tasking.
4. Slow and inefficient cognitive processing.
5. Short-term memory problems, memory retrieval difficulties and shrinking retrograde amnesia.
6. Language problems including comprehension, visual perceptual, naming, and expressive difficulties. Nonaphasic speech disturbances also may occur. More complex problems with understanding and relating stories and humorous material are often present.
7. Behavior and emotional changes, which may include explosive behavior, catastrophic anxiety, or intractable indifference.

Variable features

1. Focal neurological deficits.
2. Visual field limitations.
3. Problems with discriminatory touch and stereognosis.
4. Hearing loss.
5. School performance below that expected from standardized testing given in a one-on-one setting.

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Discusses that "return to baseline" cognitive function as the criterion for recovery from concussion may be insufficient in adolescents.

Dixon CE, Taft WC, Hayes RL: Mechanisms of mild traumatic brain injury. J Head Trauma Rehabil 8:1–12, 1993.
Describes the pathophysiology of mechanical disruption of the injured brain, and the ensuing cascade of biochemical events contributing to the outcome of the injury.

Downs DS, Abwender D: Neuropsychological impairment in soccer athletes. J Sports Med Phys Fitness 42:103–107, 2002.
Demonstrates some evidence of cognitive impairment in career soccer players. The extent to which younger versus older athletes are at risk for soccer-related cognitive impairment is unclear.

Greenberg MK, chairperson: Practice parameter: The management of concussion in sports (summary statement). Neurology 48:581–585, 1997.
Grades concussion on the basis of loss of consciousness and mental status abnormalities. This AAN practice parameter contains detailed criteria for return to play after each grade of concussion.

Hoffman PAM, Stapert SZ, van Kroonenburgh MJ et al.: MR Imaging, single-photon emission CT, and neurocognitive performance after mild traumatic brain injury. Am J Neuroradiol 22:441–449, 2001.
Of patients presenting at emergency department with mild traumatic brain injury (with loss of consciousness less than 20 minutes) one-third had persistent cognitive complaints 6 months after the injury Of all the patients, 77% had abnormalities on MRI or SPECT. A majority had abnormalities on both studies. All of these patients had brain atrophy on volumetric analysis on follow-up.

Iverson GL, Lange RT: Examination of "postconcussion-like" symptoms in a healthy sample. Appl Neuropsych 10:137–144, 2003.
Among normal adults, between 35.9% and 75.7% endorse postconcussion-like symptoms related to any experience in the past 2 weeks. From 2.9% to 15.5% endorse more severe symptoms.

Kay T et al.: Definition of mild traumatic brain injury. J Head Trauma Rehabil 8:86–87, 1993.
A standard definition often used to define mild traumatic brain injury. This definition includes all but the most severe athletic injuries.

Lees-Hayley PR, Fox DD, Courtney JC: A comparison of complaints by mild brain injury claimants describing subjective experiences immediately following their injury. Arch Clin Neuropsychol 16:689–695, 2001.
Adults with mild traumatic brain injury, or with orthopedic injuries, reported postconcussive symptoms at similar rates.

McCrory P: Does second impact syndrome exist? Clin J Sport Med 11:144–149, 2001.
Suggests that the very rare condition of delayed catastrophic deterioration following some athletic injuries is related to diffuse cerebral swelling and is not due to the effects of repeated concussion.

Mittl RL, Grossman RI, Hiehle JF et al.: Prevalence of MR evidence of diffuse axonal injury in patients with mild head injury and normal head CT findings. Am J Neuroradiol 15:1583–1589, 1994.
Thirty per cent of persons with normal head CT and loss of consciousness less than 20 minutes show evidence of diffuse axonal injury.

Palchak MJ, Holmes JF, Vance CW et al.: A decision rule for identifying children at low risk for brain injuries after blunt trauma. Ann Emerg Med 42:492–506, 2003.
Of 304 children undergoing CT who lacked abnormal mental status, clinical signs of skull fracture, vomiting, scalp hematoma, or headache, only one had CT evidence of intracranial injury, and that child was discharged from the emergency department without complication.

Rutherford A, Stephens R, Potter D: The neuropsychology of heading and head trauma in association football (soccer): a review. Neuropsychol Rev 13:153–179, 2003.
Reviews the neuropsychological effects of concussion and repeated subconcussive blows as particularly related to soccer.

Simon B, Latourneau P, Vitorino E, McCall J: Pediatric minor head trauma: indications for computed tomographic scanning revisited. J Trauma 51:231–237, 2001.
Fourteen per cent of children treated at a Level I trauma center had CT evidence of intracranial injury despite normal neurological examination and lack of loss of consciousness. A liberal policy of CT scanning is advocated for children with mild traumatic brain injury.

Deterioration following acute brain injury

Aoki N, Masuzawa H: Infantile acute subdural hematoma: clinical analysis of 26 cases. J Neurosurg 61:273–280, 1984.
Discusses infantile subdural hematomas associated with minor trauma. Mechanism of injury is discussed with particular reference to the battered child syndrome.

Ashwal S. Brain death in the newborn. Clin Perinatol 24:859–882, 1997.
Includes thorough discussion of the relationship of absent blood flow to brain death particularly in the newborn, but also in older children.

Asikainen I, Kaste M, Sarna S et al. Early and late post-traumatic seizures in traumatic brain injury rehabilitation patients: brain injury factors causing late seizures and influence of seizures on long-term outcome. Epilepsia 40:584–589, 1999.
Young children are more prone to early seizures, and adolescents and adults, to late seizures. Late onset posttraumatic epilepsy adversely affects the outcome of brain injury.

Barlow KM, Spowart JJ, Minns RA: Early posttraumatic seizures in nonaccidental head injury: relation to outcome. Dev Med Child Neurol 42:591–594, 2000.
Out of 44 children with traumatic brain injury owing to nonaccidental trauma, 32 developed early posttraumatic seizures. The outcome in those with seizures was significantly worse than those without.

Bruce DA, Alavi A, Bilaniuk L et al.: Diffuse cerebral swelling following head injuries in children: the syndrome of "malignant brain edema." J Neurosurg 54:170–178, 1981.
Discusses deterioration caused by brain swelling in children with and without a "lucid period." The usefulness of CT in brain-injured children is illustrated. The role of hyperemia in acute brain swelling in children is presented.

Dhellemmes P, Lejeune JP, Christianens JL, Combelles G. Traumatic extradural hematomas in infancy and childhood: experience with 144 cases. J Neurosurg 62:861–864, 1985.
Discusses the incidence and clinical course of extradural (epidural) hematomas in children.

Givner A, Gurney J, O'Connor D et al.: Reimaging in pediatric neurotrauma: factors associated with progression of intracranial injury. J Pediatr Surg 37:381–385, 2002.
Children with more severe injury are more likely to show progressive lesions of edema and hematomata, especially if intracranial injury is present on the initial CT scan.

Gilles EE, Nelson MD, Jr: Cerebral complications of nonaccidental head injury in childhood. Pediatr Neurol 19:119–128, 1998.
Of 14 children, 11 (79%) had early post-traumatic seizures. Cerebral infarction developed in all survivors.

Hoskote A, Richards P, Anslow P, McShane T: Subdural haematoma and non-accidental head injury in children. Childs Nerv Syst 18:311–317, 2002.
Subdural hemorrhage in nonaccidental injury tends to present before 4 months of age. The patients are more seriously ill and have other findings such as fractures and retinal hemorrhages.

Jennett B, Teasdale G: Management of head injuries. Philadelphia, 1981, FA Davis, pp. 19–75, 211–252.
A clear presentation of the pathophysiology of diffuse brain swelling and its management. This book also discusses post-traumatic epilepsy.

Marshall LF: Head injury: recent past, present, and future. Neurosurgery 47:546–562, 2000.
A particularly cogent and articulate discussion of neurobiology and its application in the treatment of severe traumatic brain injury.

Marshman LA, Polkey CE, Penney CC. Unilateral fixed dilation of the pupil as a false-localizing sign with intracranial hemorrhage. Neurosurgery 49:1251–1255, 2001.
Dilation of the pupil contralateral to the intracranial lesion occurs in a minority of patients and thus constitutes a "false-localizing" sign. This article discusses the interaction of a variety of peripheral and central mechanisms underlying unilateral pupil dilation.

Mazzini L, Cossa FM, Angelino E et al.: Posttraumatic epilepsy: neuroradiologic and neuropsychological assessment of long-term outcome. Epilepsia 44:569–574, 2003.
In this prospective study of severely brain-injured persons, 19% developed posttraumatic epilepsy (PTE) between 1 and 39 months post injury. PTE is associated with a worse functional outcome. Agitated and aggressive behavior is more frequent and severe in PTE patients.

Oertel M, Kelly DF, McArthur D et al.: Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. J Neurosurg 96:109–116, 2002.

CT scans within 2 hours of severe head injury do not reveal the full extent of the hemorrhagic injury. Progressive hemorrhage is apparent in nearly 50% of these patients within the next 6 hours, particularly parenchymal lesions in the frontal and temporal lobes. These patients have a greater degree of intracranial pressure elevations and account for almost 25% of those who require craniotomy for hematoma removal.

Stein SC, Spettell C, Young G, Ross SE: Delayed and progressive brain injury in closed-head trauma: radiological demonstration. Neurosurgery 32:25–31, 1993.

The severity of the initial brain trauma contributes significantly to neurological outcome. The presence of delayed cerebral injury makes the outcome dramatically worse. Only 20% of patients (mostly adults) in this series with radiological worsening had subdural or epidural hematomas.

Tijssen CC: Contralateral conjugate eye deviation in acute supratentorial lesions. Stroke 25:1516–1519, 1994.

In 5 of 133 patients with conjugate eye deviation caused by an acute supratentorial lesion, the eye deviation proved to be a "false-localizing" sign with the gaze deviated to the side opposite the lesion.

Tomita H, Tone O, Ito U: Hemispheric cerebral atrophy after traumatic extra-axial hematoma in adults. Neurol Med Chir 37:819–824, 1997.

Acute swelling and subsequent atrophy are more prominent in the hemisphere underlying an acute hematoma.

van den Brink VA, van Santbrink H, Steyerberg EW et al.: Brain oxygen tension in severe head injury. Neurosurgery 46:868–876, 2000.

Discusses the measurement of brain tissue oxygenation and the role of this measure in intensive care, and in predicting outcome, in victims of severe brain injury.

Vespa PM, Nuwer MR, Nenov V et al.: Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. J Neurosurg 91:750–760, 1999.

Seizures occur in more than one in five patients during the first week after moderate-to-severe brain injury and may play a role in the pathobiological conditions associated with brain injury.

Recovery from traumatic brain injury

Baddeley A, Wilson B: Frontal amnesia and the dysexecutive syndrome. Brain Cognition 7:212–230, 1988.

A study of an amnestic patient with bilateral frontal damage and dysexecutive syndrome, who presented with poor autobiographical memory and substantial confabulations. Suggests that the deficits result from of a classic amnestic syndrome with additional problems associated with a frontal dysexecutive syndrome.

Blosser JL, DePompei R: Pediatric traumatic brain injury – Proactive Intervention, Neurogenic Communication Disorders Series. San Diego, 1994, Singular Publishing Group, Inc. pp. 27–31.

Focuses on the reintegration of children with brain injuries into community and educational systems. Written at a level that will be helpful to professionals, family members, and anyone else who wants to learn more about how to face the challenges intertwined with brain injury in young people.

Brink JD, Imbus C, Woo-Sam J: Physical recovery after severe closed head trauma in children and adolescents. J Pediatr 97:721–727, 1980.

Classic paper describing the recovery of brain-injured from coma. When coma lasts less than 3 months, a majority of children recover some mobility and are able to go to school.

Catroppa C, Anderson V: Recovery in memory function in the first year following TBI in children. Brain Inj 16:369–384, 2002.

Memory difficulties are present during the acute, 6- and 12-months following childhood TBI. Appropriate strategies and interventions for brain-injured children are discussed.

Chapman SB, McKinnon L, Levin HS, Song J, Meier MC, Chiu S. Longitudinal outcome of verbal discourse in children with traumatic brain injury: three-year follow-up. J Head Trauma Rehabil 16:441–455, 2001.

Severe TBI can have a pernicious effect on discourse abilities in children years after injury compared with children with mild/moderate injuries. Discourse measures must be sufficiently challenging when used to assess older children and children with milder forms of TBI.

Dayer A, Roulet E, Maeder P, Deonna T: Post-traumatic mutism in children: clinical characteristics, pattern of recovery and clinicopathological correlations. Eur J Paediatr Neurol 2:109–116, 1998.

Seven of 14 children in this study went through a period of total absence of verbal production lasting from 5 to 94 days, followed by the recovery of nonverbal communication skills and emotional vocalization.

Esselman PC, Dillman-Long J: Morbidity and management conference: an approach to quality improvement in brain injury rehabilitation. J Head Trauma Rehabil 17:257–262, 2002.

Rehabilitation medicine has a long history of working as a coordinated multidisciplinary team caring for complex patients with chronic conditions and is in a position to be a leader in QI activities.

Ewing-Cobbs L, Barnes MA, Fletcher JM et al.: Early brain injury in children: development and reorganization of cognitive function. Dev Neuropsychol 24:669–704, 2003.

Development and recovery after brain injury reflects both restoration and reorganization of cognitive functions.

Fischer RS, Alexander MP, D'Esposito M, Otto R: Neuropsychological and neuroanatomical correlates of confabulation. J Clin Exp Neuropsychol 17:20–28, 1995.

A common profile from nine confabulatory patients suggests that spontaneous confabulations require extensive, simultaneous disruption of medial basal forebrain and frontal cognitive systems resulting in profound executive and memory deficits.

Garth J, Anderson V, Wrennall J: Executive functions following moderate to severe frontal lobe injury: Impact of injury and age at injury. Pediatr Rehabil 1:99–108, 1997.

Twenty-two children with moderate to severe frontal lobe injuries (FLI) were examined on several tasks of executive functioning, and on intelligence, to determine the impact of FLI on the development of executive functioning through childhood.

Hanten G, Zhang L, Levin HS: Selective learning in children after traumatic brain injury: a preliminary study. Neuropsychol Dev Cog Sect C Child Neurospychol 8:107–120, 2002.

Selective learning is the ability to select important items to learn from among other items of lesser importance. Traumatically brain injured children are disproportionately compromised in selective learning compared to simple word recall.

Hawley CA, Ward AB, Magnay AR, Mychalkiw W: Return to school after brain injury. Arch Dis Child 89:136–142, 2004.

One-third of teachers were unaware of the TBI. Two-thirds of children with TBI had difficulties with school work, half had attention/concentration problems and 26 (39%) had memory problems. Compared to other pupils in the class, one-third of children with TBI were performing below average.

Heilman KM, Valenstein E: Clin Neuropsych, 4th edn. New York, 2003, Oxford.
Focuses on the clinical presentation of the major neurobehavioral syndromes. Includes clinical descriptions, neuropsychological mechanisms that might account for the disorders, brain pathology associated with the conditions, and possible aspects of therapy and management.

Hutchison HT: Traumatic encephalopathies In: David RB, editor: Pediatric Neurology for the Clinician. Norwalk, 1992, Appleton & Lange. p. 180.
The first edition of this chapter defines the hallmarks of traumatic brain injury.

Jaffe KM, Fay GC, Polissar NL et al.: Severity of pediatric traumatic brain injury and neurobehavioral recovery at one year: a cohort study. Arch Phys Med Rehabil 74:587–595, 1993.
Children between the ages of 6 and 15 who suffered mild, moderate, or severe TBI were followed for one year after injury. Neurobehavioral outcomes were statistically evaluated on three levels: a case score, case-control scores, and case/difference scores minus control/difference scores. Results showed that the use of population normative values to evaluate impairment was misleading. Although the mean scores of all severity groups fell within the normal range of standardized tests, the means for the moderately and severely injured were substantially below those of their matched controls on many tests.

Jaffe KM, Polissar NL, Fay GC, Liao S: Recovery trends over three years following pediatric traumatic brain injury. Arch Phys Med Rehabil 76:17–26, 1995.
This cohort study shows chronic neurobehavioral deficits across all 3 years for moderately and severely injured children. They show a strong improvement rate during the first year, but a negligible rate of change during the following 2 years postinjury in most domains. Domains investigated include intelligence, real-world functioning, behavior, and academic achievement. Mildly injured children, however, exhibit negligible deficits or change in performance over time.

Kolb B, Whishaw I: Fundamentals of human neuropsychology, 4th edn. New York, 1996, WH Freeman & Co., pp. 387–416.
An examination of neuropsychology from the perspective of cognitive neuroscience, human and nonhuman studies, and recent advances in the technology of brain study. This work covers general topics related to neuropsychology, in addition to specific topics related to clinical brain disorders.

Koskiniemi M, Kyykka T, Nybo T, Jarho L: Long-term outcome after severe brain injury in preschoolers is worse than expected. Arch Pediatr Adolesc Med 149:249–254, 1995.
This study followed 39 preschoolers with severe TBI into adulthood. Outcome measures of ability to work and living independently indicated the overall outcome is worse than originally thought.

Krauss JK, Jankovic J: Head injury and posttraumatic movement disorders. Neurosurgery 50:927–940, 2002.
Movement disorders after severe head injury have been reported in 13–66% of patients, and may be delayed in appearance. Although movement disorders after mild or moderate head injury are frequently transient and, in general, do not result in additional disability, kinetic tremors and dystonia may be a source of marked disability in survivors of severe head injury.

Kriel RL, Krach LE, Luxenberg MG, Jones-Saete C, Sanchez J: Outcome of severe anoxic/ischemic brain injury in children. Pediatr Neurol 10:207–212, 1994.
Cognitive and motor outcomes were correlated with the severity of injury as indicated by the duration of unconsciousness. All children who regained language skills or the ability to walk were unconscious less than 60 days.

Johnson DA, Rose FD, Brooks BM, Eyeres S: Age and recovery from brain injury: legal opinions, clinical beliefs and experimental evidence. Pediatr Rehabili 6:103–109, 2003.
Despite scientific evidence to the contrary, many medical practitioners maintain that children recover from brain injury better than adults.

Levin HS et al.: Neurobehavioral consequences of closed head injury. New York, 1982, Oxford, pp. 189–207.
A classic treatise on outcome issues, including assessment, pathophysiology, and rehabilitation. Chapter 10, in particular, is devoted to children.

Levin HS, Song J, Scheibel RS et al.: Concept formation and problem solving following closed head injury in children. J Int Neuropsychol Soc 3:598–607, 1997.
Three measures of executive functioning were used in 151 head-injured children, and 89 controls, from 5 to 18 years of age. Fifty-seven of the patients were included in a longitudinal study (3 months and 36 months). The three measures of executive functioning were evaluated in relation to age, severity of injury and time post injury. All three EF measures depicted changes in performance over 3 years.

Levin HS, Hanten G, Chang CC et al.: Working memory after traumatic brain injury in children. Ann Neurol 52:82–88, 2002.
Traumatic brain injury results in preferentially impaired working memory and diminished inhibition in children.

Lezak MD: Neuropsychological assessment, 3rd edn. New York, 1995, Oxford.
Discusses the brain-behavior relationships underlying neuropsychologic assessment. This book also contains a detailed compendium of testing instruments.

Rivara JB, Jaffe KM, Pollissar NL et al.: Family functioning and children's academic performance and behavior problems in the year following traumatic brain injury. Arch Phys Med Rehabil 75:369–379, 1994.
Poor academic and cognitive outcomes at 1 year were associated with injury severity and, to a lesser degree, poor preinjury family and child functioning. In contrast, most of the variation in behavioral outcomes was explained by preinjury child or family factors.

Roberts SD et al.: The FRESNO: A pediatric functional outcome measurement system. J Rehabil Outcomes Meas 3:11–99, 1999.
The FRENSO is useful for the concurrent measurement of performance of brain-injured children during rehabilitation, and after discharge.

Ruff RM, Marshall LF, Crouch J et al.: Predictors of outcome following severe head trauma: follow-up data from the Traumatic Coma Data Bank. Brain Inj 7:101–111, 1993.
Among former students who had suffered traumatic brain injury, 62% had returned to school by 6 months after injury. Age, length of coma, speed for both attending and motor movements, spatial integration, and intact vocabulary were all significantly related to returning to work or school.

Schwartz L, Taylor HG, Drotar D, Yeates KO, Wade SL, Stancin T: Long-term behavior problems following pediatric traumatic brain injury: prevalence, predictors, and correlates. J Pediatr Psychol 28:251–263, 2003.
The risks of long-term posttraumatic behavior problems are multifactorial, and correlates include child dysfunction and family sequelae.

Slomine BS, Gerring JP, Grados MA et al.: Performance on measures of executive function following pediatric traumatic brain injury. Brain Inj 16:759–772, 2002.
This study followed 68 children with moderate to severe TBI between the ages of 7 and 15 in an attempt to investigate the relationships between

age at injury, neuroanatomic lesion location and executive function in a pediatric population. Results supported the vulnerability theory for the pediatric population. Younger age at injury places children at greater risk of impairment on measures of EF. Performance on measures of EF depends on brain variables other than frontal lobes including extrafrontal cortical brain areas and total number of lesions. The relationship between extrafrontal brain regions and EF suggests that domain-specific cognitive content (i.e. language or visuospatial analysis), mediated by the parietal or temporal lobes, may disrupt underlying cognitive processes necessary for successful performance on measures of EF. In addition, the association between total number of lesions and EF may be related to disconnections and disruption of frontal/subcortical systems.

Taylor HG, Yeates KO, Wade SL, Drotar D, Stancin T, Minich N: A prospective study of short- and long-term outcomes after traumatic brain injury in children: behavior and achievement. Neuropsychology 16:15–27, 2002.

Behavioral and academic sequelae for moderate to severe TBI pediatric patients were evaluated taking into account family environment, and how that influences recovery. Mixed model analyses revealed persistent neuropsychological sequelae of TBI that generally did not vary as a function of time postinjury. Some recovery occurred during the first year post injury, but recovery reached a plateau after that time, and deficits were still apparent at the extended follow-up. Further recovery was uncommon after the first year post injury. The findings suggest that pediatric TBI has long-term effects on behavior and achievement but that post injury progress is influenced by the family environment.

Yeates K, Taylor HG, Drotar D et al.: Pre-injury family environment as a determinant of recovery from traumatic brain injuries in school-aged children. J Int Neuropsychol Soc 3:617–630, 1997.

A prospective study emphasizing environmental factors as determinants of brain injury recovery in children aged 6–12 years. Outcomes were assessed at 6- and 12-month follow-ups. Measures of preinjury family environment consistently predicted both the level of cognitive and behavioral functioning at 12 months post injury, and the rate of intraindividual change during the 12-month period, even after taking into account group membership (Severe TBI, Moderate TBI, Orthopedic injury), and injury severity.

CHAPTER 8

The Epilepsies

Carl E. Stafstrom, MD, PhD

OUTLINE

Introduction and epidemiology
Classification of seizures and epilepsies
Pathophysiology and genetics
Evaluation of the child with seizures
Treatment of the child with seizures and epilepsy
Partial seizures
Generalized seizures
Epilepsy syndromes in children
Status epilepticus
Prognosis of childhood epilepsy
Nonepileptic disorders that may mimic epilepsy

Introduction and epidemiology

This chapter reviews current standards of care in the diagnosis and treatment of epilepsy in childhood. Several excellent resources discuss childhood epilepsy in greater detail (Holmes 1987; Pellock *et al.* 2001; Arzimanoglou *et al.* 2004a).

A *seizure* is defined as a sudden, involuntary, time-limited alteration of neurologic function caused by the abnormal discharge of neurons in the central nervous system (CNS). The term *epileptic seizure* is used to distinguish a seizure caused by abnormal neuronal firing from a nonepileptic seizure such as a pseudoseizure, which is not caused by hypersynchronous neuronal firing. *Epilepsy* is a chronic condition of recurrent, unprovoked seizures. Epilepsy is not a single disease but rather a sign of underlying brain dysfunction. An *epilepsy syndrome* refers to a group of clinical characteristics that consistently occur together, with seizures as a primary manifestation. Such characteristics might include similar age of onset, electroencephalogram (EEG) findings, precipitating factors, inheritance pattern, natural history, prognosis, and response to antiepileptic drugs (AEDs). The term "seizure disorder" should be avoided – it lacks semantic precision and does not add any understanding of the child's seizure type, epilepsy syndrome, or prognosis. Referring to epilepsy as a seizure disorder is like calling any neoplasia a "cancer disorder" rather than specifying its type, stage, location, etc.

Seizures provoked by a reversible insult (e.g. fever, hypoglycemia, or acute head trauma) do not fall under the definition of epilepsy because they are a short-lived, secondary condition rather than a chronic state. Although epilepsy is a chronic condition, it is not necessary lifelong, and remissions occur frequently in children.

Epilepsy is a common disorder, with an incidence of approximately 50 new cases per year per 100 000 population (Hauser 1995; Shinnar & Pellock 2002). Approximately 1–2% of the population suffers from epilepsy. The highest incidence occurs in childhood, with a second peak of increased incidence in the elderly. Approximately 75% of persons who develop epilepsy do so before the age of 20 years.

Classification of seizures and epilepsies

The most widely accepted classification of epileptic seizures is the International Classification of Epileptic Seizures (ICES, Table 8.1) (Commission 1981), developed by the International League Against Epilepsy (ILAE). The ICES is based on three factors: (1) clinical seizure manifestations, (2) ictal EEG patterns, and (3) interictal EEG patterns. In this classification scheme, seizures are subdivided into two broad categories: partial (focal) or generalized. Using clinical criteria, partial seizures begin focally in the brain and present with focal clinical signs, while generalized seizures begin simultaneously in both hemispheres, without a focal onset (Fig. 8.1). Seizures are then further classified by their interictal and ictal EEG features, if available. Based on a reliable history and interictal EEG, the physician can often classify the seizure, after which an appropriate diagnostic evaluation and treatment plan can be formulated.

Although the ICES adequately describes the seizure event itself, it does not consider the many epilepsy syndromes that occur in children. Therefore, the International Classification of Epilepsies and Epilepsy Syndromes was developed (Commission 1989). Two broad categories are used to shape the major classes of epilepsies and epileptic syndromes (Table 8.2). The first category separates generalized epilepsy syndromes (generalized epilepsies) from those with partial or focal onset (localization-related partial or focal epilepsies). The other category separates epilepsies of known etiology (symptomatic or secondary epilepsies) from those that are idiopathic (primary) or cryptogenic (cause unknown).

TABLE 8.1

International Classification of Epileptic Seizures

Partial (focal) seizures
Simple partial
Motor signs
Somatosensory or special sensory symptoms
Autonomic symptoms or signs
Psychic symptoms
Complex partial
Simple partial onset followed by impaired consciousness
Consciousness impaired at onset
Partial seizures with secondary generalization (tonic, clonic, or tonic–clonic)
Simple partial seizures evolving to generalized seizures
Complex partial seizures evolving to generalized seizures
Simple partial seizures evolving to complex partial seizures evolving to generalized seizures
Generalized seizures (convulsive or nonconvulsive)
Absence
Typical
Atypical
Myoclonic
Clonic
Tonic
Tonic-clonic
Atonic
Unclassified epileptic seizures

From Commission 1981

The classifications of seizures and epilepsies just described may not fully account for modern genetic and clinical data, particularly in children (Nordli 2002). A new classification system is being developed by the ILAE, which takes into account ictal phenomenology, seizure type, syndrome diagnosis (if present), etiology, and degree of functional impairment (Table 8.3) (Engel 2001). This classification scheme shares some features of the Diagnostic and Statistical Manual (DSM) scheme used to classify psychiatric disorders, with "axes" used to denote various levels of description and functional impairment. Obviously, classification schemes must evolve to reflect growing knowledge about the epilepsies.

Pathophysiology and genetics

As indicated above, the majority of epilepsy begins in childhood (Hauser 1995). The developing brain is especially prone to seizures, for a variety of physiological reasons (Stafstrom 1998; Sanchez & Jensen 2001). Any factor that distorts the usual balance between excitation and inhibition in the brain in favor of excitation, may lead to a seizure (Table 8.4). Such factors can be genetic or acquired. Regarding genetic pathologies leading to epilepsy: hyperexcitability can occur anywhere from the circuit level (e.g. abnormal synaptic connections in a cortical dysplasia or disorder of cerebral development), to the receptor level (e.g. abnormal gamma-aminobutyric acid (GABA) receptor subunits in Angelman syndrome), to abnormal ionic channel function (e.g. potassium channel mutations in benign familial neonatal convulsions). Similarly, acquired cerebral insults can alter circuit function (e.g. structural alterations of hippocampal circuitry following prolonged febrile seizures or head trauma). Even in the normal developing brain, excitatory synaptic function develops prior to inhibitory synaptic function, favoring enhanced excitation and seizure generation. In addition, perhaps paradoxically, GABA can act as an *excitatory* neurotransmitter early in life (Ben-Ari 2002). These observations explain, at least in part, why the very young brain is especially prone to seizures. However, seizures seem to cause less structural damage in the developing brain compared to the adult brain (Holmes & Ben-Ari 1998).

There has been a recent explosion of new information regarding the genetic basis of epilepsy syndromes (Willmore & Ueda 2002; Noebels 2003; Scheffer & Berkovic 2003), some of which is summarized in Table 8.5. Both monogenic and polygenic mutations can lead to epilepsy. It is clear that mutations in a wide variety of physiological functions can lead to the state of hyperexcitability that underlies epilepsy. As these syndromes become better elucidated, there is hope that syndrome-specific therapeutic interventions can be designed.

Evaluation of the child with seizures

The history and neurologic examination remain the cornerstones of neurologic diagnosis. It is important to determine by history whether the patient had a seizure, and if so, its clinical manifestations, duration, ictal features, and postictal signs. Identification of an epileptic syndrome is critical to determine the nature and extent of the evaluation, treatment, and prognosis. If there is uncertainty about the diagnosis, it is usually better to withhold treatment and wait for another attack than to embark on an extensive workup and initiation of AEDs.

Diagnostic studies

Following the diagnosis of a seizure, the clinician should try to determine its underlying or precipitating cause. The initial workup is determined partly by how the child presents. The child who arrives at the emergency room in status epilepticus or coma or is febrile is obviously approached differently from one who has completely recovered from the seizure by the time of presentation. In the former conditions, there is an urgency to determine if the child has an

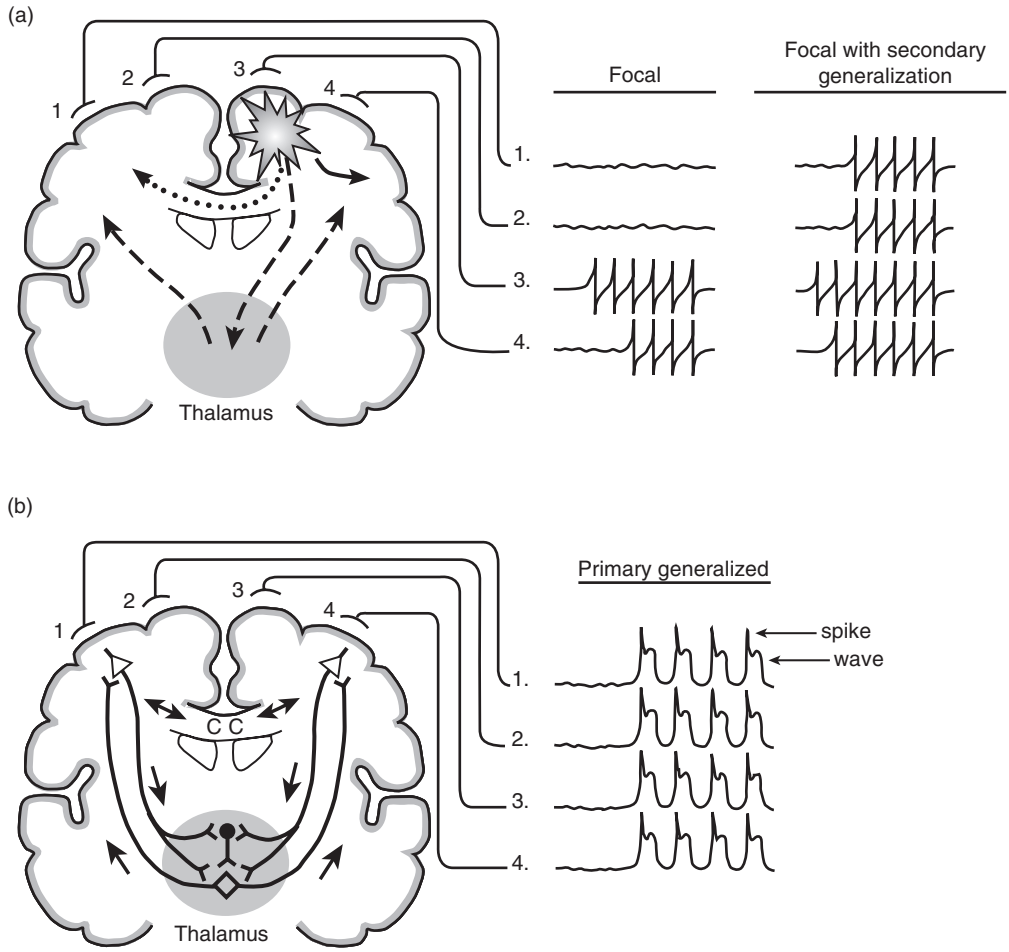

Fig. 8.1 Coronal brain sections depicting seizure types and potential routes of seizure spread. (a) Focal area of hyperexcitability (star) and spread to nearby neocortex (solid arrow), via corpus callosum or other commissures to the contralateral cerebral hemisphere (dotted arrow), or via subcortical pathways (e.g. thalamus, brainstem; downward dashed arrow) resulting in secondary generalization (upward dashed arrows). Accompanying EEGs show brain electrical activity under numbered electrodes. Focal epileptiform activity (spikes) is maximal at electrode 3 and is also seen nearby at electrode 4 (left traces). If a seizure secondarily generalizes, spike activity may be seen synchronously at all electrodes, after a delay (right-most traces). (b) A primary generalized seizure begins simultaneously in both hemispheres. The characteristic bilateral synchronous "spike-wave" pattern on EEG is generated by interactions between cortex and thalamus, with rapid spread via corpus callosum (CC) contributing to the rapid bilateral synchrony. One type of thalamic neuron (filled circle) is a GABAergic inhibitory cell with intrinsic oscillatory properties; it is able to fire in bursts of action potentials due to a specific type of calcium channel, allowing these cells to modulate ongoing excitatory corticothalamic activity. Cortical neurons send impulses to both inhibitory thalamic neurons (filled circle) and excitatory thalamic relay neurons (diamond), setting up oscillations of excitatory and inhibitory activity, which gives rise to the rhythmic spike waves on EEG.

acute cause for the seizures, such as infection, brain injury, or metabolic disturbance. Investigations must be performed promptly. A child with focal neurologic findings on examination requires urgent neuroimaging.

Electroencephalography

An EEG is a recording of the brain's electrical activity. It can detect abnormal electrical activity such as focal spikes or waves (indicating a partial epilepsy) or diffuse, bilateral spike waves (indicating a generalized epilepsy). A routine EEG should be obtained on any child with a suspected seizure unless there is a clearly defined, reversible etiology, e.g. hyponatremia, or hypocalcemia. It is desirable to obtain recordings during wakefulness and sleep. Epileptiform activity may occur only during sleep; in some cases, a mild sedative such as chloral hydrate can be used to induce sleep. Combined video-EEG monitoring (which can be performed continuously for several days) can increase the diagnostic yield or differentiate an epileptic seizure from a nonepileptic event.

Table 8.6 summarizes typical EEG findings in various seizure types and syndromes. A caveat is that the EEG can

TABLE 8.2

International Classification of Epilepsies and Epilepsy Syndromes

Localization-related (focal, partial) epilepsies

Idiopathic
- Benign childhood epilepsy with centrotemporal spikes (rolandic epilepsy)
- Childhood epilepsy with occipital paroxysms
- Primary reading epilepsy

Symptomatic or cryptogenic (presumed to be symptomatic but cause is unknown)
- Temporal lobe epilepsy
- Frontal lobe epilepsy
- Occipital lobe epilepsy
- Parietal lobe epilepsy
- Chronic progressive epilepsia partialis continua

Generalized epilepsies

Idiopathic (with age-related onset, listed in order of age)
- Benign neonatal convulsions
- Benign familial neonatal convulsions
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Epilepsy with generalized tonic–clonic seizures on awakening

Symptomatic
- Nonspecific etiology
- Early myoclonic encephalopathy
- Early infantile epileptic encephalopathy with suppression burst
- Other symptomatic generalized epilepsies

Cryptogenic
- West syndrome (infantile spasms)
- Lennox–Gastaut syndrome
- Epilepsy with myoclonic-astatic seizures (Doose syndrome)
- Epilepsy with myoclonic absences

Specific syndromes (disease states in which seizures are present as a predominant feature)

Indeterminate epilepsies

Generalized and focal features
- Neonatal seizures
- Severe myoclonic epilepsy of infancy (Dravet syndrome)
- Epilepsy with continuous spike waves during slow wave sleep
- Acquired epileptic aphasia (Landau–Kleffner syndrome)

Other indeterminate epilepsies without unequivocal generalized or focal features

Special syndromes

Situation-related seizures
- Febrile seizures
- Isolated seizures or status epilepticus

Seizures caused by an acute or toxic event, such as alcohol or drugs, eclampsia, or hyperglycemia

From Commission 1989

be normal in a child with epilepsy, especially those with partial-onset seizures of frontal or temporal lobe origin. In such cases, intracranial EEG monitoring may be necessary to detect the seizure focus. However, the diagnosis of epilepsy is based on clinical information, and the EEG should be regarded as confirmatory, not diagnostic. We are encour-

TABLE 8.3

Proposed New Diagnostic Scheme for Persons with Epileptic Seizures or Epilepsy

Axis	Comments	Example
1. Ictal phenomenology	Detailed description of the ictal event	Right lower facial clonus and dysarthric speech
2. Seizure type	Specify localization within the brain and precipitating stimuli for reflex seizures when appropriate	Focal motor with elementary clonic motor signs (simple partial)
3. Syndrome	Syndrome diagnosis is not possible in every patient	Benign childhood epilepsy with centrotemporal spikes (rolandic epilepsy)
4. Etiology	When possible, list specific pathology or genetic defect	Idiopathic (genetic basis assumed)
5. Impairment	Specific impairments of function associated with the epilepsy	a. Anxiety associated with stigma of epilepsy b. Fatigue associated with anticonvulsant medication

TABLE 8.4

Some Factors Predisposing the Developing Brain to Hyperexcitability and Seizures

- Early development of excitatory sodium and calcium channels
- Earlier development of excitatory synapses and neurotransmitters
- Delayed development of inhibitory synapses and neurotransmitters
- Exuberant axonal branching pattern early in life (more excitatory synapses)
- Paradoxical depolarizing action of GABA early in development
- Delayed ability of glia to clear extracellularly accumulated potassium ions

GABA, gamma-aminobutyric acid

TABLE 8.5

Epilepsy Genetics in Selected Syndromes

Syndrome	Chromosome(s)	Genes
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	20q13, 1p21	Acetylcholine receptors
Benign familial neonatal convulsions (BFNC)	20q13, 8q24	Potassium channels
Generalized epilepsy with febrile seizures plus (GEFS+)	19q13, 2q24	Sodium channels
	5q34	GABA-A receptors
Severe myoclonic epilepsy of infancy (SMEI)	2q24, 5q31	Sodium channels
Juvenile myoclonic epilepsy	5q34	GABA-A receptors
	2q22–23	Calcium channels
Childhood absence epilepsy	5q34	GABA-A receptors
	19p	Calcium channels

GABA, gamma-aminobutyric acid

TABLE 8.6

Characteristic EEG Features in Various Seizure Types

Seizure type	Interictal EEG abnormalities
Partial seizures	
Simple partial	Variable; spikes over involved area of cortex; may be normal
Complex partial	Variable; frontal/temporal lobe spikes; may be normal
Generalized seizures	
Absence	Generalized spike wave, often activated by sleep, hyperventilation, or photic stimulation
Generalized tonic–clonic	Variable; often normal
Myoclonic	Usually abnormal; generalized spike wave, multiple spike waves
Tonic/atonic	Usually abnormal; generalized abnormalities, spikes, multiple spike waves
Infantile spasms	Hypsarhythmia (interictal); electrodecrement (ictal)

aged to "treat the child, not the EEG." One exception to this dictum is absence epilepsy, in which brief generalized bursts of spike-wave activity, even if not associated with obvious clinical changes, imply a high likelihood of absence seizures. In children with incompletely treated absence epilepsy, photic stimulation or sleep will often bring out spike-wave activity on the EEG. For practical purposes, generalized spike-wave activity lasting longer than 1 second or so can be considered a seizure.

Neuroimaging

Computed tomography (CT) and magnetic resonance imaging (MRI) scans are important adjuncts to the clinical examination and EEG, in the evaluation of a child with seizures (Kuzniecky & Knowlton 2002). Neuroimaging techniques are especially sensitive for CNS structural lesions. MRI is more likely to show an abnormality in a child with partial seizures, abnormal neurologic findings, or focal paroxysmal discharges on the EEG.

MRI is a more sensitive neuroimaging study than CT and therefore MRI is the preferred imaging modality for a child with seizures. The ability to detect areas of cortical malformation or dysgenesis has been greatly aided by advances in MRI technology (Porter *et al.* 2002). MRI is also valuable in detecting hippocampal sclerosis and atrophy, commonly associated with temporal lobe epilepsy. Quantitative, computer-assisted volume analysis of the temporal lobes may allow detection of asymmetries that are not readily apparent on visual analysis of the scan.

Despite the superiority of MRI in epilepsy evaluation, CT still has a role. A nonenhanced CT is relatively inexpensive and detects many tumors and other lesions that require immediate attention, such as cerebral hemorrhage. In addition, calcified lesions are well demonstrated on CT, which may be useful in the initial evaluation of disorders such as tuberous sclerosis. In the acute situation, the physician must weigh the potential benefit of diagnostic information from a CT scan against the risk of radiation exposure; a CT scan may not always be necessary in a child that otherwise appears well.

A variety of new imaging techniques is now available to aid in the assessment of epilepsy. MRI abnormalities can be correlated directly with EEG activity. MR spectroscopy measures the concentrations of a variety of neurochemicals in the brain, and is sometimes used to help to identify a seizure focus. Positron emission tomography (PET), images the brain's regional utilization of glucose, with asymmetries suggesting areas of interictal or ictal abnormality (Henry & Heertum 2003). Single photon emission computed tomography (SPECT) compares local blood flow discrepancies, information that is most useful when recorded during an actual seizure. Another promising new technique, magnetoencephalography (MEG), assesses the brain's dynamic electromagnetic fields and can localize areas of abnormal function (Otsubo & Snead 2001). These new techniques are used primarily in epilepsy centers for presurgical evaluations.

In summary, neuroimaging is frequently abnormal in children with epilepsy and in many cases it reveals a treatable condition. Even when CT or MRI does not alter therapeutic management, it may give valuable information regarding seizure etiology. A normal neuroimaging study assures the physician and parents that there is no *major* lesion, although there is a need for close patient surveillance and a repeat study may be indicated if any changes occur in the examination or EEG.

Metabolic evaluation

The type of seizure and syndrome dictates the extent of the metabolic workup (DeVivo 2002). For example, a child with infantile spasms or Lennox–Gastaut syndrome is more likely to have a metabolic or degenerative disorder than one presenting with simple partial seizures. In metabolic disorders, seizures typically accompany other abnormal findings such as developmental delay. In neonatal seizures, a metabolic evaluation is mandatory (see below). Table 8.7 lists some recommended studies for children with a variety of seizure types and epilepsy syndromes.

TABLE 8.7

Tests to Consider in the Evaluation of a Child with Seizures

Seizure type/syndrome	Test	Comments
Simple partial	MRI	Rule out structural lesion
Complex partial	MRI	Rule out structural lesion
Generalized tonic–clonic	MRI	Rule out structural lesion
Absence	None required	
Infantile spasms and other refractory epilepsies and epileptic encephalopathies	Skin examination (Wood's lamp)	Hypopigmented lesions (tuberous sclerosis)
	MRI	Rule out congenital malformation, neuronal migration disorder
	Serum/urine amino/organic acids; serum biotinidase	Metabolic screening tests
	Serum ammonia	Screen for urea cycle defects
	Lactate/pyruvate	Screen for mitochondrial disorder
	Pyridoxine infusion	Rule out vitamin B6-dependent seizures
	Ophthalmologic examination	Chorioretinitis may indicate congenital infection. Chorioretinal lacunes may indicate Aicardi syndrome
	Lumbar puncture	Rule out neurotransmitter disorder

Treatment of the child with seizures and epilepsy

Initiating treatment

The decision to treat a child with antiepileptic therapy should consider both benefits and risks. The potential benefits of treatment (prevention of further seizures and development of epilepsy) must be weighed against potential adverse effects (cognitive/behavioral changes, toxicity, cost, stigma, etc.) (Hirtz *et al.* 2003). All AEDs have side effects, both dose-related and idiosyncratic. These include systemic effects such as bone marrow suppression, rashes, and alterations of bone density as well as central nervous system-related side effects such as drowsiness and mental slowing. The decision of whether or not to begin AEDs is related strongly to the syndrome diagnosis. For example, multiple absence seizures affecting attention span and school performance would warrant treatment. A single nocturnal seizure with an interictal EEG showing classic rolandic spikes (see below) may not require treatment.

On the other hand, the approach to a first unprovoked (nonsyndromic) seizure is more controversial, and is based on recurrence rates by 2 years of 37–54% (Stroink *et al.* 1998; Shinnar *et al.* 2000; Hirtz *et al.* 2003). Therefore, roughly half of children with a first unprovoked seizure will have another seizure in the initial 2 years (the period of greatest recurrence risk). Children with prior neurologic impairment are at the greatest risk for recurrence. Therapy does not seem to change the recurrence rate, and the EEG is a good predictor of recurrence.

Many factors need to be considered when deciding whether to start AED therapy, and each child must be evaluated individually. However, in view of the risk of adverse effects encountered with AEDs, in most children it appears reasonable to wait for a second seizure before subjecting the child to years of drug therapy.

Withdrawing antiepileptic drugs

Deciding when to withdraw AEDs from a child who is doing well can be as difficult as deciding when to start a drug initially, and again, considerations are based on age-specific risks and benefits (O'Dell & Shinnar 2001). Psychosocial as well as medical factors must be considered. If the child is tolerating the medication well, there is a tendency to leave well enough alone and continue with the drug. However, AEDs are expensive, often require laboratory monitoring, and may be associated with cognitive impairment. Therefore, the clinician should consider tapering and discontinuing AEDs in children who remain seizure-free for 2 years. A history of focal seizures is the main risk factor for seizure recurrence after AED taper in children who are well-controlled for more than 2 years, especially if the EEG remains abnormal (Hawash & Rosman 2003). As discussed later in this chapter, syndrome classification can guide the decision to withdraw AEDs. For example, children with absence epilepsy or benign rolandic epilepsy have a high likelihood of outgrowing their seizures, whereas those with juvenile myoclonic epilepsy are less likely to remit.

Pharmacology of antiepileptic drugs

The primary mode of treatment in children with epilepsy is pharmacologic, although epilepsy surgery, vagus nerve stimulation, and ketogenic diet therapy are useful in selected

cases. The medical treatment of epilepsy has changed decisively in the past decade, with regard to both the introduction of new AEDs and improved formulations and methods of administration. For children, it is fortunate that multiple formulations of AEDs are available (e.g. chewable tablets, sprinkles, suspension), as well as extended-release preparations and options to deliver the AED by different routes (sublingual, intravenous, intramuscular, rectal) (Wheless & Venkataraman 1999). These options decrease poor compliance, which is an important cause of breakthrough seizures and a source of ongoing family stress.

The goal in the pharmacologic treatment of epilepsy is to reduce or eliminate seizures while minimizing the adverse effects of treatment. It must be recognized that drug treatment is only one component of the overall management strategy. Psychological, educational, and social complications of epilepsy and its treatment must also be considered. Failure to address these quality of life issues will result in treatment program failure, regardless of whether seizures are controlled.

Although there is no single drug of choice in the treatment of epilepsy, clinical trials have demonstrated that some drugs are more effective in certain seizure types and syndromes. Some AEDs, such as ethosuximide, are highly effective in controlling only one type of seizure (absence), whereas others, such as valproic acid, are useful in a broad spectrum of seizure types. Table 8.8 lists the AEDs found to be most useful in some seizure types. Table 8.9 provides analogous information for selected epilepsy syndromes. Treatment choices are reviewed further in the discussion of individual seizure types and epilepsy syndromes.

Medical treatment should always begin with a single AED. Monotherapy controls approximately 60% of newly diagnosed epilepsy (Camfield *et al.* 1997; Kwan & Brodie 2000). Even in patients with multiple seizure types, a single drug is started and increased to high therapeutic serum levels or until toxicity ensues. If, at that time, seizures are not controlled, a second drug can be initiated while the first one is either continued or tapered. The physician should avoid the temptation of adding a second AED too soon. If more than one AED is used simultaneously, one can never be sure which one is controlling seizures or causing toxicity. Addition of a second AED will control only another 10% of patients, and the side effects of multiple medications are cumulative. "Rationale polytherapy," that is, using more than one AED, is sometimes effective, especially if the AEDs are chosen to have complementary mechanisms of action.

Therapeutic ranges, the plasma concentrations for which optimal seizure control is likely to occur without side effects, have been established for most AEDs. However, these levels should be obtained judiciously. Individual patients may have complete control with levels below the therapeutic range, while others may tolerate and require levels above the usual therapeutic range. Conversely, some children develop intolerable side effects at serum levels within the quoted therapeutic range. Signs of clinical toxicity are particularly common in patients receiving multiple AEDs, even when the level of each individual drug is within the therapeutic range. Despite these caveats, clinical responses and toxicity correlate much better with serum levels than with dosage.

TABLE 8.8 Antiepileptic Drugs of Choice in the Treatment of Childhood Seizures

Seizure type	Antiepileptic drugs	
Partial Seizures	**First Choice**	**Second Choice**
Simple partial	Carbamazepine Phenytoin Valproic acid Oxcarbazepine	Lamotrigine Topiramate Tiagabine Levitiracetam Zonisamide Gabapentin Phenobarbital Primidone Benzodiazepines
Complex partial	Carbamazepine Phenytoin Valproic acid Oxcarbazepine	Lamotrigine Topiramate Tiagabine Levitiracetam Zonisamide Gabapentin Phenobarbital Primidone Benzodiazepines
Generalized seizures	**First choice**	**Second choice**
Absence	Ethosuximide Valproic acid	Lamotrigine Acetazolamide Clonazepam
Generalized tonic–clonic	Carbamazepine Phenytoin Valproic acid Oxcarbazepine	Lamotrigine Topiramate Tiagabine Gabapentin Phenobarbital Primidone Benzodiazepines
Myoclonic	Valproic acid	Lamotrigine Clonazepam Levetiracetam
Clonic	Valproic acid	Lamotrigine Phenobarbital
Tonic	Valproic acid	Carbamazepine Phenytoin Lamotrigine Phenobarbital
Atonic	Valproic acid	Lamotrigine Clonazepam

TABLE 8.9

Antiepileptic Drugs of Choice in the Treatment of Selected Childhood Epilepsy Syndromes

	First choice	Second choice
Infantile spasms	Adrenocorticotrophic hormone Vigabatrin	Topiramate Lamotrigine Valproic acid Pyridoxine (vitamin B6)
Lennox–Gastaut syndrome	Valproic acid	Lamotrigine Topiramate Felbamate*
Childhood absence epilepsy	Ethosuximide Valproic acid	Lamotrigine Acetazolamide Clonazepam
Juvenile absence epilepsy	Valproic acid	Lamotrigine
Benign rolandic epilepsy	Carbamazepine Phenytoin Valproic acid	Gabapentin Lamotrigine Topiramate

*Consider in children refractory to several AEDs (see text).

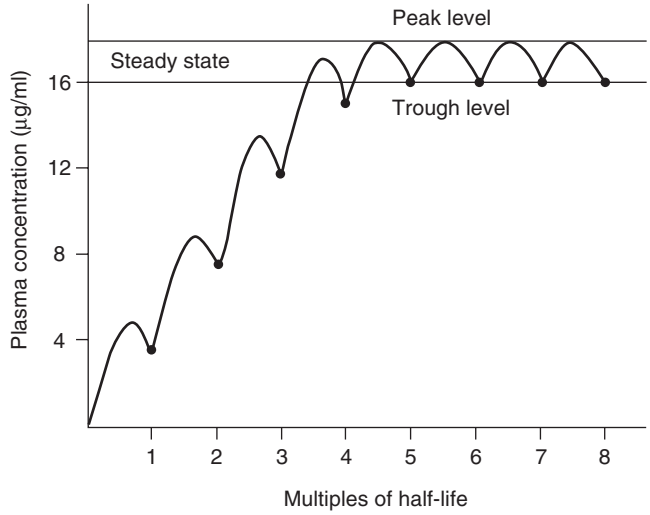

Fig. 8.2 Plasma concentration of a drug (ordinate) following repeated oral drug administration. Interval of administration is a function of the half-life of the drug. (From Holmes GL: *Diagnosis and management of seizures in children*, Philadelphia, 1987, WB Saunders.)

Physicians should be familiar with the basic principles of AED pharmacokinetics (Browne 1998). In most instances, AEDs are administered orally on a long-term basis. Following initiation of therapy, the drug accumulates in the body until such a time as the rate of elimination equals the rate of administration. Over this period, body and plasma concentrations increase exponentially until they reach a steady state or plateau. Steady state, the balance between accumulation and elimination of the AED, results in a stable level below which the concentration in the serum will not fall. The time to reach a steady state is approximately five half-lives (Fig. 8.2).

In the steady state, the range of fluctuation of plasma concentrations remains relatively constant. The minimum concentration (trough) occurs before a dose, whereas the maximum level is primarily dependent on the absorption rate. Because bioavailability varies considerably among the AEDs, it is usually preferable to obtain routine levels at trough, immediately before the next dose. AEDs with a long half-life, such as phenobarbital, have small daily fluctuations, and the timing of serum sampling is not as critical. However, when using a drug with a short serum half-life, such as carbamazepine or valproic acid, the serum level varies significantly depending on when the blood is sampled. If toxicity is the main concern, a peak level one to several hours after a dose would be most informative. Transient toxic effects of carbamazepine, such as diplopia, lethargy, and nausea, subside when the serum level decreases. Fluctuation between minimum and maximum AED levels are more pronounced in children who are on polytherapy. If a patient complains about side effects at the time of peak serum concentration, the frequency of administration may be increased without changing the total daily dose. For example, if a child is taking carbamazepine 300 mg twice daily and experiences diplopia 2 hours after taking a dose, a trial of 200 mg three times a day may be helpful.

A common mistake is to obtain a serum AED level before a steady state is reached; the serum level will be spuriously lower than the eventual steady state level. Because of the numerous drug interactions, it is important to obtain serum levels of all AEDs if the child is on polytherapy. Measurement of AED levels is expensive and levels should only be obtained when the information is clinically useful.

A summary of some important properties of the AEDs is found in Table 8.10. For further details of AED mechanisms, pharmacokinetics, dosing recommendations, and adverse effects, the reader is referred to the several comprehensive resources (Brodie & Kwan 2001; Holland 2001; Levy *et al.* 2002; Jarrar & Buchhalter 2003).

Traditional antiepileptic drugs

Carbamazepine

Carbamazepine (Tegretol, Carbatrol), introduced in 1962, is one of the most valuable and widely used AEDs in children. It is quite effective against partial seizures, secondarily generalized seizures, and generalized tonic–clonic seizures. It has no cosmetic side effects, and does not usually significantly alter mood, behavior, or cognition. Carbamazepine, like phenytoin, works by blocking active neuronal sodium channels.

Carbamazepine has linear pharmacokinetics, and the se-

TABLE 8.10

Summary of Commonly Used Antiepileptic Drugs

AED (trade names)	Starting dosage	Typical maintenance dosage	Half-life (hours)	Therapeutic range (mg/L)	Common side effects	Serious idiosyncratic side effects
Phenobarbital	<1 year: 4–6 mg/kg/day >1 year: 3–4 mg/kg/day Teenagers, adults: 3 mg/kg/day	Same as starting dosage	40–70	15–40	Irritability Hyperactivity Lethargy	Rash Hepatic failure Agranulocytosis Stevens–Johnson syndrome
Primidone (Mysoline)	1–2 mg/kg	10–25 mg/kg/day once a day at bedtime	5–8	5–12	Irritability Hyperactivity Lethargy Nausea	Rash Agranulocytosis
Phenytoin (Dilantin)	5 mg/kg/day (may need higher dose in children <5 years)	Same as starting dosage	5–34	10–20	Lethargy Dizziness Ataxia Gingival hyperplasia Hirsutism	Rash Hepatic failure Lymphadenopathy Pancreatitis Agranulocytosis Stevens–Johnson syndrome
Carbamazepine (Tegretol, Tegretol XR, Carbatrol)	5–10 mg/kg/day	10–30 mg/kg/day	8–25	6–12	Diplopia Lethargy Blurred vision Ataxia	Rash Hepatic failure Pancreatitis Leukopenia Aplastic anemia Hyponatremia
Valproic acid (Depakote, Depakene, Depacon)	15 mg/kg/day	15–60 mg/kg/day	4–14	50–100	Lethargy Weight gain (or rarely, weight loss) Hair loss Tremor	Rash Hepatic failure Pancreatitis Thrombocytopenia Anemia Agranulocytosis Stevens–Johnson syndrome Polycystic ovary syndrome
Ethosuximide (Zarontin)	10 mg/kg/day	15–40 mg/kg/day	25–40	40–100	Gastric distress Hiccups Lethargy	Rash Leukopenia Pancytopenia Systemic lupus erythematosus

TABLE 8.10 (continued)

AED (trade names)	Starting dosage	Typical maintenance dosage	Half-life (hours)	Therapeutic range (mg/L)	Common side effects	Serious idiosyncratic side effects
Gabapentin (Neurontin)	10 mg/kg/day; increase in 5 mg/kg increments	20–100 mg/kg/day; optimal dose not established	5–8	2–12 Usefulness not established	Lethargy Dizziness Ataxia Agitation Weight gain Headache	Rash
Lamotrigine (Lamictal)	Add-on therapy: If on valproate: Weeks 1–2: 0.2 mg/kg/day Weeks 3–4: 0.5 mg/kg/day If on other AEDs: Weeks 1–2: 2 mg/kg/day Weeks 3–4: 5 mg/kg/day	Add-on therapy: If on valproate: 1–5 mg/kg/day If on other AEDs: 5–15 mg/kg/day	On monotherapy: 25 On valproate: 30–70 On other AEDs: 15	4–20	Lethargy Dizziness Ataxia Headache	Rash Stevens-Johnson syndrome
Topiramate (Topamax)	0.5–1 mg/kg/day	5–9 mg/kg/day	12–24	4–10	Somnolence Dizziness Ataxia Headache Nausea Fatigue Weight loss Acidosis	Rash Glaucoma
Tiagabine (Gabatril)	0.1 mg/kg/day	0.6–1 mg/kg/day	3–9	0.1–0.3	Somnolence Dizziness Ataxia Nausea	Rash
Zonisamide (Zonegran)	1–2 mg/kg/day	4–8 mg/kg/day	30	20–40	Somnolence Dizziness Ataxia	Rash
Levitiracetam (Keppra)	10 mg/kg/day	40–60 mg/kg/day	6–8	5–40	Somnolence Dizziness Ataxia	Rash
Oxcarbazepine (Trileptal)	8–10 mg/kg/day	20–45 mg/kg/day	9 (of active metabolite, 10-monohydroxy-carbazepine)	4–12 (MHD* 12–30)	Somnolence Dizziness Ataxia Headache Nausea	Rash Hyponatremia
Felbamate (Felbatol)	15 mg/kg/day	15–45 mg/kg/day	16	30–80	Insomnia Nausea	Aplastic anemia Hepatic failure

* MHD (10-monohydroxy-carbazepine) is the active metabolite of oxcarbazepine.

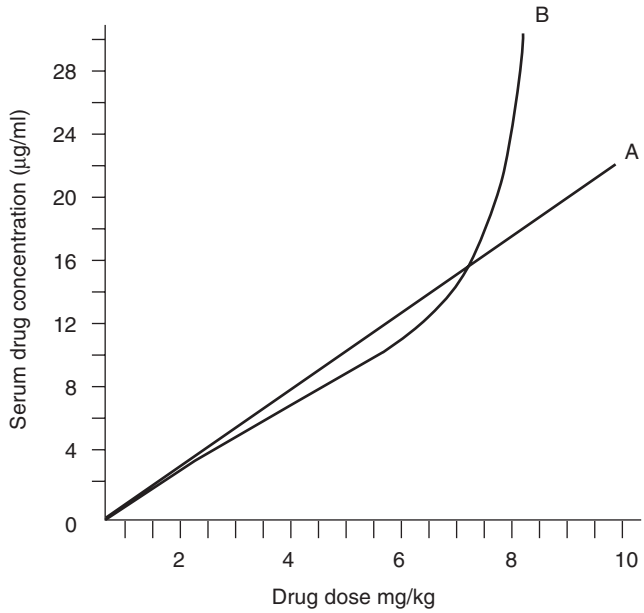

Fig. 8.3 Relationship between serum drug concentration (ordinate) and drug concentration (abscissa) for a drug observing (A) first-order kinetics (linear) and (B) zero-order kinetics. Most antiepileptic drugs follow first-order kinetics, whereas phenytoin follows zero-order kinetics. (From Holmes GL: *Diagnosis and management of seizures in children*, Philadelphia, 1987, WB Saunders.)

rum level is directly proportional to the dosage. Autoinduction, a phenomenon whereby hepatic degradation increases over time, occurs during the first month of therapy. A trough serum level should be checked several weeks after beginning therapy, and periodically thereafter. The serum level tends to stabilize after a few months of treatment. Carbamazepine has a relatively short half-life, and while three daily doses are optimal, this regimen is often not practical for families. Longer acting twice-daily dose formulations are now available (Carbatrol, Tegretol-XR). Carbamazepine increases the rate of metabolism of other AEDs but may increase phenytoin levels. Some common drugs, particularly erythromycin, decrease carbamazepine clearance and inadvertent coadministration can result in carbamazepine toxicity.

Carbamazepine has been associated with both dose-related and idiosyncratic reactions. The dose-related side effects are common but not life-threatening, whereas the idiosyncratic reactions are rare but serious. Common dose-related side effects include drowsiness, ataxia, nausea, diplopia, headache, irritability, and dizziness. These symptoms usually occur at peak serum concentrations and can often be alleviated by increasing dose frequency without changing total daily dose.

Idiosyncratic reactions of most concern involve the bone marrow. Most cases of carbamazepine hematopoietic toxicity occurred in patients on other AEDs. The estimated prevalence of carbamazepine hematologic toxicity is 0.002% for aplastic anemia, 10% for transient leukopenia, 2% for persistent leukopenia, 2% for thrombocytopenia, and less than 5% for anemia. Pancreatitis has also been reported with carbamazepine. Rash occurs in about 5% of children. As with phenytoin, rashes from carbamazepine can be mild or serious (e.g. Stevens–Johnson syndrome). The serious cutaneous reactions tend to occur in the first few months of treatment, and usually in patients with hypersensitivity to other medications. Carbamazepine may exacerbate some seizure types, most commonly atypical absences (Shields & Saslow 1983; Guerrini *et al.* 1998).

It is recommended that a complete blood count (CBC) and liver transminases be obtained before therapy is initiated, at 2–4 weeks, at 2 months, and then every 6 months. These guidelines are less stringent than previous recommendations, but seem reasonable unless there is clinical evidence of hepatic or hematologic dysfunction. A mild leukopenia, as noted earlier, occurs in many patients and does not usually require discontinuation of the drug. Unfortunately, there are no well-established guidelines regarding the management of leukopenia. In some children, the white blood cell (WBC) count decreases when the dose is increased. It is recommended that the daily dose of carbamazepine be reduced if the absolute neutrophil count falls below 900 mm^3. Families should be advised to contact their physician for such signs as easy bruising or petechiae.

Ethosuximide

Ethosuximide (Zarontin) is an excellent first-line AED for the treatment of absence seizures. It is rarely used for other seizure types. Ethosuximide works by blocking calcium channels in thalamic neurons that project to neocortex, interrupting the thalamocortical feedback loop that underlies the generalized spike-wave discharges of absence seizures. Mild side effects occur in approximately one-third of children upon initiation of therapy, and include nausea, anorexia, dizziness, headaches, and drowsiness. Serious side effects are very rare and include leukopenia and pancytopenia. It is recommended that periodic CBCs be obtained.

Phenobarbital

Phenobarbital, available since 1912, is the oldest AED still used. It is a relatively safe, inexpensive drug that is effective in several seizure types. However, side effects such as hyperactivity (especially in toddlers and preschoolers) and concerns about adverse effects on cognition and behavior have limited its use. It acts by enhancing GABAergic inhibition, by prolonging the time that chloride channels are open in response to GABA.

Phenobarbital is a broad spectrum AED that has proven efficacy in generalized tonic–clonic, simple partial, and complex partial seizures. It is not effective against absence and myoclonic seizures. Phenobarbital prevents recurrences of febrile seizures and is one of the primary drugs used to treat status epilepticus. Because of its favorable pharmacokinetic profile (long half-life), phenobarbital remains the drug of

first choice for neonatal seizures (see below). As an inducer of liver enzymes, phenobarbital can accelerate the metabolism of other AEDs, theophylline, cyclosporine, warfarin, and other drugs.

Phenobarbital causes few serious side effects. Rashes are common, but discontinuation of the drug is not required unless the rash is severe or persistent. The major side effects of phenobarbital are lethargy, learning difficulties, and behavioral changes such as hyperactivity (especially in toddlers), mood lability, irritability, and sleep disturbance. In both children and adults, phenobarbital can affect cognitive abilities such as memory and perceptual-motor function.

Primidone

Primidone (Mysoline), a congener of phenobarbital, is useful in the treatment of generalized tonic–clonic and partial seizures. It differs from many AEDs in that both the parent compound and metabolites have anticonvulsant properties. Primidone is metabolized through oxidation to phenobarbital and splitting of the ring to form phenylethylmalonamide (PEMA). Primidone, phenobarbital, and PEMA all have anticonvulsant actions, and primidone sometimes controls seizures that do not respond to phenobarbital. The side effects and drug interaction profile of primidone are similar to phenobarbital.

Phenytoin and fosphenytoin

Phenytoin (Dilantin) is one of the most frequently prescribed, inexpensive, effective medications at the physician's disposal. Although there are numerous side effects, some of which can be serious, it is generally considered to be safe. Phenytoin is a broad-spectrum AED that is effective against generalized tonic–clonic, partial, and tonic seizures. It may also be helpful in other seizure types, with the exception of absence and myoclonic seizures. Its primary mechanism of action is use-dependent block of neuronal sodium channels.

Phenytoin is metabolized in the liver, but its metabolism differs from that of other AEDs because its biotransformation follows zero-order kinetics. Enzymes responsible for degradation of phenytoin become saturated within the serum therapeutic range, after which the metabolic rate is no longer dependent on substrate load but proceeds at a constant pace (zero-order or nonlinear kinetics). Therefore, once hepatic enzyme saturation occurs, small increases in dosage result in a large increase in serum level and subsequent clinical toxicity (Fig. 8.3). After the child has a level in the lower therapeutic range, further increases in dose should be small, generally no more than 25 mg/day once the serum level is above 10 μg/mL. Owing to the complex metabolism of phenytoin, monitoring serum levels is important. Phenytoin is highly protein bound; therefore, in conditions of low serum proteins, it may be useful to obtain free and total phenytoin levels. Phenytoin is an inducer of hepatic enzymes, with complicated interactions with AEDs and other drugs (Levy *et al.* 2002).

Because intramuscularly injected phenytoin crystallizes and is subsequently absorbed slowly and erratically, the drug should *not* be given by this route. Fosphenytoin (Cerebyx), a phosphate-ester prodrug of phenytoin, is a water-soluble form of phenytoin that can be given intravenously or as an intramuscular injection. Fosphenytoin is now a standard AED for treating status epilepticus.

Phenytoin has both dose-dependent and idiosyncratic adverse effects. Monitoring of serum levels can eliminate many of the dose-related side effects. Common dose-related side effects include lethargy, dizziness, ataxia, tremors, and nystagmus. There is a correlation between serum levels and signs of toxicity, with nystagmus appearing around 20 μg/mL, ataxia at 30 μg/mL, and drowsiness at levels greater than 40 μg/mL.

The most serious idiosyncratic reaction is a skin rash. The clinical spectrum of rash ranges from a common morbilliform rash occurring 1–14 days after the beginning of therapy, to the rare, severe toxic epidermal necrolysis, exfoliative dermatitis, and Stevens–Johnson syndrome. Although the common morbilliform rash may be benign and self-limited, it is recommended that phenytoin be discontinued with any type of skin reaction because it may be an early indication of a hypersensitivity reaction. In the case of a mild rash, therapy may be resumed after the rash clears. If the rash recurs on reinstitution of therapy, further phenytoin usage is contraindicated. Hepatic dysfunction is a rare but serious complication that usually occurs during the first 6 weeks of therapy. Lymphadenopathy is a rare complication of phenytoin treatment, requiring that the drug be discontinued.

Cosmetic side effects of chronic phenytoin use include gingival hyperplasia, hirsutism, coarsening of facial features, and acne. These cosmetic side effects reverse when phenytoin is discontinued. Chronic phenytoin use has been associated with cerebellar atrophy. With toxic serum levels, phenytoin has been associated with impairments in attention, memory, speed of information processing, and fatigue.

Valproic acid

Valproic acid (VPA, sodium valproate, Depakene, Depakote, Depacon) is one of the most important AEDs for the treatment of childhood seizures. Although VPA is very effective in some seizure types, the prescribing physician must be very familiar with its side effect profile.

VPA is a broad-spectrum AED that has been successfully used in several seizure types, including typical and atypical absence, partial, generalized tonic–clonic, and myoclonic seizures. Its mechanism of action is complex, likely involving enhanced GABAergic inhibition as well as block of sodium and calcium channels.

VPA is rapidly absorbed after parenteral administration. It is eliminated by the liver. Enzyme-inducing AEDs such as carbamazepine and phenytoin reduce VPA levels.

Mild side effects are common in children taking VPA. Transient nausea is common when starting the drug, but usually dissipates, and can be lessened by taking the drug with food or using the enteric-coated preparation. Sedation is also common upon VPA initiation, especially in children taking multiple AEDs; the sedation usually improves with continued use. Hand tremors are common and are related to serum level; the tremor is rarely severe enough to cause motor dysfunction, but if it becomes significant, lowering the dose or initiating propanolol may be helpful. Weight gain can be significant, especially in adolescent females. Mild hair loss is sometimes seen, but it tends to regrow.

The teratogenic effects of VPA are well known. Use of VPA by pregnant mothers correlates with an increased incidence of neural tube defects in the fetus. There is a 1–2% risk of neural tube defects in newborns whose mothers take valproic acid in the first trimester (Bourgeois 2001). The risk is lessened by maternal folate supplementation during pregnancy. There has also been recent concern about an association between VPA and polycystic ovary syndrome. Studies of children born to mothers with epilepsy have shown a lower mean verbal IQ in those exposed to VPA vs. other medication (Adab *et al.* 2004).

Pancreatitis is a rare but serious side effect of VPA. Symptoms include abdominal pain, vomiting, and elevated serum amylase levels. Thrombocytopenia or platelet dysfunction have been reported with VPA. Except in children undergoing surgery, these findings usually have little clinical importance. Red blood cell aplasia, neutropenia, and bone marrow suppression have also been reported.

Cases of stupor and coma have occurred at therapeutic serum VPA levels, both when VPA is used alone and in polytherapy. In some cases, these symptoms are due to hyperammonemia, but VPA-induced hyperammonemia is usually asymptomatic. It may occur in association with other evidence of hepatic dysfunction or with normal liver function tests. Elevated ammonia levels may be associated with increased seizure frequency, lethargy, stupor, and coma. However, elevated ammonia levels also occur without clinical impairment. Although there is a poor correlation between clinical symptoms and serum ammonia levels, reductions of VPA dosage in symptomatic patients may result in clinical improvement.

The most serious side effect associated with VPA is liver toxicity (Perucca 2002). This toxicity is of two types: a common, transient, dose-dependent asymptomatic rise in liver transaminases (ALT and AST), and a rare, idiosyncratic, non-dose-related symptomatic hepatitis that may be fatal. The first type usually occurs within the first 3 months of treatment and is seen in up to 30% of patients. Usually, the ALT and AST fall when the VPA dose is reduced; at other times the elevated enzymes recede spontaneously despite continuation of treatment. Concern is not usually warranted until transaminase levels exceed three times normal values.

Fatal liver toxicity due to VPA has been well documented (Bryant & Dreifuss 1996), and is heralded by jaundice, anorexia, lethargy, and clinical hepatitis. It usually occurs within the first few months of VPA treatment. The risk is highest in children under the age of 2 years on multiple AEDs. The most recent survey, covering the years 1987–1993, cites only one hepatic fatality among more than 600 000 patients on VPA monotherapy over the age of 10 years. Under age 10, the risk on monotherapy is about one in 16 000. Among patients who received VPA as part of polytherapy, the fatality rate was much higher. Under the age of 2 years, there was a 1 in 618 fatality rate, which declined to 1 in 8307 in the 3- to 10-year-old group; further declines in the fatality rate were observed in older patients. Considering all groups, of more than one million patients receiving VPA during 1987–1993, 29 developed fatal hepatotoxicity (1 in 34 691). Although routine laboratory studies are warranted, parents must be warned that the onset of hepatic dysfunction can be rapid and fulminating, and that normal laboratory determinations do not guarantee safety.

All patients on VPA require close monitoring of liver function and hematologic parameters. It is recommended that

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Pharmacology of Antiepileptic Drugs

- Published therapeutic levels of AEDs should be used only as a guide. It is likely that each patient has his or her own therapeutic level.
- Blood levels are most useful when there is a change in seizure control or toxic side effect; routine levels are often not necessary.
- The most common reason for a subtherapeutic AED level is noncompliance.
- Owing to their erratic bioavailability, the generic preparations of several AEDs (including carbamazepine, valproate, and phenytoin) can sometimes result in erratic serum levels. Before switching drugs or adding a second AED, it may be worth trying the name brand formulation.
- Blood levels obtained before the steady state is reached (five half-lives) are useful only in emergency situations. Otherwise, wait at least five half-lives after starting a new drug or changing the dosage before obtaining a level.
- The use of a single AED usually results in higher serum levels, less toxicity, and better seizure control than when polytherapy is employed.
- When using drugs with short half-lives, the timing of the level is important (best to get trough levels). In drugs with longer half-lives, timing of levels is less critical.
- When using AEDs that are highly protein bound (e.g. phenytoin or valproate), free or unbound levels can sometimes be more informative.
- The physician should pay close attention to parental observations about behavioral changes with AEDs.
- In some children with intractable seizures, a realistic goal might be to allow the child to function well at home and school even though occasional seizures occur. Cognitive side effects of AEDs can be equally or more detrimental than seizures.

baseline studies (CBC with platelet count, AST, ALT) be obtained before VPA is started. Repeat studies should then be performed within the first month and then every 3–6 months, depending on the child's age, concurrent medications, and clinical status. In patients on polytherapy, it is important to obtain levels of all AEDs, because drug interactions with VPA are common. These studies should be repeated immediately if there is any clinical indication of liver disease. An amylase level may be informative if the child has abdominal pain. The cause of easy bruising or bleeding should be pursued with a CBC, platelet count, and clotting studies. In children with lethargy or other mental status changes, serum ammonia should be checked. In children under 2 years of age on VPA, as well as any child with carnitine deficiency, carnitine supplementation is often recommended (50–100 mg/kg/day in divided doses) (DeVivo *et al.* 1998; Tein 2002). However, there are no conclusive data that coadministration of carnitine reduces the risk of hepatic dysfunction in children on VPA.

New antiepileptic drugs

Felbamate

Felbamate (Felbatol), released in the United States in 1993, is approved as monotherapy and adjunctive therapy of partial seizures with or without secondary generalization in adults 14 years of age and older, and as adjunctive therapy for partial and generalized seizures associated with Lennox–Gastaut syndrome in children 2–14 years of age. Unfortunately, in its first year of use the drug was linked to 34 cases of aplastic anemia and 18 cases of fatal hepatic failure. No child under 13 years old developed aplastic anemia, but there were children under 5 years old with liver failure (Pellock 1999). There have been no reported fatalities since then. Currently, felbamate is reserved for patients with severe refractory epilepsy, and only after the attendant risks have been explained fully. The adverse events were especially unfortunate because felbamate was the first AED shown to successfully treat seizures in children with Lennox–Gastaut syndrome. In addition, many of these children were more alert and interactive on the drug.

In children, the most common side effects of felbamate are weight loss, nausea, dizziness, anorexia, and insomnia. All of these side effects are more common with polytherapy. Close monitoring of CBCs and liver function is necessary.

Gabapentin

Gabapentin (Neurontin) was released in the United States in 1994. It is structurally related to the inhibitory neurotransmitter GABA, though its exact mechanism of action is uncertain. In patients 12 years of age or older, gabapentin has been shown to be somewhat effective for the adjunctive treatment of partial seizures with or without secondarily generalization. In pediatric studies, adjunctive gabapentin had better efficacy than placebo in children with partial seizures (Appleton *et al.* 1999).

Adverse effects of gabapentin are uncommon and include somnolence, fatigue, dizziness, nausea, and weight gain. Most of these side effects are mild and transient. A major advantage of gabapentin is that it is relatively free of interactions with other drugs. Unlike other AEDs, gabapentin is not metabolized by the liver, does not induce hepatic enzymes, and is not protein bound. It is almost completely eliminated by renal excretion of the parent compound. Gabapentin does not affect the levels of other AEDs. The dose can be escalated and tapered quickly. Despite these advantages, it does not seem to be as effective in controlling seizures as most of the older and newer AEDs.

Lamotrigine

Lamotrigine (Lamictal) was released in 1994. It is approved for the treatment of partial and secondarily generalized seizures in adults and in children and adults as add-on treatment of generalized seizures in Lennox–Gastaut syndrome (Messenheimer 2002).

Adverse effects may include diplopia, drowsiness, ataxia, and headache. Rashes have been a significant problem in children and adults. Although in some patients the rash is mild and transient, in others the severity of the rash has necessitated its discontinuation. Rash is particularly troublesome when lamotrigine is added to VPA; the rash may be avoided if lamotrigine is added very slowly. Carbamazepine and phenytoin increase the metabolism of lamotrigine, whereas VPA inhibits its metabolism. Smaller doses of lamotrigine are required when VPA is used concurrently but not when carbamazepine and phenytoin are used with lamotrigine.

Levetiracetam

Levetiracetam (Keppra) is approved for the adjunctive therapy of adults with partial seizures with or without generalization. Its mechanism of action is unknown, but it is probably different than the mechanism of other AEDs. Because very little levetiracetam is protein bound, drug interactions are not common. Since levetiracetam has not been approved for children, dosing recommendations have not been determined. However, a number of open label studies are providing some guidance on the dosing range, and spectrum of activity, of this drug in children.

Side effects include fatigue, lethargy, ataxia, and behavioral alterations, such as irritability, depression, and even psychosis. Such side effects usually appear within the first month of treatment and most are mild. The indications, adverse effect profile, and optimal dosing regimen for levetiracetam in children remain to be defined. Nevertheless, it holds promise as a drug with unique characteristics among AEDs.

Oxcarbazepine

Oxcarbazepine (Trileptal) is approved for monotherapy or adjunctive therapy of partial seizures with or without secondary generalization in adults and children 4 years and

older. Oxcarbazepine is a carbamazepine derivative that has a similar mechanism of action and a similar side effect profile to carbamazepine. However, oxcarbazepine side effects (somnolence, fatigue, headache, dizziness, nausea) seem to be milder and the efficacy may be even better than carbamazepine (Glauser *et al.* 2000). There have been anecdotal reports that oxcarbazepine, like carbamazepine, may exacerbate generalized seizures (Mandelbaum *et al.* 2002). Oxcarbazepine is a weaker hepatic enzyme inducer than carbamazepine and does not exhibit autoinduction. Hyponatremia has been reported in patients using oxcarbazepine. Allergic rashes have been observed; there is approximately 30% cross-reactivity to patients allergic to carbamazepine. Recently, a warning has been added to the prescribing information regarding reports of serious dermatological reactions including Stevens–Johnson syndrome and toxic epidermal necrolysis.

Tiagabine

Tiagabine (Gabatril) is approved as adjunctive therapy for partial seizures in adolescents and adults, although it may exacerbate generalized seizures. Tiagabine works by preventing reuptake of synaptically released GABA back into the presynaptic terminal, thus prolonging the time that GABA is available for synaptic inhibition. Common side effects include mental slowing, dizziness, lethargy, and gastrointestinal symptoms such as nausea or pain. Drug interactions with tiagabine are not prominent, although caution should be exercised, especially when VPA is added, since it may worsen tiagabine side effects.

Topiramate

Topiramate (Topamax) has been approved for adjunctive therapy for partial seizures with or without generalization and generalized seizures in adults and children over 2 years of age. It is efficacious in Lennox–Gastaut syndrome and shows some promise for infantile spasms. The mechanism of action is unknown but it may act on sodium channels, calcium channels, and glutamate receptors of the non-N-methyl-D-aspartate type.

The most common side effects are mental slowing, dizziness, somnolence, ataxia, and headache. Patients often lose weight on topiramate, which has led to its proposed use as an appetite suppressant. Because topiramate is a weak carbonic anhydrase inhibitor 1–2% of patients develop renal stones. Acute glaucoma, presenting with severe ocular pain and myopia, may occur shortly after initiation of treatment.

Vigabatrin

Vigabatrin (Sabril) is a reversible inhibitor of GABA transaminase and may exert its anticonvulsant effect by decreasing the breakdown of GABA in the brain. Although it is not available in the United States at this time, vigabatrin merits mention because of its broad efficacy in refractory partial and secondarily generalized seizures, as well as in infantile spasms (particularly in children with tuberous sclerosis). Vigabatrin has relatively low toxicity but has caused psychosis in some patients. There are reports of visual field constriction due to vigabatrin (Iannetti *et al.* 2000). Otherwise, the drug appears to be very well tolerated by children.

Zonisamide

Zonisamide (Zonegran) is a sulfonamide derivative approved in the United States for the adjunctive treatment of partial seizures in adults. However, experience worldwide has shown that it has a much broader spectrum of action and may also be useful in generalized seizures such as myoclonic, absence, and even Lennox–Gastaut syndrome and infantile spasms. The mechanism of action is unknown.

Zonisamide does not dramatically alter the metabolism of other AEDs. Patients may experience somnolence, ataxia, dizziness, fatigue, difficulty with concentration, mental slowing, or even a psychotic reaction, especially in the first few months of treatment. Renal stones occur in up to 4% of adult patients on zonisamide; data are not available for children. Severe idiosyncratic reactions are rare but have included Stevens–Johnson syndrome and aplastic anemia.

Other antiepileptic drugs

Many other medications may be useful in treating seizures in children. Clonazepam (Klonopin), a benzodiazepine, is effective in a variety of seizure types including absence, generalized tonic–clonic, and myoclonic. Clonazepam and other benzodiazepines are often used as adjunctive therapy in children with epilepsy. The development of tolerance requires progressive increases in dosage to achieve the same effect; unfortunately, side effects such as excessive drooling may then supervene. Acetazolamide (Diamox) is a carbonic anhydrase inhibitor with some anticonvulsant effect against generalized seizures such as absence and generalized tonic–clonic. Methsuximide (Celontin), like ethosuximide, may be useful in absence and partial complex seizures.

Other epilepsy therapies

Ketogenic diet

The ketogenic diet (KD) was developed in 1920 to mimic the fasting state, which was known to be anticonvulsant. The KD is a specific dietary regimen that has proven efficacious in many children with medically refractory epilepsy. The diet, which must be monitored strictly by an experienced physician and dietician, is composed of a 4:1 ratio (by weight) of fats to carbohydrates and protein. Children consuming such a diet become ketotic, as assessed by increases in serum ketone bodies (acetoacetate and β-hydroxybutyrate). It is unknown how the ketotic state reduces seizures (Stafstrom & Spencer 2000), but at some centers, up to half of children on the ketogenic diet experience a greater

than 90% seizure reduction (Vining 1999). Details of ketogenic diet formulation and administration, side effects, and sample diet plans, as well as answers to parents' frequently asked questions, are summarized in a useful handbook (Freeman *et al.* 2000).

Vagus nerve stimulation

The vagus nerve stimulator (VNS) is an implantable device that generates a programmed pattern of electrical stimulation of the vagus nerve. Afferent impulses travel to the brain along the vagus nerve and decrease seizures by an unknown mechanism, possibly by "desynchronizing" neuronal activity (Heck *et al.* 2002). The VNS was approved in the United States in 1997, and the technique is effective in diminishing seizure frequency in some patients. A major advantage is the patient's ability to activate the device when an aura is sensed, thereby averting the spread of the seizure. Disadvantages include the need for surgical implantation and its associated cost, although this must be weighed against the cost of AEDs and their attendant side effects. Minor side effects include a cough or hoarse voice during stimulations. Although the VNS is effective in some children, its place among antiepileptic therapies is still not fully defined (Sheth & Stafstrom 2002).

Epilepsy surgery

Some children with medically refractory seizures will benefit from epilepsy surgery. Epilepsy surgery has become an accepted therapeutic modality with good outcome and low morbidity. The issues of patient selection, surgical options and workup, and prognosis are reviewed elsewhere (Cross 2002; Holmes 2002; Sheth 2002). Table 8.11 lists some of the more common epilepsy surgery techniques in children. Overall, the evidence suggests that earlier surgery is associated with a better neurodevelopmental outcome, since brain plasticity is greater at younger ages (Stafstrom *et al.* 2000).

Focal lesions, such as dysplasias or developmental tumors, can be resected with an excellent chance of seizure resolution. In adolescents with mesial hippocampal sclerosis (perhaps due to a prolonged febrile seizure or other insult early in life), temporal lobectomy has been shown to be very successful in affording seizure freedom. Corpus callosotomy is occasionally performed to reduce atonic seizures, though the success rate is modest. Hemispherectomy is most useful for children with Rasmussen's encephalitis (see below), a focal encephalitis affecting the entire hemisphere (McNamara *et al.* 1999).

Summary of antiepileptic therapy

From the plethora of treatment options discussed above, it is clear that the physician has many choices available to treat the child with epilepsy. Of course, if the seizures are due to a systemic derangement (e.g. hypocalcemia or hypoglycemia), the primary etiology can be corrected without AED therapy. Once the decision to treat with an AED is made, the

TABLE 8.11

Summary of Selected Surgical Procedures for Children with Medically Intractable Seizures

Procedure	Seizure types	EEG	Risks	Benefits
Temporal lobectomy	Simple or complex partial ± secondary generalization	*Interictal*: Temporal or frontal spikes, sharp waves *Ictal*: Initially, focal temporal lobe discharges; later, spread	Visual field defect; cerebrovascular accident; third nerve palsy; memory/speech impairment	Seizure reduction or control
Nontemporal resection	Partial ± secondary generalization	*Interictal*: Focal spikes or sharp waves, occasionally generalized spike wave *Ictal*: Focal spikes, beta activity or polyspike wave	Dependent on surgical site; hemiparesis; visual field cut	Seizure reduction or control; improved development
Corpus callosotomy	Partial ± secondary generalization; tonic; atonic, drop attacks	*Interictal*: Multifocal spikes/sharp waves, generalized spike wave, polyspike wave *Ictal*: Rapid spikes, polyspike wave	Disconnection syndrome; speech deficits; increase in frequency or intensity of partial seizures	Reduction in "drop" and generalized seizures; rarely do seizures totally remit
Hemispherectomy	Unilateral partial ± secondary generalization	*Interictal*: Lateralized discharges over involved hemisphere; may have bilateral spikes *Ictal*: Lateralized seizure onset over involved hemisphere	Hemiparesis; hemosiderosis; hydrocephalus	Seizure control; improved behavioral and cognitive status

choice of agent will depend on the child's age, lifestyle, syndrome, and concurrent medical conditions and treatments, as well as the side effect profile of the AED and its cost, potential toxicity, kinetics, and drug interactions. Therefore, the decision is not always straightforward and must be tailored individually to the patient. While the newer AEDs tend to have fewer idiosyncratic reactions, the full spectrum of drug interactions and side effects will not become clear until these newer AEDs have been used more extensively. For traditional AEDs, we have a better appreciation of the range of adverse reactions and side effects, but their efficacy is often not optimal. Finally, for refractory epilepsy, the complexities of multiple concurrent AEDs must be dealt with, and consideration given to alternative epilepsy treatments such as the ketogenic diet, vagus nerve stimulation, and epilepsy surgery. Treatment of the child with epilepsy is truly a challenging undertaking.

FEATURES

Table 8.12 Simple Partial Seizures

Discriminating feature

1. No impairment of consciousness

Consistent features

1. Seizures are usually brief and stereotyped
2. Symptoms and signs are referable to a particular brain region

Variable features

1. Motor symptoms
2. Somatosensory symptoms
3. Psychic symptoms
4. Autonomic symptoms
5. Postictal symptoms
6. Association with structural brain lesion
7. Interictal EEG abnormalities
8. Responsiveness to AEDs

Partial seizures

Simple partial seizures

Classification

Partial (focal) seizures are those in which the first clinical and EEG changes indicate activation of neurons limited to part of one cerebral hemisphere. Partial seizures are further classified as to whether or not consciousness is impaired during the attack. When consciousness is not impaired, the seizure is termed a simple partial seizure. When consciousness is impaired, that is, the child is unable to respond normally to exogenous stimuli by virtue of altered awareness or responsiveness, the seizure is classified as a complex partial seizure (Table 8.12).

Clinical characteristics

The clinical manifestations of partial seizures are determined by the cortical area involved. For example, a simple partial seizure arising from the occipital lobe presents with visual phenomena; from the precentral gyrus, with motor activity; and from the postcentral gyrus, with sensory symptoms. Seizures arising from the temporal lobe are usually associated with an altered state of consciousness and are therefore complex partial seizures.

The most common type of simple partial seizure involves motor symptoms. Depending on the site of origin in the motor strip, any portion of the body may become involved in focal seizure activity. The seizure phenotype may vary from those involving only small groups of muscles, such as rhythmic twitching of a single finger or part of the tongue, to those involving multiple muscles, such as clonic jerking of the whole arm or leg. Partial seizures may remain strictly focal or they may spread to contiguous cortical areas, producing a sequential involvement of body parts, called a "Jacksonian march" (after the 19th century epileptologist, Hughlings Jackson). Following partial motor seizures, there may be paralysis of the muscle groups previously involved in the seizure. This weakness, termed Todd's paralysis, may last from minutes to hours and is helpful in localizing the seizure focus. A common type of simple partial seizure with motor manifestations is seen in benign rolandic epilepsy, described in more detail later in this chapter.

Autonomic symptoms consist of a variety of complaints, including abdominal pain, tachycardia, diaphoresis, papillary dilation, flushing, and piloerection. Abdominal pain as a manifestation of epilepsy is rare and is termed abdominal epilepsy. Because the abdominal pain usually occurs during a complex partial seizure, it is discussed in the next section.

Simple partial seizures can also arise from somatosensory cortex, with clinical manifestations dependent upon the area of sensory cortex involved. Typically, the patient complains of paresthesias or numbness. Like partial seizures with motor symptoms, somatosensory seizures may spread to other cortical areas. Olfactory sensations, usually in the form of

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Simple partial seizures

- Simple partial seizures are usually short, lasting less than a minute.
- Structural brain lesions must be considered in children with simple partial seizures.
- The lack of an EEG abnormality during a seizure does not rule out the possibility of a simple partial seizure.
- The choice of AEDs for treatment of simple partial seizures is the same as that for complex partial seizures.

unpleasant odors, may occur. Gustatory sensations may be pleasant or odious tastes and vary in complexity from crude (for example, salty or sour) to sophisticated. Many patients describe a metallic taste sensation.

All of the manifestations of simple partial seizures – motor, autonomic, somatosensory, special sensory, and psychic – may precede either a complex partial seizure or a generalized tonic–clonic seizure. A simple partial seizure preceding a complex partial or generalized seizure is termed an "aura." The aura may be the only part of the seizure recalled by the patient and serves as a warning that a more extensive seizure is imminent.

Differential diagnosis

Seizures with somatosensory, psychic, or special sensory symptoms may be confused with migraine. This differential diagnosis is discussed under complex partial seizures. In addition, movement disorders such as tics and chorea may be confused with partial motor seizures (see below)

Electroencephalography

The EEG is frequently but not always abnormal in children with simple partial seizures. Focal spikes or sharp waves are seen in 40–85% of patients. At times the epileptogenic area is so limited that the EEG is normal, even during a clinical seizure, especially one of frontal lobe origin.

Etiology

The etiologies of complex and simple partial seizures are similar and these are discussed under complex partial seizures.

Aura

A CPS may start either as a simple partial seizure followed by impairment of consciousness or with impairment of consciousness initially. If there is a simple partial onset to the seizure, the initial phase of the seizure is termed an aura. Therefore the aura is defined as the portion of the seizure that occurs before consciousness is lost and for which memory is retained afterward. The aura may consist of any of the manifestations of a simple partial seizure, with the specific symptom dependent on the location of the ictal discharge. An aura varies considerably from patient to patient and may include somatosensory, auditory, visual (e.g. hallucinations), olfactory and gustatory symptoms, visceral sensations (e.g. epigastric "rising" sensations), or complex subjective experiences (e.g. fear, *déjà vu*, or *jamais vu*). An "aura" is, in fact, a partial seizure and should be recognized as such.

Automatisms

Automatisms are common in CPSs. They consist of involuntary motor activity occurring during the period of impaired consciousness, either during the ictus or postictal period. The child has little or no memory of events during the seizure. Examples of automatisms include chewing, tongue movements, lip smacking, swallowing, hand gestures, scratching, crying, laughing, and repeating a word or phrase. The activity may be complex and quasipurposeful such as playing cards, drawing, or playing music. Automatisms can also be seen in other seizure types, including absence seizures and the postictal phase of generalized tonic–clonic seizures.

Complex partial seizures

Complex partial seizures (CPSs) are one of the most common seizure types both in children and adults. Because CPSs often arise from the temporal lobe, an area concerned with memory and emotion, clinical symptoms may be complex and variable, encompassing the entire range of neuropsychiatric symptoms. The common overlap of psychogenic behavioral manifestations and clinical phenomena associated with CPSs makes the differential diagnosis and management challenging (Table 8.13).

Clinical characteristics

CPSs usually last from 30 seconds to several minutes. They can occur during either wakefulness or sleep. When CPSs occur in sleep, they are most likely to appear soon after sleep begins or during the early morning hours, when the patient cycles frequently through stage 2 and REM sleep. When occurring at night, CPSs may be difficult to differentiate from a parasomnia.

FEATURES

Table 8.13 Complex Partial Seizures

Discriminating feature

1. Consciousness is impaired

Consistent features

1. May begin with an aura
2. Clinical features are stereotyped from seizure to seizure
3. Gradual onset and termination

Variable features

1. Automatisms
2. Affective and psychic symptoms
3. Somatosensory symptoms
4. Aura
5. Postictal impairment
6. Duration
7. Association with structural brain lesions
8. Interictal EEG findings
9. Response to AEDs

Autonomic symptoms
Like simple partial seizures, CPSs may be associated with a variety of autonomic symptoms (Freeman & Schachter 1995). Partial seizures with abdominal pain and vomiting as components have been termed abdominal epilepsy. Abdominal epilepsy, which occurs principally in children, is a form of CPS with impairment of consciousness. The pain of abdominal epilepsy is often colicky, severe, and periumbilical in location. The pain seldom lasts longer than 10–15 minutes and occurs at unpredictable intervals. The attacks may be accompanied by other autonomic phenomena (e.g. borborygmi, sweating, salivation, flatus).

Psychic symptoms
Although psychic symptoms occur commonly in CPSs, they frequently precede the alteration of consciousness and serve as the patient's aura. Psychic symptoms are defined as disturbances of higher cerebral function and include dysphasia, cognitive changes, affective symptoms, dysmnesic symptoms, illusions, and hallucinations.

Affective symptoms
Any emotional change, including various combinations of fear, sadness, depression, embarrassment, or ecstasy, may constitute an ictal event in CPSs. Unfortunately, because children often have difficulty verbalizing their experiences, their emotional state may only be evident as a change in mood or facial expression. Fear, perhaps the most common ictal emotion accompanying CPSs, may be evidenced by the child's facial expression or the need to seek a parent's comfort.

Dysmnesic symptoms
Dysmnesic symptoms consist of a distortion of memory and may consist of a sensation as if an experience had occurred before (e.g. *déjà vu* if visual, *déjà entendu* if auditory). Vivid flashbacks of specific events in the past may be reported. Dysmnesic symptoms often occur as a simple partial seizure before there is an impairment of consciousness, constituting the patient's aura. Dysmnesic symptoms are unusual in children.

Special sensory symptoms
Alterations of sensory perception may occur during CPSs. These may consist of unusual clarity of vision or hearing but usually take the form of illusions or hallucinations. Illusions, defined as distortions of perception, may consist of macropsia (objects appearing larger than normal), micropsia (objects appearing smaller than normal), or analogous distortions of sounds (macroacusia or microacusia). The patient may experience altered body perception, depersonalization (a feeling of being outside one's own body), or a dissociative state. Hallucinations, defined as perceptions without corresponding external stimuli, may also occur.

Seizures arising from primary receptive areas give rather primitive, poorly formed hallucinations, whereas seizures involving the association areas result in better defined, more complex hallucinations. For example, children with primary occipital lobe discharges may have hallucinations consisting of sparkling, scintillating lights, whereas those with seizures involving the visual association area would be more likely to have well-formed visions such as faces.

Seizures in which the child has an olfactory or gustatory hallucination have been termed uncinate fits or seizures. The olfactory and gustatory sensations usually have a disagreeable character and are accompanied by movements of the lips and tongue.

Postictal symptoms
Postictal confusion and tiredness with a gradual return of the mental status to the preictal state occur commonly. It is often difficult to differentiate the ictal from the postictal period, because there is rarely an abrupt transition between the two. Although fatigue frequently follows CPSs, deep sleep is unusual, as opposed to the postictal phase of generalized tonic–clinic seizures. The most common postictal finding following CPSs is confusion.

Differential diagnosis
Because CPSs may consist of simple staring, with or without automatisms, the seizures may sometimes be confused with absence seizures. Helpful distinguishing features of typical absence seizures include a sudden onset, lack of an aura, brief duration (less than 30 seconds), and sudden cessation with immediate resumption of preictal activity and clarity of mind. CPSs usually last longer than absence seizures and are frequently followed by confusion and fatigue. Another key differentiating point is that hyperventilation easily induces an absence seizure in an untreated child, whereas a CPS is much less likely to be induced by hyperventilation. The EEG is also helpful in differentiating the two seizures types. As discussed above, some of the very effective AEDs for partial seizures (e.g. carbamazpine, oxcarbazepine) sometimes exacerbate generalized seizures such as absences. The clinical and EEG features that differentiate CPS from absence seizures are listed in Table 8.14.

Differentiating CPSs from psychotic behavior may be challenging. Like psychiatric disease, CPSs may be associated with hallucinations, agitation, anger, fear, irritability, and confusion. Unlike the affective symptoms and hallucinatory symptoms of psychiatric disease, those of CPSs are usually short in duration, intermittent, and stereotyped. In addition, these symptoms in CPSs are associated with other epileptic phenomena, such as impaired consciousness, speech arrest, and autonomic symptoms. Some patients with CPSs are aware that their symptoms are incongruous, as if superimposed on normal consciousness. This insight

TABLE 8.14

Diagnosis of Typical Absence Seizures and Complex Partial Seizures

Clinical data	Absence seizures	Complex partial seizures
Frequency per day	Multiple	Rarely more than 1 or 2
Duration	Frequently less than 10 seconds; rarely longer than 30 seconds	Average duration over 1 minute; rarely shorter than 10 seconds
Aura	Never	Frequently
Onset and termination	Abrupt	Gradual
Eye blinking	Common	Occasionally
Automatisms	Common	Frequently
Postictal impairment	None	Common
Seizures activated by		
Hyperventilation	Very frequently	Occasionally
Photic stimulation	Frequently	Rarely
EEG		
Ictal	Generalized spike wave	Usually unilateral or bilateral temporal or frontal discharges
Interictal	Usually normal	Variable; may be spikes or sharp waves in frontal or temporal lobes

usually distinguishes these phenomena from psychotic hallucinations and illusions.

Children with nonepileptic episodic rage, or dyscontrol, may be misdiagnosed as having CPSs. Adding to the difficulty in differentiating these attacks from CPSs is that many patients with episodic dyscontrol have organic cerebral dysfunction, and some may even have documented epilepsy. Children with episodic rage usually have other behavioral problems as well. Both CPSs and nonepileptic rage attacks may be of similar duration, lasting several minutes, and both are frequently followed by fatigue, confusion, and amnesia for the event (Table 8.15). Unlike rage attacks, CPSs are rarely associated with violence directed at another person. During CPSs, patients may become combative, especially if restrained, but directed violence is rare. Conversely, in rage attacks, violence directed against individuals commonly occurs. Another differentiating point is that CPSs are usually stereotyped compared with the widely divergent features of rage attacks. The most helpful differentiating point is that usually rage attacks are precipitated by some event, however trivial, that is disturbing to the child.

Occasionally, migraines may be confused with CPSs which have autonomic or sensory symptoms. The differentiation of migraine from abdominal epilepsy can be difficult. Like abdominal epilepsy, migraines may result in episodic abdominal pain. In children with migraine, the abdominal symptoms may not be associated with the headache. In addition, interictal EEGs may be abnormal in both epilepsy

TABLE 8.15

Differentiation of Rage Attacks from Partial Complex Seizures

Clinical data	Complex partial seizures	Rage attacks
Duration	Seconds to minutes	Minutes
Stereotype of attacks	Variable but usually have consistent patterns	Patterns widely diverse
Aura	Frequent	Rare
Violence	Unusual, rarely directed	Frequent, may be directed
Precipitating event	None	Usual
Amnesia for event	Partial to total	None to total
Postictal confusion, lethargy, sleepiness	Common	Occasionally
Response to AEDs	Usually	Occasionally
EEG		
Ictal	Variable, temporal or frontal lobe spikes	Normal or nonspecific abnormalities
Interictal	Unilateral or bilateral temporal or frontal discharges	No change

with abdominal features and childhood migraine. Because abdominal epilepsy usually occurs as a CPS, there is impairment of consciousness during the attack, whereas abdominal pain with migraine is rarely associated with impaired consciousness. A family history of migraines may also be a clue to the diagnosis. In children with suspected abdominal epilepsy, a trial of AEDs may be useful. However, a response to AEDs does not necessarily mean the diagnosis of abdominal epilepsy is established, because migraines also respond to several AEDs (Cutrer 2001). Unless an attack is recorded on the EEG, the diagnosis may not be established until other unequivocal symptoms of migraines or seizures surface.

Electroencephalography

The interictal EEG findings in patients with CPSs are variable and may include spikes, sharp waves, spike-wave discharges, or focal slow activity. Although complex partial seizures are frequently associated with focal interictal epileptiform activity, some patients show generalized or diffuse abnormalities. The most frequently encountered interictal EEG abnormality is temporal spikes. Bilateral temporal spikes, occurring either independently or synchronously, are seen in up to one-third of patients with CPSs. Interictal discharges may be located in other areas, especially the frontal lobe. Focal abnormalities on EEG should alert the clinician to the possibility of a structural lesion.

Sleep deprivation is a powerful activator of epileptiform activity and the likelihood of recording an abnormality is increased by recording during sleep. If an abnormality is not detected on the initial EEG, a repeat study with sleep deprivation may be useful. The addition of supplementary electrodes, such as sphenoidal electrodes, may also increase the yield of the EEG. Hyperventilation and photic stimulation usually do not activate seizures in children with CPSs.

Complex Partial Seizures

PEARLS & PERILS

- The child with epileptic staring spells, especially if they occur less than once per day, is more likely to have complex partial seizures than absence seizures.
- Children with complex partial seizures who do not respond to trials of two AEDs are unlikely to achieve complete seizure control, and the possibility of surgery should be considered.
- Violent behavior is rarely caused by an epileptic seizure. Although patients may become agitated during a seizure or in the postictal period especially if they are restrained, directed violence is extremely uncommon.
- Seizures rarely cause abdominal pain. Abdominal epilepsy, a very rare disorder, is usually partial complex in type and is associated with impairment of consciousness.

The diagnosis of CPS is made based on clinical criteria, and a normal EEG should never be used to rule out a CPS. Conversely, the clinician must be aware that epileptiform EEG patterns may occur in children who do not have seizures and never will have. An abnormal EEG should never be construed as definite evidence of CPSs in the absence of a compatible clinical history.

Etiology

In a study of CPSs of temporal lobe origin, 35% of 100 children had a major cerebral insult to the CNS before the seizures began (Ounsted *et al.* 1966). Antecedent factors included birth asphyxia, head injury, infections, and tumors. In another 32%, status epilepticus occurred before the recurrent CPSs, and in 33% no etiology could be determined.

Much has been learned about the etiology of CPSs through pathologic examination of tissue obtained at the time of total or partial temporal lobectomies for intractable seizures. Pathological examination of temporal lobes from 100 patients (primarily adults) with CPSs of temporal lobe origin revealed 47 with mesial temporal lobe sclerosis, 24 with small cryptic tumors, 13 with miscellaneous focal lesions such as scars or infarcts, and 22 with equivocal lesions such as subpial and white matter gliosis (Falconer *et al.* 1964). Tumors must be considered in any patient presenting with partial seizures. Further information about the etiologies of CPSs can be found elsewhere (Bourgeois 1998; Avanzini *et al.* 2001).

Evaluation

CPSs rarely occur more than once or twice per day, unlike absence seizures, which usually occur several times a day. Therefore it is very unlikely that the physician will have an opportunity to actually observe a seizure. For that reason, the history is critically important. Altered consciousness is the *sine qua non* of CPSs and if the child is fully alert and responsive during the attack, a diagnosis of CPS cannot be made. Precipitating factors, if any, should be identified because knowledge of these factors may be important in attaining seizure control. Sleep, fatigue, stress, and hypoglycemia may play a role in inducing seizures.

The past medical history may offer clues to the etiology of the seizures. As has been discussed, frequent causes of CPSs include birth asphyxia or trauma, head injuries, severe febrile seizures, and meningitis or encephalitis. A recent history of headaches, especially if they are associated with vomiting or occurrence at night, should raise the possibility of a structural lesion.

A careful neurologic examination on a child with CPSs may reveal subtle asymmetries in strength, tone, or reflexes. An asymmetry in somatic size (e.g. nailbeds) may be an additional clue to a focal brain lesion. Any abnormal neurologic finding on physical examination in a child without

prior documented neurologic impairment requires further evaluation.

Electroencephalography is discussed above. EEGs are most useful in CPSs if there is a change in the neurologic examination, in the character of the seizures, or in the seizure frequency. The EEG may also be of value in deciding when to withdraw AEDs.

It is recommended that all children with CPSs have an MRI scan. Tumor, dysgenetic lesions, mesial temporal sclerosis, vascular malformations, and other structural lesions will be readily detected by MRI and may lead to an alteration in management.

Treatment

Carbamazepine, phenytoin, and valproate have been the primary AEDs used in the treatment of CPSs. Barbiturates are also effective but are used less often because of the frequent behavioral and cognitive changes. CPSs are frequently refractory to pharmacologic therapy. Only 25–60% of treated children have either complete or near-complete cessation of seizure activity. Several of the new AEDs may be effective in CPSs either as monotherapy or adjunctive therapy (Table 8.8).

Children who continue to have partial seizures, even with optimal pharmacologic management, may be candidates for surgical treatment. Surgical resection of focal pathologic areas of the brain that engender refractory seizures is now a well-accepted and effective therapy (Table 8.11).

There are no firm guidelines as to when AEDs should be withdrawn in patients who are free of seizures. Recurrence risk is related to a number of factors, including age of onset, seizure frequency, location of the epileptogenic zone and presence or absence of abnormal findings on neurologic examination. All of these factors must be considered in each patient. The traditional recommendation has been that once a child is free of seizures for 2 years, a slow AED withdrawal can be undertaken.

Generalized seizures

Generalized tonic–clonic seizures

Clinical characteristics

Generalized tonic–clonic (GTC) seizures, formerly called *grand mal* seizures, consist of bilaterally symmetric convulsive movements of all limbs, with impairment of consciousness. Some children have prodromal symptoms, such as headache, insomnia, irritability, or a change in appetite, mood, activity level, or color, hours or days before an impending seizure. Prodromal symptoms are to be distinguished from the aura, which generally precedes the GTC by seconds or minutes. The aura is a partial seizure, whereas a prodrome is not associated with epileptiform discharges.

The aura is useful in distinguishing between a GTC seizure that begins focally from one that does not secondarily generalize. Auras vary considerably from patient to patient and may encompass any of the manifestations of simple partial seizures including focal motor, sensory, autonomic, or psychic symptoms.

The stereotyped nature of the motor activity in GTC seizures is dramatic and easily recognized. The tonic phase is characterized by rigid extension of the arms and legs. The mouth is tightly closed, and biting of the tongue may occur. As the thoracic and abdominal muscles contract, air may be forced over taut vocal cords, resulting in a cry. Apnea may occur at this time and may persist through the clonic phase. During the clonic phase, muscle relaxations are interspersed with tonic contractions. The alternating increase and decrease in muscle tone results in rhythmic jerks, which decrease in frequency as the seizure continues. The combination of a rigidly closed jaw and increased secretions during the seizure may cause partial airway obstruction and result in noisy, labored respirations. Between the last clonic jerk and the immediate postictal phase, the bladder sphincter relaxes and incontinence may occur. The duration and extent of postictal impairment is related to the duration of the GTC seizure. However, some patients have prolonged postictal periods following relatively short seizures.

Differential diagnosis

GTC seizures are readily diagnosed and only rarely present the clinician with a difficult differential diagnosis. Pseudoseizures (psychogenic seizures) may resemble GTC seizures, although there are usually clinical features that help the physician differentiate between the two (Table 8.16). Brief GTC seizures may also follow breathholding spells or syncopal attacks. GTC seizures in such settings are not epileptic seizures *per se*, but rather are due to reflex anoxia secondary to transient interruption of the brain's oxygen supply. Similar nonepileptic seizures can be seen immediately after head trauma (within seconds of the injury) or during such metabolic derangements as hyponatremia or hypoglycemia. None of these nonepileptic seizures predispose to later epilepsy, and they do not require treatment with anticonvulsants.

Generalized Tonic–Clonic Seizures

PEARLS & PERILS

- Most generalized tonic–clonic seizures are secondarily generalized, that is, the seizures have a focal onset and then become generalized.
- Seizures in a given child are typically stereotyped. In patients who experience different symptoms with different spells, pseudoseizures should be considered.

TABLE 8.16

Criteria Useful for Differentiation of Epileptic Seizures from Pseudoseizures

Clinical data	Pseudoseizures	Generalized tonic–clonic seizures
Changes in seizure frequency with medication change	Rare	Usual
Increased seizures with stress	Frequent	Occasional
Combativeness	Common	Rare
Vulgar language	Frequent	Rare
Self-injury	Rare	Common
Incontinence	Rare	Common
Tongue biting	Rare	Common
Nocturnal occurrence	Rare	Common
Stereotype of attacks	Often variable	Little variation
Postictal confusion, lethargy or sleepiness	Rare	Frequent
EEG		
Interictal	Often normal	Frequently abnormal
During attack	Normal	Always abnormal

Electroencephalography

The interictal manifestations of GTC seizures are quite varied. The EEG may be normal during both the awake and sleep states. Focal or multifocal paroxysmal activity consisting of spikes, sharp waves, or slow activity is seen on the interictal EEG of up to 40% of patients with GTC seizures.

Etiology

GTC seizures may be idiopathic or secondary to acquired lesions (symptomatic). Idiopathic GTC seizures are strongly related to genetic factors. It is likely that with improving neurodiagnostic and neuropathologic capabilities, more patients with "idiopathic" GTC or focal seizures will be demonstrated to have structural lesions. Toxins, environmental stress, or systemic disease may result in a GTC seizure. By far the most common identifiable stress in children is fever (see Chapter 23), whereas in adults, withdrawal from drugs, especially alcohol, is very common. Systemic disorders such as hypoglycemia, uremia, hepatic failure, and hypoxia may result in GTC seizures.

Evaluation

The type and extent of the evaluation of a child with GTC seizures is largely dependent on whether the seizures are idiopathic or symptomatic. It is therefore important to obtain a careful description of the seizures. An aura or focal onset indicates that the patient has a secondarily GTC seizure. A history of absence seizures is frequently obtained in patients with idiopathic GTC seizures. Children with idiopathic GTC seizures may have a family history of absence or GTC seizures. Idiopathic GTC seizures are often associated with normal neurologic and developmental examinations, whereas children with symptomatic GTC seizures are more likely to have an abnormal neurologic examination or impaired cognitive development.

If the child is seen immediately following a GTC seizure, laboratory studies should include serum glucose, blood urea nitrogen (BUN), electrolytes, CBC, toxicology screen, and often serum calcium and liver function tests. Some authors use a postictal prolactin level to distinguish an epileptic seizure from a nonepileptic seizure, but the clinical utility of prolactin levels is controversial and can be unreliable (Fein *et al.* 1997). If there is a possibility of a CNS infection, a lumbar puncture is indicated. Patients with evidence of increased intracranial pressure should undergo a CT scan immediately. All children with an unexplained GTC seizure should receive an MRI scan.

Treatment

The drugs of first choice in the treatment of afebrile idiopathic GTC seizures are similar to those for partial seizures: carbamazepine, phenytoin, and valproate; some of the newer AEDs may be beneficial as well (Table 8.8). Children with partial seizures that secondarily generalize and do not respond to AEDs may benefit from a focal surgical resection. No firm rules are available as to when to withdraw AEDs in a patient with GTC seizures. As a general guideline, consideration should be given to withdrawing AEDs after the child has been seizure-free for 2 years (O'Dell & Shinnar 2001).

Absence seizures

The main feature of absence seizures is staring with altered alertness (Table 8.17). Absence seizures can be part of numerous epilepsy syndromes, including childhood absence epilepsy (discussed below), juvenile absence epilepsy, and

FEATURES

Table 8.17 Absence Seizures

Discriminating features

1. Usually brief (<15 seconds)
2. Ictal EEG consists of generalized spike waves

Consistent features

1. Impairment of consciousness
2. Abrupt onset and termination
3. No aura or postictal period

Variable features

1. Duration
2. Automatisms
3. Changes in body tone
4. Autonomic dysfunction
5. Response to ethosuximide or valproate

juvenile myoclonic epilepsy (discussed below). Because they are brief and nonconvulsive, absence seizures are probably the most frequently missed seizure type. Even though absence seizures are not life-threatening, their recognition is important because if they are not detected, they may cause a decline in school performance or result in injury. Fortunately, absence seizures often respond quite readily to AEDs (Table 8.8).

Classification

The term *petit mal* has been replaced by *absence seizures*. *Petit mal* is still used, however, by a large number of health care professionals and the public. Absence seizures are divided into typical and atypical varieties, as discussed later. Some authors further classify absence seizures into simple absences (staring only) and complex absences (involving more prominent motor phenomena).

Clinical characteristics

Absence seizures usually begin during the early school years. The hallmark of a typical absence spell is the suppression of mental function, usually to the point of complete abolition of awareness, responsiveness, and memory. The seizures start abruptly, without aura, and generally last from 5 to 15 seconds (range 1–30 seconds). Ongoing activity is suddenly interrupted; the child's facial expression changes, and he or she becomes transfixed (like a statue). In a simple absence attack, the child stares with a motionless, distant appearance, but no repetitive motor activity occurs. At the end of the seizure, the child returns to the original gesture, conversation, or other activity that was interrupted by the seizure. Postictal fatigue never occurs, although the child may be momentarily confused owing to the time loss. This time loss serves as a clue to the child that a seizure occurred, even though there may be complete amnesia for events during the seizure.

At times, the suspension of mental function is less complete. This is particularly true for brief attacks (those lasting less than 5 seconds) and for certain longer attacks that may consist of mild confusion without complete loss of awareness. When this happens, the child may be able to continue simple and automatic behavior. Occasionally, the impairment of consciousness is so slight that it passes unnoticed by observers and may be detected only during EEG monitoring.

Although it is often assumed that simple absence seizures are common, they actually comprise a small fraction of absence seizures. Only about 10% of absence seizures involve staring without some accompanying motor activity of the face, eyes or mouth.

Automatisms occur frequently in absence seizures. Automatic behavior may consist of licking the lips, chewing, grimacing, scratching, or fumbling with clothes. Occasionally, however, much more complex activity may occur, such as dealing playing cards, moving pieces in a game, or playing patty-cake. There is almost always a slowing of activity, although this may not be discernible to the casual observer. Formed speech may occur during absence seizures.

The frequency of absence seizures varies considerably from day to day and even hour to hour. The majority of untreated children have over 10 absence seizures per day and may have several hundred in a day. Stress and fatigue increase the frequency of absence seizures.

The majority of children with typical absence seizures have a normal neurologic examination and intelligence, although school performance may be impaired if seizures are frequent. GTC seizures eventually occur in 10–20% of patients with typical absence seizures.

Electroencephalography

The ictal EEG pattern in an absence seizure consists of the sudden onset of generalized symmetric spike or multiple spike- and slow-wave complexes. In a typical absence seizure, these discharges usually occur at a frequency of 3 Hz

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Absence Seizures

- A helpful test in the office to determine whether a child's absence seizures are well controlled is to have the child hyperventilate for 3 minutes (e.g. by blowing on a pinwheel). Failure to induce an absence attack indicates that the child's seizures are under satisfactory control.
- Most children who stare are not having a seizure. Staring as the sole manifestation of absence seizures is unusual; most children with absence seizures have other clinical changes during the seizure, such as eye blinking, facial clonus, or head nods.

(range: 2.5–3.5 Hz), whereas in an atypical absence seizure (see below), the spike-wave frequency is less than 2.5 Hz.

Hyperventilation is a potent activator of absence seizures. Failure to induce an absence seizure with several trials of hyperventilation of 3- to 5-minutes duration in an untreated patient would make the diagnosis of absence seizures unlikely. Photic stimulation may also induce an absence seizure, although less reliably than hyperventilation.

Atypical absences

Atypical absence seizures involve an altered state of awareness or staring, with an onset and cessation that are not as abrupt as a typical absence seizure. Atypical absences, like typical absences, may be associated with automatisms, clonic components, autonomic components, and changes in tone. Atypical absence seizures are usually longer than typical absences, sometimes lasting several minutes.

Unlike the usual 3 Hz spike-and-wave discharges that occur in typical absence seizures, slower spike-and-wave discharges occurring at 1.5–2.5 Hz are more characteristic of atypical absence seizures. The interictal EEG is usually abnormal in children with atypical absences, the majority of whom have the Lennox–Gastaut syndrome (discussed below).

Differential diagnosis

Diagnosing absence seizures is usually straightforward. The differential diagnosis of staring attacks includes CPSs and daydreaming as well as absence seizures. Absence seizures can often be confirmed by having the child hyperventilate for 3–5 minutes. The routine EEG should include hyperventilation, photic stimulation, and sleep. Although a normal EEG does not rule out absence seizures, the likelihood that the child is having frequent absence seizures is slim. If clinical suspicion remains, the child may require repeated EEGs or prolonged EEG monitoring.

Etiology

Typical absence seizures have a genetic basis, although a single gene mutation has not yet been found. In childhood absence epilepsy, some families have been identified with GABA receptor loss of function mutations (Crunelli & Leresche 2002). EEG studies of families with absence epilepsy have shown increased incidences of spike-wave abnormalities among siblings, with an age-related expression. Therefore, the EEG abnormality is a marker for genetic susceptibility to absence epilepsy, although the seizures will not manifest in all family members with the EEG trait. It has been postulated that the EEG abnormality is the expression of an autosomal dominant gene with the unusual characteristic of having a very low penetrance at birth, then rising rapidly to nearly complete penetrance during early childhood and the teenage years before decreasing again. Atypical absence seizures are usually seen in neurologically impaired children and have a wide variety of genetic and acquired causes.

Evaluation

In a child with typical absence seizures, an ictal EEG with 3-Hz spike-and-wave activity, a normal interictal EEG, and a normal neurologic examination, no further diagnostic studies are necessary. In a patient with an abnormal developmental history, abnormal neurologic findings, or evidence of focality on the EEG, an MRI scan is recommended. Although a treatable lesion is unlikely, the MRI scan may give helpful information regarding etiology and prognosis.

Because absence seizures are brief and frequently subtle, their frequency can be grossly underestimated by parents. Each follow-up evaluation should include 3–5 minutes of hyperventilation. Activation of a seizure by hyperventilation indicates that the seizures are not under optimal control, regardless of the history supplied by the parents, teacher, or other observers.

Treatment

The aim of AED therapy in typical absence seizures is to treat with a medication that reduces seizure frequency without producing drug toxicity. Ethosuximide, VPA, and clonazepam are all effective in the treatment of absence seizures. A previously untreated patient starting on any one of these three drugs will have over 70% chance of having a significant reduction or total elimination of seizures. Ethosuximide is regarded by many neurologists as the drug of first choice for the treatment of typical absence seizures. Comparison studies of ethosuximide and VPA demonstrated that both drugs are equally effective, but because of the fear of adverse reactions to VPA, this drug has been generally reserved for children who do not respond to ethosuximide or who have adverse side effects from it. VPA should be considered the drug of choice in a patient who has both absence and GTC seizures. Because of the relatively high incidence of side effects, primarily drowsiness and behavioral changes, clonazepam is usually not used initially in absence seizures, with its use reserved for refractory cases.

Children who do not respond to either ethosuximide or VPA as a single agent may respond to a combination of the two drugs. This appears to be one of the rare situations in the treatment of epilepsy in which two drugs may work better than one. As with other drug combinations, the child should be watched closely for signs of toxicity.

There are no firm rules about when to withdraw medications. Although typical absence seizures have a favorable prognosis, the age at which remission occurs is variable. Although it is often stated that children outgrow their seizures at puberty, absence seizures may persist into adulthood. A general guideline is to withdraw AEDs slowly after the child has been seizure-free for 2 years and no longer has generalized spike-and-wave discharges on the EEG (including a 3- to 5-minute hyperventilation trial). Spike-and-wave discharges on the routine EEG are indicative of a high recurrence risk if the medication were to be withdrawn. In a child

who is free of side effects and seizures (at least by parental report) but continues to have 3-Hz generalized spike-wave discharges, one should consider optimizing AED treatment since such a child remains at high risk for absence seizures.

Myoclonic seizures

Myoclonus consists of sudden, brief ("lightning-like") movements that are not associated with any obvious disturbance of consciousness. These brief involuntary muscle contractions may affect one or several muscles. No common etiologic, anatomic, or physiologic features bind all types of myoclonus together. Myoclonus can be associated with lesions of the cortex, cerebellum, brainstem, or spinal cord.

Myoclonus can have numerous causes. Myoclonic movements may be totally normal phenomena such as hypnogogic jerks or sleep starts. Conversely, myoclonus can be associated with virtually any severe insult to the brain, including toxic, metabolic, infectious, traumatic, or degenerative insult. Likewise, the pathophysiology of myoclonus varies; some types of myoclonus are nonepileptic and classified as a movement disorder, whereas other types of myoclonus are epileptic phenomena (Table 8.18).

Differential diagnosis

Myoclonus must be differentiated from other movement disorders including tics, chorea, athetosis, and tremors. Differentiating tics from myoclonus may be difficult. In children, tics involve primarily the head, neck, and shoulders and consist of complex movements such as facial grimacing, eye blinking or rolling, head nodding or turning, and shrugging of the shoulders. Tics can often be suppressed voluntarily, at least temporarily, whereas myoclonus cannot. In chorea, the movements occur randomly, usually in multiple muscle groups, whereas myoclonus is usually characterized by repetitive, stereotyped movements affecting the same muscle groups. Although the muscle jerking in other types of myoclonus is less predictable, it does not have the characteristic continuous flow of movements that is so distinctive of chorea. When myoclonus occurs rhythmically it may be confused with tremors. Tremors can usually be diagnosed by the smooth to-and-fro movements, compared with myoclonus, which is more abrupt and has discrete intervals between each movement.

FEATURES

Table 8.18 Myoclonic Seizures

Discriminating features

1. May be confused with atonic seizures. EMG monitoring demonstrates increased muscle activity during a myoclonic seizure and decreased muscle activity during an atonic seizure

Consistent features

1. Very brief
2. Sudden onset without aura or postictal impairment

Variable features

1. Distribution of muscle groups involved
2. Frequency
3. Severity varies greatly; some myoclonic seizures are subtle and difficult to recognize, others may cause child to fall to the ground
4. Association with structural brain lesions
5. Response to VPA or clonazepam

PEARLS & PERILS

Myoclonic Seizures

- In children, epileptic myoclonus is most frequently seen as a component of absence epilepsy or juvenile myoclonic epilepsy.
- Not all myoclonus is epileptic in origin. Nonepileptic myoclonus can be seen in conditions varying from benign sleep states to devastating degenerative disorders.

Classification

Table 8.19 presents a classification of myoclonus that is based on both etiology and pathophysiology. Physiologically, myoclonus can be broadly divided into nonepileptic and epileptic types. The spectrum of nonepileptic myoclonus varies from normal physiologic events to severe disabling movements involving single or multiple muscle groups. Epileptic myoclonus may be either symptomatic or primary. In symptomatic cases, the myoclonus is secondary to a static insult or active disease process. In these cases, the myoclonus is usually only one of many neurologic symptoms. In primary epileptic myoclonus, the myoclonic seizures constitute the primary abnormality and the etiology is either familial or idiopathic. Although this classification system is helpful in organizing myoclonus, some overlap between categories can occur. For example, although infantile spasms and Lennox–Gastaut syndrome are categorized under primary epileptic myoclonus, in some children a specific etiology can be identified.

Etiology of myoclonus

Nonepileptic myoclonus. Physiologic or nonepileptic myoclonus can occur in normal children and adults. An example of physiologic myoclonus is sleep starts, also termed hypnagogic jerks. They are nonperiodic, occur at sleep onset or awakening, and simultaneously involve the muscles of the trunk and extremities. In some infants and toddlers, sleep myoclonus can be striking. These movements are not associated with EEG abnormalities. In addition, many normal children will have an occasional, isolated, myoclonic jerk

TABLE 8.19

Classification of Myoclonus

Nonepileptic myoclonus

- Physiologic myoclonus
  - Sleep starts (hypnic jerks)
  - Benign awake myoclonus
- Pathologic myoclonus
  - Hyperekplexia (startle disease)
  - Shuddering attacks
  - Periodic movements of sleep (sleep myoclonus)
  - Restless leg syndrome
  - Benign neonatal sleep myoclonus
  - Benign myoclonus of early infancy
- Benign familial myoclonus
- Segmental myoclonus
  - Brainstem
    - Opsoclonus
    - Palatal myoclonus
- Spinal cord

Symptomatic epileptic myoclonus

- Infections
  - Subacute sclerosing panencephalitis
  - Creutzfeldt-Jakob disease
  - Encephalitis
- Congenital brain anomalies
- Toxins
- Systemic diseases (uremia, hepatic insufficiency)
- Medications
- Postanoxic
- Component of inherited progressive neurologic disease
  - Progressive myoclonic epilepsy with Lafora bodies
  - Progressive myoclonic epilepsy without Lafora bodies
  - Ramsay Hunt syndrome
- Metabolic disorders
  - Neuronal ceroid lipofuscinosis
  - Gaucher's disease
  - Sialidosis (cherry red-spot myoclonus)
  - Gangliosidosis (GM1, GM2)
  - Mitochondrial disorders
    - Myoclonic epilepsy with ragged red fibers (MERRF)
    - Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)

Primary epileptic myoclonus

- Generalized epileptic myoclonus of early childhood
- Juvenile myoclonic epilepsy
- Focal cortical myoclonus
- As a component of other epilepsies
  - Absence with myoclonic component
  - Eyelid myoclonus with absences
  - Component of generalized tonic–clonic seizures
  - Myoclonic–astatic absence (Doose syndrome)
  - Lennox–Gastaut syndrome

during the awake state.

Epileptic myoclonus. Epileptic myoclonus may be secondary to a large number of entities. As a general rule, epileptic myoclonus is associated with severe CNS disorders. Epileptic myoclonus may occur in slow viral infections such as subacute sclerosing panencephalitis, following severe hypoxic-ischemic injuries, in severe metabolic abnormalities such as hepatic encephalopathy, as a component of a congenital brain anomaly such as porencephaly or hydranencephaly. Myoclonic seizures are also a feature of the progressive myoclonic epilepsies, a group of degenerative disorders that includes neuronal ceroid lipofuscinosis, Lafora body disease, Unverricht–Lundborg disease (also known as Baltic myoclonus), myoclonus epilepsy with ragged red fibers (MERRF, a mitochondrial disorder), and the sialidoses (Conry 2002; Lehesjoki 2003). Myoclonic seizures are often a component of epilepsy syndromes that include other seizure types as well. One important example is juvenile myoclonic epilepsy (discussed later).

Evaluation

Because of the diverse etiologies that can result in myoclonus, it is necessary to individualize the workup of each patient. The history provides important clues to the etiology, and should include a detailed description of the pregnancy, birth, and perinatal periods, motor and mental development, and exposure to drugs, chemicals, and infectious diseases. A detailed account of other family members with neurologic disease is necessary because many disorders with myoclonus are hereditary.

The physical examination is also helpful in establishing the diagnosis. For example, funduscopic abnormalities may be present in subacute sclerosing panencephalitis and some lysosomal enzyme disorders. The abdominal examination may be abnormal in children with the opsoclonus-myoclonus syndrome or with hepatic or renal disease. Neurologic abnormalities are likely in children with hypoxic-ischemic encephalopathy, segmental myoclonus, an infectious, metabolic disorder or progressive familial disorder, and following ingestion of a toxin.

Treatment

The drugs of choice in the treatment of the myoclonic epilepsies are the benzodiazepines and VPA. Approximately 75% of children with myoclonic seizures improve with VPA. Myoclonic seizures are usually resistant to phenytoin, barbiturates, and carbamazepine, although these drugs may be useful in treating other seizure types that may accompany the myoclonic seizures. The ketogenic diet is occasionally helpful in controlling myoclonic seizures. Adrenal steroids and adrenocorticotrophic hormone (ACTH) have been used in the treatment of myoclonic seizures that are refractory to other drugs.

Epilepsy syndromes in children

Some examples of childhood epilepsy syndromes are now discussed. These were selected based on their importance or frequency, and are categorized according to the ILAE scheme discussed above (Epilepsy 1989), although new classifications will eventually replace this one (Engel 2001). One common and important syndrome, febrile seizures, is discussed extensively in Chapter 23.

Generalized epilepsy syndromes

Idiopathic generalized epilepsy syndromes

Benign familial neonatal convulsions

Benign familial neonatal convulsions (BFNC) is a neonatal epilepsy syndrome in which seizures begin in the first week of life. The seizure type is focal clonic or focal tonic (although it is classified as a generalized epilepsy), often accompanied by apnea. The seizures are usually frequent for a few days, and then stop. The seizures are usually brief, lasting 1–2 minutes, but may occur as many as 20–30 times per day. In one study of EEG recordings from children with BFNC, all seizures occurred during sleep and were characterized by an initial generalized flattening of EEG waveforms, followed by bilateral discharges of spikes and sharp waves (Hirsch *et al.* 1993). The authors argued that the seizures were a form of GTC activity whose expression may be asymmetric. Other than seizures, the infants are normal, and evaluation fails to detect an etiology for the seizures. The key to the diagnosis is a positive family history of newborn or infantile seizures with benign outcome. However, even with a positive family history, other more ominous causes of seizures should be ruled out before concluding that the seizures are inherited.

Infants can be treated with phenobarbital until seizures remit. The prognosis of BFNC is good, although about 10–15% of affected infants continue to have seizures beyond the neonatal period, even into adulthood.

BFNC is a familial disorder that has been linked to at least two chromosomal loci (Table 8.5). The identified genes (KCNQ2 on chromosome 20q and KCNQ3 on chromosome 8q) code for voltage-gated potassium channel subunits that appear to regulate the "M-current," a muscarine-activated neuronal current that turns off potassium channels. The M-current ordinarily stabilizes resting membrane potentials, so its dysfunction will predispose to heightened neuronal excitability and seizures. It is not known why seizures affect neonates primarily, since the genetic defect is presumably present throughout life.

Generalized epilepsies with febrile seizures plus

Generalized epilepsies with febrile seizures plus (GEFS+) is a recently described disorder in which children have febrile seizures beyond the age at which febrile seizures usually stop (5 years) (Scheffer & Berkovic 1997). In addition, these children may develop additional seizure types, including generalized tonic–clonic, absence, myoclonic, and atonic, *without fever*. Therefore, this syndrome is not the same as simple febrile seizures, and represents a genetically increased predisposition to epilepsy. It is transmitted in an autosomal dominant fashion with high penetrance. In different pedigrees, genetic defects have been identified in neuronal sodium channels and GABA receptors. Dysfunction of those genes causes enhanced seizure predilection. There may be a spectrum of disorders, with different phenotypes, caused by sodium channel dysfunction. For example, the same sodium channel mutation has been identified in *severe myoclonic epilepsy of infancy* (Dravet's syndrome) (Singh *et al.* 2001). In GEFS+, the outcome is variable; some children's seizures resolve, whereas in others, the epilepsy persists.

Childhood absence epilepsy

The syndrome of childhood absence epilepsy (CAE) is characterized by typical absence seizures (described in detail above), a normal interictal EEG, an ictal EEG pattern of 3-Hz spike-wave discharges, and normal intelligence and neurologic examination. Some children have learning disabilities or psychosocial difficulties. The onset of seizures is between 4 and 10 years. CAE has a genetic basis (Table 8.5). Treatment with ethosuximide, VPA, or lamotrigine is effective. The prognosis is good, with most children outgrowing the absence seizures during adolescence. However, at least 15% of children with CAE have persistent seizures or evolve into JME (Camfield & Camfield 2002).

Juvenile myoclonic epilepsy

Myoclonic seizures in children may occur as a component of an epileptic syndrome known as juvenile myoclonic epilepsy of Janz (juvenile myoclonic epilepsy, JME) (Table 8.20). This age-dependent epilepsy syndrome typically begins in adolescence. The myoclonic seizures in JME are usually mild to moderate in intensity and involve the neck, shoulders, and

FEATURES

Table 8.20 Juvenile Myoclonic Epilepsy

Discriminating features

1. Bursts of generalized fast spike-wave discharges (4–6 Hz) on EEG

Consistent features

1. Myoclonic jerks, especially in the morning
2. Onset in adolescence
3. Normal examination and intelligence
4. Response to valproic acid

Variable features

1. Photic sensitivity
2. Generalized tonic–clonic seizures

arms. They can occur either singly or repetitively and may cause the patient to drop objects. Only rarely are they severe enough to cause a fall. The patient or parent may attribute the myoclonus to nervousness or clumsiness. Although the myoclonic seizures most often occur within an hour or two of awakening from sleep, in some patients they may continue all day. The myoclonic seizures may increase again at the end of the day when tiredness ensues, and the seizures are aggravated by sleep deprivation and alcohol use.

GTC or clonic–tonic–clonic seizures also occur in the vast majority (up to 90%) of patients with JME, and in fact, the syndrome often presents with GTC seizures. Like the myoclonic seizures, GTC seizures often occur shortly after awakening or during early morning sleep. At times, a series of myoclonic seizures culminates in a GTC seizure.

A substantial number (up to 35%) of patients with JME also have absence seizures. As with the other seizure types, absences often occur upon awakening. Myoclonic status is a state in which myoclonic jerks occur every few seconds or in salvos of 3–5 jerks. Although consciousness is preserved, the child may be incapacitated by the continuous myoclonic jerks.

The general physical and neurologic examinations are usually normal in JME, and normal intelligence is the rule. Studies have linked the gene to chromosome 6p, a locus that appears to be dominantly inherited. A responsible gene has not yet been identified.

The interictal EEG in JME is distinctive, consisting of bursts of fast (3.5- to 6-Hz) spike-and-wave or multiple spike-and-wave complexes. This pattern contrasts with the 3-Hz spike-and-wave complexes seen in childhood absence epilepsy and the slow (1.5- to 2.5-Hz) spike-and-wave complexes of Lennox–Gastaut syndrome. Photic stimulation may activate the epileptiform discharges in JME. If the diagnosis is suspected and the awake EEG is normal, it is imperative that an EEG be obtained during sleep deprivation.

VPA therapy is the treatment of choice for JME, though other broad-spectrum AEDs (e.g. lamotrigine, topiramate, methsuximide) may also be effective. Although the seizures in JME may be easily controlled with VPA, the disorder requires long-term treatment. Attempts to withdraw the drug are usually not successful. Only rarely do the seizures remit spontaneously, and 90% of patients relapse after withdrawal of medication. This has significant implications for women who likely will be on medication during their childbearing years. The disorder is considered benign because most children continue to have normal neurologic examinations and intelligence despite dependence on medication for seizure control.

Cryptogenic or symptomatic generalized epilepsy syndromes

Infantile spasms

Infantile spasms are a unique form of epilepsy confined to early childhood. The characteristic features of this syndrome are epileptic spasms, hypsarhythmic EEGs, and mental retardation. This triad is referred to as West syndrome (Fukuyama 2001). The syndrome is also referred to in the literature as massive spasms, salaam seizures, flexion spasms, jackknife seizures, massive myoclonic jerks, and infantile myoclonic seizures.

Infantile spasms are an age-specific disorder occurring only in children during the first 18 months to 2 years of life, with approximately 90% beginning before 12 months of age. The peak age of onset is between 4 and 6 months (Table 8.21). Spasms may persist beyond the 2 years, representing a very refractory population (Sotero & Rho 2002).

Clinical manifestations

Infantile spasms vary considerably in their clinical manifestations. Some seizures are characterized by brief head nods, whereas others consist of violent flexion of the trunk, arms, and legs. The duration of a spasm is intermediate between myoclonic jerks (which are quicker) and tonic seizures (which are more sustained). The diagnosis of infantile spasms is often delayed because the parents and even the child's physician may not recognize the spasms as seizures.

The seizures in infantile spasms are of three types: flexor, extensor, and mixed flexor-extensor types. Flexor spasms consist of brief contractions of flexor musculature of the neck, trunk, arms, and legs. Spasms of the muscles of the upper limbs result either in adduction of the arms in a self-hugging motion or in abduction of the arms to either side of the head, with the arms flexed at the elbow. Extensor spasms consist predominantly of extensor muscle contractions, producing abrupt extension of the neck and trunk with extensor abduction or adduction of the arms, legs, or both. Mixed

FEATURES

Table 8.21 Infantile Spasms

Discriminating features

1. The clustering of infantile spasms differentiates them from tonic or myoclonic seizures
2. Interictal EEG pattern usually demonstrates hypsarhythmia or modified hypsarhythmia

Consistent features

1. Begin in the first year of life
2. Each spasm is brief (less than 5 seconds)
3. Response to treatment with adrenocorticotrophic hormone or vigabatrin

Variable features

1. Clinical spasms may be flexor, extensor, or, most commonly, mixed flexor and extensor
2. Response to valproate, clonazepam, or topiramate
3. Developmental stagnation or regression (more likely if symptomatic)

flexor-extensor spasms are the most common type and include flexion of the neck, trunk, and arms and extension of the legs or flexion of the legs and extension of the arms. Asymmetric spasms may also occur and resemble a "fencing" posture. Eye deviation or nystagmus frequently occur.

Infantile spasms characteristically occur in clusters; each spasm within a cluster is considered a single seizure. The intensity and frequency of individual spasms within a cluster may increase to a peak before progressively decreasing. The seizures are very brief, and a single spasm may be missed by the casual observer. The number of seizures per cluster varies considerably, with some clusters having as many as 150 seizures. The number of clusters per day also varies, with some children having as many as 60 clusters per day. Clusters typically occur on awakening from sleep. Crying or irritability during or after a flurry of spasms is commonly observed.

Differential diagnosis

Infantile spasms are often misdiagnosed as colic or other nonepileptic phenomena. Occasionally, the clinical course is atypical, and the spasms do not occur in clusters or involve only slight movements or episodes of akinesia. In these infants, the EEG is helpful because it is invariably abnormal.

Several disorders may be confused with infantile spasms. *Benign myoclonus of early infancy* is a disorder in which infants have clusters of tonic or myoclonic movements. The movements consist of rapid flexion or extension of axial or limb musculature. Unlike infants with infantile spasms, these infants are normal neurologically and developmentally and have normal EEGs. In all cases the movements stop by age 18 months. *Benign neonatal sleep myoclonus* consists of myoclonic jerks that typically occur in a bilaterally symmetric manner only when the child is asleep. The jerks are quicker than in infantile spasms. The myoclonus occurs during non-REM sleep and ceases if the child awakens. The neurologic examination and EEG are normal, and treatment is unnecessary.

Electroencephalography

The EEG in children with infantile spasms is markedly abnormal. The most common interictal pattern is hypsarhythmia, consisting of very high voltage, random slow waves and spikes in multiple cortical areas. The spikes vary from moment to moment in duration and location. The resulting chaotic appearance of the EEG gives the impression of a near-total disorganization of cortical voltage regulation. A sleep tracing may be necessary to detect hypsarhythmia. Variations of this pattern (modified hypsarhythmia) include hypsarhythmia that is more prominent over one hemisphere or a focus of spike activity superimposed on the hypsarhythmia. Some children with infantile spasms do not have a hypsarhythmic EEG pattern at the onset of the seizures but develop it later. Although hypsarhythmia is primarily associated with infantile spasms, it may also occur in other disorders such as Angelman syndrome, Down syndrome, and postanoxic encephalopathy.

There are several ictal EEG patterns in infantile spasms, the most common being a generalized slow wave followed immediately by generalized attenuation of background electrical activity in all EEG channels, which is replaced by low-voltage fast rhythms. This so-called electrodecremental response is usually accompanied by a clinical spasm.

Etiology

On the basis of history, physical examination, and laboratory studies, cases of infantile spasms have been conventionally classified into those in which there is no identified preceding neurologic disorder or etiology (cryptogenic) and those in which a pre-existing pathologic event or disorder is demonstrated (symptomatic). With modern neuroimaging and other diagnostic advances, the proportion of cryptogenic cases is shrinking; about 10–15% of cases are currently considered cryptogenic.

Several disorders have been associated with infantile spasms. Common etiologies include hypoxic-ischemic encephalopathy, neonatal intracranial hemorrhage, congenital infection, meningitis, encephalitis, congenital abnormalities of the CNS, and metabolic diseases. Tuberous sclerosis is associated with an especially high incidence of infantile spasms. Up to half of patients with tuberous sclerosis develop infantile spasms. It is intriguing that infantile spasms often begin many months after a neurologic insult, which might relate to the pathophysiological mechanism (Schwartzkroin & Rho 2002).

Infantile spasms have been reported following immunization with several vaccines including smallpox, influenza, Japanese encephalitis, and pertussis. The diphtheria-pertussis-tetanus vaccine has been the vaccine most frequently implicated. Of the three components, pertussis has raised the most concern. However, most of the reports of the association of vaccines with infantile spasms have been anecdotal and no causal relationship has been proven. Vaccines are given at the time of peak incidence of infantile spasms, and therefore a temporal coincidence would be expected in a large number of cases. In addition it is often difficult to determine the exact time of onset of the spasms. When

PEARLS & PERILS

Infantile Spasms

- Drugs that work in infantile spasms usually do so within days or weeks of starting therapy.
- If the spasms have a focal onset, a surgical evaluation should be considered.

documented cases are reviewed carefully, the link between vaccination and infantile spasms is weak.

It is not known why some children develop infantile spasms. The fact that some infants have infantile spasms while other infants with similar brain disturbances do not develop them suggests that genetic factors may be important.

Evaluation

The infant who presents with infantile spasms requires a thorough evaluation, which includes a developmental assessment, neurologic examination, and laboratory studies to determine an etiology. In addition, the neurologic and developmental examinations at the time of diagnosis are important indicators of prognosis.

Tuberous sclerosis is difficult to diagnose during the first year of life because the characteristic skin lesion, adenoma sebaceum (facial angiofibromas), rarely occurs before the age of 3 years. However, infants may have hypopigmented macules only detectable by Wood's lamp examination in a darkened room. A CT scan may demonstrate intracranial calcifications. Abdominal ultrasound may reveal characteristic renal cysts (angiomyolipomas), and an echocardiogram will show cardiac tumors in 30–40% of cases. The MRI may show uncalcified cortical tubers or other cortical dysplasia not visualized by CT scan.

Laboratory studies will be guided largely by the history and physical examination. Every child with the possible diagnosis should have an EEG and neuroimaging. A normal EEG (including sleep) would raise questions about the diagnosis and might suggest that the child has benign myoclonus of early infancy. A CT or MRI scan is recommended in every child with infantile spasms because it may provide valuable information regarding the etiology. Abnormal neuroimaging results are seen in 70–80% of children with infantile spasms. The most common abnormality seen in large series has been diffuse cerebral atrophy. In addition, brain anomalies such as agenesis of the corpus callosum, porencephaly, and hydranencephaly can be detected on the CT or MRI scan. Cranial calcifications may indicate tuberous sclerosis or a congenital infection.

Because pyridoxine dependency has been associated with infantile spasms, in children in whom an etiology cannot be definitely established, an infusion of 50–100 mg pyridoxine intravenously during EEG monitoring may be useful. Infants with pyridoxine dependency should have an improvement in the seizures and EEG within minutes. Infants with frequent vomiting, lethargy, failure to thrive, peculiar odors, and unexplained neurologic findings should have urine amino and organic acid screening, serum ammonia and liver function tests. Because most children will be placed on ACTH, electrolytes, calcium, phosphorous, glucose, and urine analysis should be obtained. Examination of the spinal fluid is indicated if there is concern about an active infection or a metabolic disorder (in which case CSF glycine should be assessed).

Treatment

ACTH and corticosteroids are the primary drugs used in the treatment of infantile spasms, and the new drug vigabatrin appears to be promising, especially for children with tuberous sclerosis. The anticonvulsant mechanism of ACTH in infantile spasms is not known. Theories include an effect on the hypothalamic-pituitary axis or a direct action on neuronal excitability (Brunson *et al.* 2001).

The effects of ACTH and other therapies on long-term outcome remain controversial. For example, several authors have found no developmental differences between patients who did or did not receive treatment. For the large number of infants who exhibit pre-existing brain damage, it is unlikely that any form of therapy will greatly influence the long-range outcome in terms of mental and motor development. An important question is whether treatment of cryptogenic infantile spasms in children who were normal before the onset of seizures alters outcome. Long-term studies on infants with cryptogenic infantile spasms who received either ACTH, oral steroids, or other AEDs, show that those who received ACTH had a lower incidence of seizures and better psychomotor development than infants treated with the other agents (Lombroso 1983).

The optimal ACTH dosage and treatment duration remain controversial (Mackay *et al.* 2002; Hancock *et al.* 2003). In view of this lack of consensus, the following approach is necessarily empirical. A reasonable starting dose of ACTH is 40 international units (IU) per day given intramuscularly. A nonsynthetic form of ACTH gel should be used. The ACTH is given for a minimum of 1 month following the cessation of seizures. At that time a taper can begin, decreasing by 10 units a week. If the seizures do not completely resolve by 2 weeks, the dosage should be increased by 10 IU increments every week until the seizures cease or a daily dose of 80 IU is reached. If at that point the seizures still persist, a trial of VPA, topiramate, or a benzodiazepine can be undertaken. If relapse occurs during the taper or after discontinuation of ACTH, the ACTH can be restarted at the dosage that originally stopped the spasms; of course, one must always be vigilant for adverse ACTH side effects, especially at higher doses. Following control of the seizures, ACTH should be continued for 1 month before tapering is attempted again. The response to ACTH is often dramatic, with cessation of seizures and marked improvement of the EEG within a few days.

Although ACTH and corticosteroids can be very effective in stopping spasms, they can result in many side effects. Steroid therapy is invariably associated with cushingoid obesity. In addition, growth retardation, acne, and irritability may ensue. With short-term use of steroids, these side effects are less concerning. More serious side effects include infec-

tion, hypertension, cardiomyopathy, intracerebral hemorrhage, osteoporosis, gastrointestinal bleeding, hypokalemic alkalosis, and other electrolyte disturbances.

Children treated with ACTH or adrenal corticosteroids should be monitored closely. Blood pressure and stool guaiac should be checked twice weekly; and electrolyte levels should be checked weekly. If the child develops hypertension or hypokalemic alkalosis, a reduction in dosage is recommended. However, patients who have a relapse once the dosage is decreased may be restarted at the effective dose and managed with salt restriction or antihypertensives. If this is not effective, it is prudent to change to a synthetic glucocorticoid such as methylprednisolone, which has less of a sodium-retaining effect. Fever should be investigated promptly, as infections are more likely in the setting of steroid-induced immunosuppression.

Because of the high incidence of adverse effects with steroids, it is hoped that other AEDs will replace this mode of therapy. Vigabatrin, a structural analog of GABA, is a selective inhibitor of GABA-transferase, which has been shown to have a favorable effect in the treatment of infantile spasms, especially in children with tuberous sclerosis (Elterman *et al.* 2001). Vigabatrin is not yet approved for use in the United States. There have been some reports of vigabatrin-induced visual field defects. Other therapies that might be beneficial in the treatment of infantile spasms are topiramate and the ketogenic diet.

Some infantile spasms have a focal or partial onset and, if this focal onset can be consistently demonstrated, the infant may benefit from surgery. A structural lesion such as a hamartoma or an area of focal dysgenesis may correlate with the focal EEG and clinical features. Some infants with cryptogenic infantile spasms and normal MRI scans have deficits of cerebral metabolism (detected by positron emission tomography). When this area of cortical hypometabolism is removed under the guidance of intraoperative corticography, the seizures may be reduced or eliminated (Shields 2002).

Prognosis

Infantile spasms are one of the most devastating epilepsies that affect infants. The poor prognosis has been confirmed in several studies. A significant number of children have psychomotor retardation and persistent seizures. With age, the seizure type usually changes from spasms to mixed seizures of the types seen in the Lennox–Gastaut syndrome (see below). More than two-thirds of affected children are mentally retarded. In addition, a significant number of patients have neurologic impairments such as cerebral palsy. Because a large number of children have neurologic impairment before the onset of the spasms, it is not surprising that the prognosis is so poor. Prognosis is directly related to etiology, with cryptogenic cases having a significantly better prognosis than symptomatic ones (Riikonen 2001).

Lennox–Gastaut syndrome

The Lennox–Gastaut syndrome (LGS) presents one of the most difficult challenges to the physician dealing with children with seizures. These children usually have very frequent, medically intractable seizures and are often profoundly retarded (Table 8.22). LGS is classified as a generalized epilepsy syndrome, and can be operationally defined as having the following characteristics: (1) a slow spike-and-wave EEG pattern (less than 3 Hz) during a portion of the awake EEG, (2) mental retardation, and (3) intractable seizures of various types.

Clinical characteristics

The onset of seizures in LGS is usually between the ages of 1 and 6 years. It is unusual for the syndrome to begin after the age of 10 years. However, as the child matures, the clinical seizure characteristics may change. The child with LGS has a mixture of seizure types. The most frequently occurring are tonic, GTC, atypical absence, and head drops, which represent a form of atonic, tonic, or myoclonic seizures.

Tonic seizures consist of periods of sustained muscle contractions accompanied by altered consciousness. Brief tonic seizures are especially frequent during sleep. The duration of impaired consciousness during tonic seizures averages 10 seconds and ranges from a few seconds to a minute. Postictal impairment, if present, is usually brief.

Atonic (astatic) seizures, or drop attacks, begin suddenly, without warning, and if standing, the child will quickly fall to the floor. Because there may be total loss of tone, the child has no means to protect himself or herself, and head or facial injuries often occur. The fall usually happens so quickly that even close observers may not be able to prevent the child from injury. If the patient is seated, a fall forward can cause injury to the face. Consequently, these children often need

Table 8.22 Lennox–Gastaut Syndrome

FEATURES	
Discriminating features	
1. Tonic seizures during sleep	
Consistent features	
1. Severe, mixed seizures	
2. Mental retardation	
3. Slow spike-wave discharges on EEG	
Variable features	
1. Types of seizures (usually tonic, myoclonic, atypical absence, generalized tonic–clonic)	
2. Frequency of seizures	
3. Symptomatic or idiopathic etiology	

Lennox–Gastaut Syndrome

PEARLS & PERILS

- Complete seizure control in children with Lennox–Gastaut syndrome is unlikely. Avoid the temptation to place the patient on multiple AEDs. Usually one or two drugs work better than three or four.
- Daily seizure frequency varies considerably in patients with Lennox–Gastaut syndrome. Avoid changing AEDs too quickly.

to wear protective head and face gear. Although consciousness is momentarily impaired during the fall, the child often regains alertness promptly. Atonic attacks are frequently associated with myoclonic jerks either before, during, or after the atonic seizure. The loss of tone may affect the head only; such head drops can occur singly or in a series of head nods. Like total body atonic seizures, the period of impaired consciousness is extremely brief, and postictal impairment is rare.

Myoclonic jerks are sudden, brief (under 1 second) shocklike contractions that may be generalized or confined to that face and trunk or one or more extremities. When the entire body is involved, the sudden jerks may throw the child to the floor and significant injury can occur. When confined to the upper trunk, the movements are often characterized by a head drop with associated arm extension. The attack can last from less than 1 second to several seconds. There is no postictal impairment. At times it may be difficult to differentiate myoclonic seizures from atonic seizures. In these cases simultaneous EEG and electromyographic (EMG) monitoring is necessary. Decreased muscle activity occurs with atonic seizures while increased EMG activity is seen with myoclonic seizures.

Atypical absences occur in approximately half of children with LGS. As noted in the section on absence seizures, in atypical absences the seizure onset and cessation can be gradual. Atypical absences frequently involve clonic components, automatisms, autonomic changes, and alterations in muscle tone. Myoclonic jerks may also occur in association with absence seizures. Atypical absences may be prolonged, during which the child has a dull appearance, with confusion, drooling, and behavioral arrest. Unlike a typical absence seizure, the child may be able to follow some commands and speak, although speech is slurred. It is often difficult to tell when one seizure ends and the next one begins, because alertness and activity level may not improve between the absences. GTC seizures occur in 60–70% of children with LGS, usually occurring at night or during sleep transitions.

Children with LGS typically have very frequent seizures. Depending on the seizure type, seizures can occur hundreds of times a day. Seizure frequency varies from day to day or even during the course of a day, and appears highest during drowsiness and inactivity. In many children there is a weekly or monthly periodicity in seizure frequency that is unrelated to AED therapy. Periods of prolonged repetitive seizures of a mixed type are interspersed with periods of relative freedom from attacks. During seizure-free periods, marked improvement in alertness and motivation can be seen. Unfortunately, these periods are usually short-lived, leading to a considerable frustration for the child, parents, school personnel, and medical professionals.

All series of patients with LGS report a high incidence of cognitive impairment. Neurologic abnormalities have been reported in 40–90% of children with LGS. More than 60% of affected children have motor abnormalities such as quadriparesis or hemiparesis.

Electroencephalography

The characteristic EEG finding in LGS is generalized slow spike-and-wave discharges, which occur at a frequency of 1.5–2.5 Hz. Typically these discharges occur in long runs during the awake state and are even more frequent in sleep.

Etiology

LGS may arise in a previously well child, but it usually occurs in a child who is already neurologically or mentally handicapped. The etiology of LGS has, therefore, been divided into primary and secondary cases. In primary cases, the etiology is idiopathic (one-third of cases), whereas in secondary cases, the disorder is symptomatic of a definable etiology, such as hypoxic brain damage, a cerebral malformation, or a neurocutaneous disorder. The etiologies of LGS overlap those of infantile spasms. The majority of children with LGS with a determined etiology have a static disorder. Rarely, patients with degenerative disorders such as neuronal ceroid lipofuscinosis present with LGS.

Evaluation

In some children, an etiology will be clear from the medical history. In the absence of an obvious medical condition, the child needs to be thoroughly evaluated. Diagnostic studies will depend on the history and physical examination. In view of the devastating nature of the syndrome, every effort should be made to rule out a treatable disorder.

Abnormalities on neuroimaging are common in LGS. The most frequent abnormality is cortical or subcortical atrophy. Newer imaging modalities such as SPECT and PET may detect focal areas of dysgenesis.

Treatment

Treatment of the child with Lennox–Gastaut syndrome is often challenging, as many affected children are notoriously refractory to AEDs (Hancock & Cross 2003). Because the syndrome is heterogeneous, there is some variability in how the children will respond to an antiepileptic regimen. Drug therapy should be individualized to address the types and frequency of seizures in each child. Children with LGS ben-

efit variably from VPA, clonazepam, lamotrigine, or topiramate, or some combination thereof. Felbamate is reserved for particularly refractory cases.

Because of the intractable nature of the seizures, there is a tendency to place the children on numerous AEDs. This polypharmaceutical approach usually results in children who are drug toxic with somnolence, fatigue, nausea, ataxia, and rarely good seizure control. Combination drug therapy frequently results in additive toxicity without any improvement in seizure control.

Prognosis

The poor prognosis in LGS has been noted by numerous authors (Wheless & Constantinou 1997; Dulac 2001). With advancing age, the atonic, myoclonic, and atypical absence seizures usually decrease in frequency, but GTC seizures increase and partial seizures often emerge. In addition to debilitating seizures, children are often hindered in leading independent lives because of intellectual impairment. Some children have a progressive deterioration in mental function despite vigorous attempts to control their seizures.

Localization-related epilepsy syndromes

Idiopathic localization-related epilepsy syndromes

Benign childhood epilepsy with centrotemporal spikes (rolandic epilepsy)

Benign childhood epilepsy with centrotemporal spikes (BCECTS or benign rolandic epilepsy [BRE]), is a common, distinct epilepsy syndrome of childhood. BRE is characterized by seizures arising from the lower rolandic area of cortex. The EEG pattern is characteristic, consisting of midtemporal-central spikes. It is important for the clinician to be aware of this syndrome because its evaluation and prognosis differ considerably from those of other focal epilepsies.

Clinical characteristics

BRE is limited to children. Seizures begin between the ages of 2 and 12 years; the typical age of onset is between 5 and 10 years. Seizures of BRE usually remit spontaneously in early adolescence. The neurologic examination is normal, though studies have raised concerns about possible cognitive difficulties in these children (Deonna *et al*. 2000). The classic presentation is a nocturnal seizure with clonic movements of the mouth and face, salivation, garbled speech, and gurgling noises from the throat. Secondary generalization of the seizure occurs frequently. The initial focal motor component may be brief, and this portion of the seizure may be missed by parents, who are typically awakened by the child's guttural noises. Motor phenomena during daytime attacks are usually restricted to one side of the body, typically the face but sometimes the arm or leg as well. Speech arrest may occur and the child may describe stiffness or spasms of the tongue or a choking sensation. Consciousness is rarely impaired during daytime attacks, and postictal confusion or amnesia is rare. Generalized tonic–clonic seizures are unusual during the day. These seizures are distinguished from partial complex seizures because they lack automatisms, auras, illusions, hallucinations, and affective symptoms (Table 8.23).

Electroencephalography

A very distinctive EEG pattern characterizes BRE. The classic interictal EEG shows a normal background with superimposed high-amplitude spikes, followed by a prominent slow wave. These spike-wave complexes appear singly or in groups over the midtemporal and central (rolandic) regions. As with other spikes, rolandic spikes are not diagnostic of epilepsy, and may occur in children without a history of seizures.

Genetics

BRE has a strong familial occurrence. The EEG trait, but not the clinical syndrome, is inherited in an autosomal dominant fashion with incomplete penetrance and age-dependency (Neubauer 2002). Fifty per cent of close relatives (siblings, children, and parents of probands) demonstrate the EEG abnormality between the ages of 5 and 15 years. Before 5 and after 15 years of age, there is low penetrance, with few patients exhibiting the EEG abnormality. Only about 12% of patients that inherit the EEG abnormality develop seizures.

Evaluation

If the child has a clinical history and EEG characteristic of BRE, plus a normal neurologic examination, further workup

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Table 8.23 Benign Rolandic Epilepsy

Discriminating features

1. Partial seizures with or without secondary generalization
2. Unilateral or bilateral independent central-temporal spikes

Consistent features

1. Begins before 13 years of age; not seen after second decade
2. Nocturnal generalized tonic–clonic seizures or diurnal seizures, or both, with clinical signs referable to the lower rolandic region (speech arrest, facial clonus, and sometimes tonic–clonic activity of ipsilateral upper extremity)
3. Normal neurologic examination
4. Benign prognosis

Variable features

1. Response to carbamazepine and most other AEDs
2. Seizures may occur day, night, or both
3. EEG abnormality may be seen during wakefulness, sleep, or both

Benign Rolandic Epilepsy

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- Children with BRE and a normal neurologic examination do not require neuroimaging. However, if seizures do not respond to AEDs, focal slowing develops on EEG, or the neurologic examination changes, an MRI scan should be obtained.
- BRE has a strong genetic basis.
- Many children with BRE have only one or two clinical seizures, and AED treatment may not be necessary in every case.

is not necessary. If the neurologic examination is abnormal or the EEG demonstrates changes other than the typical epileptiform discharge, further evaluation with a brain MRI is indicated.

Treatment and prognosis

Because the seizures are benign and usually infrequent, many physicians choose not to treat the first or even the second seizure. When treated, the seizures are usually controlled with a single AED. The AEDs used for simple and complex partial seizures, i.e. carbamazepine (usually the first choice), phenytoin, or valproate, are usually effective. The efficacy of the newer AEDs in BRE is not known. In Europe, sulthiame has proven effective in clinical trials.

It is recommended that the child be treated for 1–2 years before the AED is withdrawn. Although a normal EEG at the time of tapering is reassuring, there is variable correlation between seizure recurrence and EEG abnormalities. The prognosis is generally excellent, with children outgrowing both seizures and the characteristic EEG abnormalities around the time of adolescence. However, some caution is advised, especially if atypical clinical or electrographic features are present (Ong & Wyllie 2000; Camfield & Camfield 2002).

Benign childhood epilepsy with occipital paroxysms

Benign childhood epilepsy with occipital paroxysms (BEOP) resembles BRE in that focal seizures occur in neurologically normal children, who tend to outgrow their epilepsy before adulthood. The syndromes differ in the localization of the epileptiform discharges and the phenomenology of the seizures. In BEOP, seizures are quite variable but often consist of elementary visual phenomena such as hallucinations, illusions, blindness, or phosphenes, though any seizure type may occur. Interictal occipital rhythmic spikes are maximal upon eye closure. Peak onset is from 5 to 9 years. A genetic etiology is not proven, but is assumed based on the idiopathic nature of the disorder.

Panayiotopoulos syndrome is a subtype of BEOP (Panayiotopoulos 2002). It is seen in a slightly younger age range (3–7 years). Nocturnal seizures predominate, accompanied by eye deviation and vomiting, but description of visual phenomena may be minimal. This syndrome also remits by adolescence. Both BEOP and Panayiotopoulos syndrome are commonly associated with migraine, and each of these disorders may share some pathogenetic mechanism (Andermann & Zifkin 1998).

Symptomatic localization-related epilepsy syndromes

Symptomatic localization-related epilepsy syndromes are those that arise in a particular region of brain, due to an acquired or congenital lesion. Etiologies include tumors, scars (e.g. hippocampal sclerosis), cortical dysplasias, porencephalic cysts (resulting from perinatal infarction), and vascular malformations. The seizure semiology is related to the region of brain affected; usually, these will entail simple partial or complex partial seizures that may secondarily generalize. EEG features are focal spikes, sharp waves, or slow waves, again related to the area of brain involved.

These syndromes are sometimes divided into those originating in the neocortex or mesial temporal structures (Benbadis 2001). In children, a neocortical localization is more common, while in adults, the mesial temporal lobe is a frequent epileptogenic site. Neocortical etiologies in children may include low-grade neoplasms and the wide spectrum of migrational and developmental dysplasias. Symptoms and EEG findings are related to the area of brain affected. Seizure features of the various lobes of origin were discussed above. On EEG, the epileptogenic zone is often hard to localize since discharges are spread widely over the neocortical surface.

Some important childhood localization-related epilepsy syndromes involve an entire hemisphere. *Rasmussen's encephalitis* is a focal encephalitis that affects only one hemisphere, and results in progressive hemiparesis, intractable epilepsy (partial seizures that may progress to epilepsia partialis continua), and cognitive decline. The etiology of Rasmussen's encephalitis is unknown but it might have an autoimmune basis, with antibodies to certain glutamate receptor subunits (McNamara *et al.* 1999). The unilateral pathology is hypothesized to be due to focal breakdown of the blood-brain barrier. Neuroimaging shows progressive unilateral cortical atrophy. Another hemispheric syndrome, *Sturge-Weber syndrome* (encephalotrigeminal angiomatosis), consists of hemispheric vascular malformation, leading to intractable epilepsy and hemiparesis. The degree of cerebral involvement is reflected by the degree of facial angiomatosis. Some authorities feel that early surgery (hemispherectomy) affords a better prognosis in any of the hemispheric localization-related epilepsy syndromes (Cross 2002).

Indeterminate epilepsy syndromes

Landau–Kleffner syndrome

Landau–Kleffner syndrome (LKS; acquired epileptic aphasia) is a rare disorder in which a child loses previously acquired language abilities and has seizures or epileptiform

abnormalities on EEG. In its pure form, LKS occurs in previously normal children with normal language development, who gradually lose the abilities to understand spoken language and produce speech (Landau & Kleffner 1957). Recently, some authors have expanded the syndrome to include a variety of behavioral and cognitive deterioration, including symptoms seen in autistic spectrum disorders (Ballaban-Gil & Tuchman 2000). Regression of social and language skills is frequently seen in children with autism, with or without accompanying seizures, so the differentiation of autism and LKS can be difficult. In LKS, compared to autism, social skills are better preserved. The pathophysiology of LKS is unknown. Imaging studies are generally negative although recent PET scans have shown bitemporal abnormalities, supporting the hypothesis that language-related brain regions are dysfunctional in LKS (Table 8.24).

EEG abnormalities are present in all children with LKS, and are quite variable; they may include generalized, focal, or multifocal spikes, spike waves or sharp waves. If focal, the discharges commonly involve unilateral or bilateral temporal or temporo-parietal (perisylvian) regions. The hypothesis arose that the epileptiform discharges interfere with language production, although it is possible that both the language dysfunction and EEG abnormalities are independent consequences of the same underlying brain pathology. Successful treatment of the seizures or even the EEG discharges is not usually accompanied by language or behavioral improvement. The outcome is quite variable; some children recover completely, usually in adolescence, while others have persistent aphasia in adulthood.

Evaluation should include hearing testing, an extended (overnight) EEG and an MRI scan. The seizures usually respond readily to AEDs (VPA, benzodiazepines), while the language disorder does not. Attempts to treat children with steroids or even subpial resection have been controversial (Camfield & Camfield 2002).

FEATURES

Table 8.24 Landau–Kleffner Syndrome

Discriminating feature

1. Loss of language following a period of normal language development

Consistent feature

1. Loss of receptive language ("word deafness") precedes loss of expressive language

Variable features

1. Autistic behaviors; compared to autism, social skills are better preserved in LKS
2. EEG findings
3. Response to AEDs
4. Age of language loss (usually age 5–7 years)

Electrical status epilepticus of sleep (ESES; continuous spike-wave discharges during slow-wave sleep)

ESES is an electrographic diagnosis (Tassinari *et al.* 2000). Children have normal language development prior to the onset of seizures, which are usually partial complex in type, followed by language and cognitive or behavioral deterioration. The cognitive changes may range from inattention to psychosis.

The EEG shows a fairly normal background during wakefulness and rapid eye movement (REM) sleep, but more than 85% of the slow-wave sleep (nonREM) record consists of generalized spike-wave discharges (although focal spikes or fragmentary generalized spike wave can be seen during wakefulness). These discharges are often slow (1.5–2 Hz) and have a frontocentral predominance. The cognitive and behavioral deterioration is often less dramatic than in children with LKS, and ESES remits during adolescence. Similar treatment options are used in ESES and LKS. Carbamazepine may worsen the syndrome. The outcome of ESES is quite variable; some children eventually regain normal language function.

Neonatal seizures

Neonatal seizures are classified as "indeterminate" because the typical seizure types in newborns do not conform to the ILAE scheme. Seizures may be the first and only sign of a CNS disorder in a newborn, so their recognition is extremely important. Despite recent advances in obstetrics and perinatal care, seizures continue to be a significant predictor of poor neurologic outcome. Because of the unique features of seizures in this age group, the physician caring for these children requires a thorough knowledge of neonatal pathophysiology (Stafstrom 1998).

Clinical characteristics

The clinical features of seizures in the neonatal period (first 30 days of life) differ considerably from those seen in older children and adults, making recognition of seizures in neonates difficult (Table 8.25). Owing to immature myelination and cortical organization, the neonatal brain is unable to sustain organized generalized epileptiform discharges. GTC seizures are rarely, if ever, seen in neonates, and absence seizures never occur.

Neonatal seizures are classified clinically into four types, based on behavioral manifestations: subtle, generalized tonic, focal or multifocal clonic, and myoclonic (Volpe 1989). The manifestations of subtle seizures may include repetitive sucking and other oral-buccal-lingual movements, assumption of an abnormal posture, pedaling movements of the legs or arms, blinking, momentary fixation of gaze with or without eye deviation, nystagmus, or apnea. Although clinically the events may not seem impressive, subtle seizures are often associated with severe CNS insults.

FEATURES

Table 8.25 Neonatal Seizures

Discriminating features

1. Occurrence in first 30 days of life
2. May be difficult to differentiate from nonepileptic behavior without the aid of EEG monitoring

Consistent feature

1. Stereotyped activity with clear onset and cessation

Variable features

1. Clinical manifestations are variable – may consist of focal clonic, multifocal clonic, tonic, or myoclonic seizures, subtle manifestations, or autonomic dysfunction
2. Associated with virtually any insult to the neonatal brain
3. Response to AEDs

Tonic neonatal seizures resemble decerebrate or opisthotonic posturing and consist of intermittent tonic extension of the arms, legs, or all four extremities. They are usually associated with severe brain lesions and most often occur in preterm infants.

Clonic seizures consist of rhythmic jerking of groups of muscles and occur in either a focal or multifocal pattern. In multifocal clonic seizures, movements may migrate from one part of the body to another. Focal seizures may be seen with localized brain malformations or insults, such as a perinatal stroke, as well as in disorders that diffusely affect the brain, such as asphyxia, hypoglycemia, or infection.

Myoclonic seizures are similar to those seen in older children, consisting of rapid, isolated jerks. The myoclonic seizures usually consist of bilateral jerks, although occasionally unilateral or focal jerks are seen.

Clinicians have long suspected that some of the stereotyped behaviors in neonates may not be epileptic seizures. Simultaneous EEG and video monitoring techniques have been used to differentiate behaviors with EEG correlates from behaviors that did not have associated EEG changes (Mizrahi & Kellaway 1987) (Table 8.26). Clonic seizures had the highest correlation with EEG ictal abnormalities. Focal clonic seizures consisted of rhythmic twitching of facial, limb, or axial muscles and were further divided into unifocal, multifocal, hemiconvulsive, and axial. Unifocal clonic seizures consisted of rhythmic jerking of one extremity or one side of the face, whereas in multifocal seizures the clonic movements shifted from limb to limb or from face to limb on the same or the opposite side, in a random manner. In hemiconvulsive seizures, one entire side of the body had rhythmic, clonic jerks. Axial seizures consisted of rhythmic jerking movements of the tongue, hips, or shoulders or rapid, irregular respiratory movements. In focal clonic seizures there was usually a one-to-one relationship with EEG seizure discharges.

Many behaviors considered to be subtle seizures on clinical grounds (for example, chewing, pedaling movements, blinking, apnea) were not associated with EEG abnormalities, leading to the conclusion that these behaviors were not epileptic in nature (Mizrahi & Kellaway 1987). It has not been determined with certainty whether subtle seizures are "brainstem release" phenomena or epileptic seizures originating from deep subcortical structures not recordable on surface EEG. In any case, subtle seizures often reflect severe CNS dysfunction. It should be noted that apnea can rarely represent the sole manifestation of a neonatal seizure, although apnea as part of a seizure is usually associated with other abnormal ictal manifestations.

Myoclonic and tonic events are variable in their relationship to EEG abnormalities. Focal tonic seizures consisting of sustained asymmetric posturing of the limbs or trunk, or sustained deviation of the eyes are associated with EEG ictal abnormalities, whereas generalized tonic episodes do not have a consistent relationship to EEG ictal discharges. Myo-

TABLE 8.26

Classification of Neonatal Seizures

Seizures with a close association to EEG seizure discharges
Focal clonic
Unifocal
Multifocal
Alternating
Migrating
Hemiconvulsive
Axial
Myoclonic
Focal tonic
Apnea
Seizures with an inconsistent or no relationship to EEG seizure discharges
Motor automatisms
Oral-buccal-lingual movements
Ocular signs
Progression movements
Pedaling
Stepping
Rotary arm movements
Generalized tonic
Extensor
Flexor
Mixed flexor/extensor
Myoclonic
Generalized
Focal
Fragmentary

(From Mizrahi & Kellaway 1987)

Neonatal Seizures

PEARLS & PERILS

- All neonates with unexplained seizures must have a lumbar puncture to rule out meningitis.
- Pyridoxine should be given to every neonate with seizures when the etiology has not been determined or standard AEDs fail.
- Although rare, apnea may be the sole manifestation of a seizure in a neonate.
- Neonatal seizures may be over-diagnosed or under-diagnosed. When there is doubt, it is better to withhold AED treatment.
- In neonatal seizures, the priority should be to determine the etiology rather than rushing to treat.
- When treating neonatal seizures with phenobarbital, it usually takes a full 15–20 mg/kg loading dose to reach a therapeutic level; giving two 10 mg/kg boluses separated in time often under-treats the seizures.
- It is prudent to have intubation equipment ready when treating neonates with seizures.

clonic seizures, both focal and generalized, are sometimes associated with EEG ictal abnormalities.

Neonatal jitteriness needs to be distinguished from neonatal seizures (Rosman *et al.* 1984). Jitteriness is an involuntary movement of the limbs in newborns that appears intermittently and may thus mimic a seizure. The movements resemble a coarse tremor of the limbs and are not accompanied by eye deviation. Although the movements are often spontaneous, they can also be evoked by limb movement or suppressed by passive flexion of an involved extremity. The pathogenesis is poorly understood, but jitteriness often appears in the context of other CNS excitation, such as irritability and excessive startle. It is often seen in the context of drug-abusing mothers and in hypoxic-ischemic encephalopathy. The EEG can be helpful in ensuring that the jitteriness is not ictal, but the clinician must be aware that some of the same etiologies that cause jitteriness also cause seizures.

Electroencephalography

The EEG is an essential tool to assess cerebral function in newborns. Although the EEG is usually not specific for etiology, it may supply the physician with clues about the severity of a CNS insult and indicate whether it is transient or permanent. The EEG is valuable in supporting the clinical diagnosis of seizures in infants with atypical or minimal behavioral manifestations if the recording includes the episode in question. The EEG may also document seizure discharges that are not accompanied by overt clinical manifestations ("uncoupling" of electrographic and clinical seizures). In infants who are paralyzed and dependent on respiratory support, the EEG may be the only objective means for assessing cerebral function and monitoring the presence of seizure activity.

For prognostic purposes, the background EEG patterns are more important than patterns of epileptiform discharges. In a prospective study of 74 preterm and full-term neonates with clinical seizures, the EEG background activity correlated highly with outcome, whereas interictal discharges were much less reliable as a predictor of outcome (Rowe *et al.* 1985). Ictal discharges, when analyzed separately from interictal discharges, were also associated with a poor outcome.

Etiology

Establishing the etiology of a neonatal seizure is critical because this dictates therapy and is also highly correlated with outcome (Stafstrom 1995). Unfortunately, the ill neonate may present with a constellation of disturbances, each of which may contribute to the development of seizures. For example, asphyxia, hypoglycemia, hypocalcemia, and intraventricular hemorrhage, each sufficient alone to cause seizures, may all occur in the same infant.

Major causes of neonatal seizures include hypoxic-ischemic encephalopathy, hypocalcemia, hypoglycemia, hyponatremia and hypernatremia, intracranial hemorrhage, infection, congenital malformations, genetic factors, inherited metabolic disorders, and drug withdrawal.

Hypoxic-ischemic encephalopathy is the most common cause of neonatal seizures. Most asphyxia occurs before delivery (20% of cases), during delivery (35% of cases), or a combination of antepartum and intrapartum (35% of cases); only 10% of cases result from postnatal causes (Volpe 2001). Intrauterine factors leading to asphyxia are secondary to insufficient gas exchange across the placenta and include both maternal considerations, such as hypotension, and placental disorders, such as infarcts, cord hematomas, placenta previa, and placental abruption. Events during delivery that may result in asphyxia include meconium aspiration and cord compression. Respiratory insufficiency, persistent fetal circulation, and severe right-to-left cardiac shunts are causes of asphyxia following birth. Hypoxic-ischemic encephalopathy is a primary factor in periventricular-intraventricular hemorrhages in preterm infants and in subarachnoid hemorrhage in term infants, both of which may lead to seizures.

Hypocalcemia, defined as a serum calcium level of less than 7.5 mg/dL in the preterm infant and 8 mg/dL in the term infant, was formerly among the most frequent causes of neonatal seizures. In recent years, hypocalcemia as a primary etiology is less common. Hypocalcemia has two major peaks of incidence in the newborn. The first occurs during the first 3 days of life and is associated with prenatal morbidity (e.g. small-for-date infants, maternal preeclampsia, diabetes, polyhydramnios) or perinatal insults (e.g. asphyxia, intracranial hemorrhage, trauma).

Late-onset hypocalcemia (5–14 days) occurs primarily in term infants consuming a nonhuman milk preparation with a suboptimal ratio of phosphorus to calcium. In the United States, this type of hypocalcemia has become rare. Hypomagnesemia, defined as a magnesium level of less than 1 mEq/L, may accompany hypocalcemia or occur independently of it. Therapy consists of replenishment of the deficient ion.

Most authors define *hypoglycemia* as a blood glucose level under 20 mg/dL in a preterm infant and 30 mg/dL in a full-term baby. Like hypocalcemia, hypoglycemia is often associated with other neonatal disorders such as trauma, hemolytic disease, or asphyxia. Infants of diabetic and toxemic mothers, infants who are small for gestational age, and twins are at particular risk. The duration of hypoglycemia is an important determinant in the development of neurologic signs. These signs include jitteriness, hypotonia, lethargy, and apnea, in addition to seizures.

Hyponatremia also occurs in association with other disorders, such as intracranial hemorrhage or meningitis, and is secondary to the inappropriate secretion of antidiuretic hormone. Hypernatremia is usually iatrogenic, most often due to the improper mixing of formula.

Primary subarachnoid hemorrhage occurs in both term and preterm infants. Bleeding is from venous structures and is often associated with asphyxia or trauma. Although many subarachnoid hemorrhages are mild and inconsequential except for causing transient seizures, some result in a stormy course with hydrocephalus and parenchymal brain damage.

Intraventricular or periventricular hemorrhage is the most common type of intracranial hemorrhage and accounts for a large percentage of morbidity and mortality, especially in preterm infants. Hemorrhage usually occurs within 72 hours of birth, and the manifestations vary from no clinical signs to catastrophic deterioration with hypotonia, apnea, seizures, and a bulging fontanel. Seizures occur in 15–50% of infants with intracranial hemorrhage.

Subdural hematomas are most common in term infants and usually follow traumatic deliveries. With improved obstetric techniques, they have become rare. Seizures are usually associated with an underlying cerebral contusion.

Intrauterine or postnatal *CNS infections* may also lead to neonatal seizures. Intrauterine causes include rubella, toxoplasmosis, cytomegalovirus, herpes simplex, human immunodeficiency virus, and coxsackievirus B. Intrauterine infections are usually associated with other systemic signs, such as microcephaly, jaundice, rash, hepatomegaly, and chorioretinitis. Common postnatal infections include *Escherichia coli* and group B streptococcus. Any infant without a clear etiology for seizures requires a prompt lumbar puncture.

Virtually all *disorders of brain development*, including those affecting neuronal migration and synaptic organization (such as polymicrogyria, neuronal heterotopias, lissencephaly, holoprosencephaly, and hydranencephaly), may lead to severe neonatal seizures. Many of these dysgenetic CNS conditions occur in isolation with normal facies and without systemic abnormalities. Although CT scans and cranial ultrasound detect the most severe abnormalities, MRI is the most sensitive imaging modality to define cerebral malformations.

Although the differential diagnosis of neonatal seizures includes *inherited metabolic disorders*, these conditions are fortunately rare and usually produce other prominent symptoms such as peculiar odors, protein intolerance, acidosis, alkalosis, lethargy, or stupor (Hyland & Arnold 1999; DeVivo 2002). In most cases of metabolic disease, pregnancy, labor, and delivery are normal. Formula intolerance may be the earliest indication of a systemic abnormality, and seizures are commonly the first specific clue to CNS involvement. If untreated, metabolic disorders commonly lead to lethargy, coma, and death. In surviving infants, weight loss, poor growth, and failure to thrive are common. Metabolic disorders that may lead to neonatal seizures include maple syrup urine disease, nonketotic hyperglycinemia, organic acidemias such as propionic acidemia and methylmalonic acidemia, and urea cycle defects such as carbamoyl phosphate synthetase deficiency or ornithine transcarbamoylase deficiency. The disorders tested on neonatal panels offered by state laboratories vary from state to state in the United States.

Vitamin B6 (pyridoxine) dependency is an extremely rare metabolic disturbance in which the quantity of combined ingested and circulating B6 is insufficient for cofactor function in metabolic pathways (Baxter 2001; Gospe 2002). Pyridoxine dependency may be associated with intrauterine convulsions, detected by the mother as unusually strong, rhythmic contractions. Because the clinical spectrum of abnormalities is broad, any child with unexplained seizures should receive an injection of 50–100 mg of pyridoxine intravenously during EEG monitoring. Termination of a seizure or ictal EEG discharges would strongly suggest pyridoxine dependency, so the child would need to receive daily vitamin B6 supplements.

A significant cause of neonatal seizures in urban hospitals is *drug withdrawal* from narcotic-analgesics, sedative-hypnotics, and alcohol. Infants born to heroin- or methadone-addicted mothers have an increased risk of seizures, although the most common neurologic findings are "jitteriness" and irritability. Infants of methadone-addicted mothers may have late withdrawal symptoms, with seizures occurring as long as 4 weeks after birth.

Although rare, seizures may be a prominent feature in infants poisoned with *local anesthetics*. Inadvertent fetal anesthetic injection may occur at the time of local anesthesia administered for episiotomy. The infant presents at birth with bradycardia, apnea, and hypotonia. Seizures usu-

ally occur within the first 6 hours and are usually tonic in type. The infants may have mydriasis and loss of lateral eye movements and pupillary light reflexes. When anesthetic intoxication is suspected, the infant should be closely inspected for needle marks. The diagnosis can be confirmed by measuring serum levels of the offending drug. Treatment consists of maintaining adequate ventilation and facilitating elimination of the drug by diuresis, urine acidification, or exchange transfusion when renal function is impaired. AEDs are of questionable benefit, and seizures subside with clearance of the local anesthetic.

Neonatal epilepsy syndromes

Most neonatal seizures are not the result of epilepsy but are reactions to a neurologic insult. However, recently, several neonatal epilepsy syndromes have been defined (Mizrahi 2001), a few of which are discussed here. *Benign familial neonatal convulsions* were discussed above.

Early myoclonic encephalopathy (EME) is characterized by sporadic and erratic fragmentary myoclonus, usually in combination with other seizure types. The EEG demonstrates burst suppression. A variety of etiologies has been associated with EME, including metabolic diseases, cerebral dysgenesis, and hypoxic-ischemic insults. The prognosis is very poor. Most infants die within a year or survive with severe neurologic sequelae.

Ohtahara syndrome, or *early infantile epileptic encephalopathy* (EIEE), is a disorder with onset in early infancy. Severe, frequent tonic seizures occur, with burst suppression on the EEG. The infants have severe developmental deficits. EIEE may evolve into West syndrome. As with EME, a host of etiologies has been described in EIEE, but cerebral dysgenesis is the most common association.

Treatment

Determining the etiology is of utmost importance in the neonate with seizures. After ventilation and adequate glucose levels are ensured, initial goals are to establish the underlying cause and institute appropriate therapy. The ready availability of accurate and timely chemistry screening panels has largely obviated the need for empirical infusions of glucose and calcium as the first steps in treatment. Chemical abnormalities should be corrected when documented and antibiotics given when appropriate.

The decision to treat an infant with recurrent seizures is based on a number of factors, including duration and frequency of seizures, associated autonomic dysfunction, etiology, and EEG abnormalities. Unfortunately, it is not yet known whether the treatment of neonatal seizures alters prognosis. If seizures are brief and not associated with autonomic dysfunction, the clinician may decide not to treat or to treat with a short-acting benzodiazepine. Conversely, infants with frequent seizures, especially if they interfere with ventilation, require prompt and vigorous treatment.

Phenobarbital remains the primary drug used in the neonate with seizures. The half-life of phenobarbital varies widely in newborns, ranging from 45 to 175 hours. With maturation, the infant's ability to metabolize phenobarbital improves dramatically. The following dosage recommendations for phenobarbital have been formulated: the initial loading dose should be 15–20 mg/kg intravenously with a maintenance dosage of 3–6 mg/kg/day. Neither the loading dose nor the maintenance dose of phenobarbital appears to be influenced by gestational age or birth weight. Because of its long half-life, phenobarbital can be given once or twice daily. Most infants require serum levels between 10 and 40 mg/dL to suppress seizures, but the dose is often pushed higher before resorting to polytherapy. As with older children, levels above 40 mg/dL may result in lethargy.

If phenobarbital is ineffective in stopping neonatal seizures, a second drug must be added, such as phenytoin (usually as the fosphenytoin form). As with phenobarbital, the range in half-life for phenytoin is extremely wide in newborns. The greatest variability and widest range of phenytoin half-life is encountered in the first week of life, varying from 6 to 140 hours. The apparent half-life decreases with postnatal age from an average of 58 hours in the first week to 20 hours in the fourth week. As in older children, phenytoin follows nonlinear kinetics in the newborn period. The drug is usually administered in two boluses of 10 mg/kg intravenously. This loading dose of 20 mg/kg results in a blood level of 15–20 mg/dL. Unfortunately, phenytoin is not well absorbed from the gastrointestinal tract of newborns, and it is often difficult to maintain therapeutic levels using the oral route. When phenytoin is administered intravenously, the recommended maintenance dose is 3–4 mg/kg/day, whereas if oral treatment is attempted, up to 8 mg/kg/day is sometimes required to obtain a therapeutic level, due to poor gastrointestinal absorption of the drug in neonates. Commonly, phenobarbital or phenytoin will suppress clinical seizures but the baby continues to have electrographic seizures ("uncoupling") (Scher *et al.* 2003). In such cases, the physician must decide, in the context of the clinical situation, how far to push medications to suppress electrographic seizures.

Diazepam and lorazepam are commonly used to treat neonatal seizures. Like phenytoin and phenobarbital, the diazepam half-life has a wide range in neonates (31–54 hours). A diazepam dose of 0.2–0.5 mg/kg intravenously is recommended for the acute management of neonatal seizures. Owing to its short distribution phase, diazepam is not optimal as a maintenance AED.

Alternative treatments for neonatal seizures include primidone, midazolam, clonazepam, carbamazepine, lidocaine, paraldehyde, and VPA (Mizrahi 2001). However, there is little information regarding their efficacy, since large-scale studies have not been done. There is also little information regarding the effectiveness of additional AEDs

after metabolic abnormalities are corrected, ventilation and perfusion are satisfactory, and loading with phenobarbital and phenytoin is complete. An attempt to wean anticonvulsants should be undertaken as soon as medically feasible, preferably before discharge from the nursery.

Status epilepticus

Status epilepticus is one of the most frequent and serious neurologic emergencies encountered by physicians working with children. Status epilepticus has been defined traditionally as more than 30 minutes of continuous epileptic seizure activity, or two or more sequential seizures without full recovery of consciousness between seizures (Table 8.27). However, this arbitrary definition is being revised, and as little as 5 minutes of continuous seizure activity may qualify as status epilepticus (Lowenstein *et al.* 1999). In practical terms, a child arriving at the emergency room seizing should be considered to be in status.

As with epilepsy in general, status epilepticus is most common at the extremes of life, in children and in the elderly. Any seizure type can progress into status epilepticus. There is unequivocal clinical and experimental evidence that status epilepticus can lead to brain damage and therefore must be stopped as quickly as possible.

Clinical features

Status epilepticus can be divided into convulsive and nonconvulsive status. In convulsive status the seizure type is usually tonic or tonic–clonic. During generalized convulsive status, there are significant autonomic manifestations, including tachycardia, hyperpnea, mydriasis, and hypersecretion. If the seizure continues, the patient may develop fever, hypotension, acidosis, and respiratory depression. Serious metabolic consequences occur so quickly after the start of a seizure that convulsive status epilepticus is considered a medical emergency.

Nonconvulsive status refers to absence or partial (either simple or complex) seizures. These nonconvulsive seizures can produce a continuous or fluctuating epileptic twilight state. In addition, partial seizures may involve motor function (epilepsia partialis continua), sensory symptoms, or focal impairment of function (for example, aphasia) not associated with altered consciousness.

Etiology

The etiologies of status epilepticus are as varied as those of epilepsy in general. Status epilepticus has been classified as either idiopathic or symptomatic, with symptomatic cases outnumbering idiopathic cases by 3:1. In series limited to children, nonspecific febrile illness, hypoxic-ischemic encephalopathy, and CNS infection account for the majority of cases of symptomatic status epilepticus, whereas in adults, tumor- and trauma-related causes are more common. In patients already being treated for epilepsy, status epilepticus can be precipitated by abrupt withdrawal of anticonvulsant medications, sleep deprivation, or intercurrent infection. Rapid discontinuation of AEDs, particularly barbiturates and benzodiazepines, can lead to status epilepticus. Sleep deprivation is unlikely to be the sole factor responsible for status epilepticus.

Prognosis

The risk of death with status epilepticus is decreasing with improved medical management (Mitchell 2002). In a study of 193 children with status epilepticus (defined as any continuous seizure lasting more than 30 minutes or a series of seizures during which the patient failed to regain conscious-

FEATURES

Table 8.27 Status Epilepticus

Discriminating features

1. Diagnosis of convulsive status epilepticus is usually straightforward. Nonconvulsive status epilepticus may be mimicked by drug intoxication, psychosis, or migraine, and may require EEG monitoring for diagnosis
2. Defined as clinical or EEG seizure activity lasting 30 minutes or more, or intermittent seizures over a 30-minute period without full return of awareness between seizures. This definition may be too restrictive (see text)

Consistent features

1. Convulsive status epilepticus is associated with hypoxia, hyperthermia, and other toxic and metabolic derangements

Variable features

1. Clinical seizures may be convulsive (i.e. tonic, clonic, or tonic–clonic) or nonconvulsive (i.e. absence or partial complex)
2. Etiologies are as broad as for any seizure
3. Response to AEDs

PEARLS & PERILS

Status Epilepticus

- The water-soluble form of phenytoin (fosphenytoin) can be given intramuscularly to treat status epilepticus.
- Failure to give a sufficient dose of an AED is a common error in the treatment of status epilepticus.
- While benzodiazepines are critical in the acute treatment of status epilepticus, the patient should also be loaded with a longer-acting, chronic AED such as phenobarbital or phenytoin.
- Children who remain stuporous or comatose after a prolonged seizure should have an EEG to determine whether the symptoms are due to nonconvulsive status.

ness for at least 30 minutes), only 7 children died within 3 months of having the seizure (Maytal *et al.* 1989). In all fatal cases, the child had an identifiable CNS insult. The authors concluded that the underlying cause of the status, not the status itself, was responsible for the deaths.

The incidence of neurologic deficits following status epilepticus is also decreasing with improved intensive care. In the above study, only 9% of survivors of status had new neurologic deficits, most of whom had acute or progressive neurologic disorders (Maytal *et al.* 1989). It is likely that the improved mortality and morbidity rate associated with status epilepticus is due to earlier and improved methods of treatment. These results also suggest that the prognosis of status in children is more favorable than in adults.

A long-term prospective study was carried out on 150 Finnish children who had the onset of epilepsy between 1961 and 1964 (Sillanpaa & Shinnar 2002). They were followed for the occurrence of status epilepticus until 1997. Those who developed status epilepticus did so early, usually within 2 years of epilepsy onset. Risk factors for status epilepticus included age of onset 6 years or younger, a remote symptomatic cause, and partial seizures. Unless the there was a pre-existing neurologic disorder, the majority of children had excellent educational and psychosocial outcomes in adulthood.

TABLE 8.28 Sequence of Steps for Emergency Treatment of Status Epilepticus

1. Place patient in safe position
2. Assess cardiorespiratory function
3. Insert oral airway and administer oxygen
4. Insert intravenous catheter
5. Draw venous blood for measurement of AED levels, CBC, BUN, electrolytes, glucose, and ammonia
6. Draw arterial blood gases
7. Give 50% glucose solution (1–2 mL/kg)
8. Start maintenance fluids unless there is evidence of fluid overload, concern about increased intracranial pressure, or dehydration
9. Give diazepam or lorazepam (Table 8.29)
10. If seizures stop, a longer-acting AED (phenobarbital or phenytoin/fosphenytoin) must be given to prevent recurrence of status
11. If status continues, give phenobarbital or phenytoin/fosphenytoin (Table 8.29)
12. If status continues, intubate child and admit to intensive care unit. Give propofol bolus then drip. Alternatively, use a midazolam bolus (0.15–0.3 mg/kg) and maintenance (1–4 mg/kg/min)
13. If status continues, consider general anesthesia

Treatment

Status epilepticus cannot be diagnosed until a seizure has lasted 30 minutes, but pharmacologic treatment should begin whenever a seizure lasts 5 minutes or so. The therapeutic end point is cessation of clinical and EEG seizures. Although brain damage can occur in the absence of systemic abnormalities, it is clear that the hyperpyrexia, hypoglycemia, hypotension, and hypoxia that may occur during status epilepticus can increase the cerebral damage. Failure to treat systemic abnormalities quickly and successfully may result in neurologic sequelae or death. It is important, therefore, to achieve systemic metabolic stability as well as to stop the seizures. As the status is being treated, it is also imperative to continue searching for precipitating causes.

Proper management of status epilepticus therefore requires close attention to basic principles of life support (Table 8.28). Initial therapy is aimed at providing satisfactory ventilation, maintaining adequate cardiac output and cerebral perfusion, and preventing injury as a result of the violent motor activity. A team approach in an emergency room or intensive care unit is imperative for the management of status epilepticus.

Because cerebral hypoxia can be both a cause and consequence of status epilepticus, immediate needs are to assess cardiorespiratory function and insert an oral airway. Oxygen should be administered by nasal cannula or mask. Although endotracheal intubation may be needed, administration of an AED may eliminate the need or make the intubation significantly easier. However, it is always better to intubate before respiratory compromise than after hypoxia and hypercapnia have occurred. While the patient is in status epilepticus, arterial blood gas monitoring is essential.

Once the airway is secure, intravenous access should be obtained, both for drawing blood studies and administering glucose and AEDs. As soon as the line is established, blood should be obtained for electrolytes, BUN, glucose, ammonia, AED levels, and toxin screen. Then, glucose should be given by bolus injection (2–4 ml/kg of 25% glucose or 1–2 mL/kg of 50% glucose). Maintenance fluids should be started using 5% dextrose in half-normal or normal saline unless there is indication of fluid overload, increased intracranial pressure, or dehydration. Because prolonged seizures may result in hypoglycemia, it is important to continue monitoring serum glucose. Rhabdomyolysis can result from excessive muscle activity and ischemia, and the urine should be monitored for this complication.

Although hypotension is unusual during the initial phases of status epilepticus in children, it is important to monitor blood pressure, especially when AEDs are administered. Hypotension can lead to ineffective cerebral perfusion and potentiate excitotoxic brain damage. Tissue hypoxia and excessive muscle contractions may lead to lactic acidosis and autonomic instability. Bicarbonate should be given intravenously to raise the pH if it falls below 7.2. Likewise,

temperature, which may rise quickly during status, should be monitored continuously. If hyperthermia is present the patient should be cooled rapidly using a cooling blanket or ice packs. Hyperthermia may exacerbate electrolyte imbalance, hypertension, and cardiac arrhythmia.

No studies are available that adequately address the question of selection or order of administration of drugs for status epilepticus in children. At present, five drugs are widely used in the treatment of status epilepticus in children: diazepam, lorazepam, phenytoin, phenobarbital, and midazolam (Table 8.29). All five drugs are highly efficacious. Although there is no single standard treatment, it is imperative that the clinician use the correct dosage and have an understanding of the pharmacokinetics and adverse effects of each of these AEDs.

Diazepam

Diazepam has gained wide acceptance as a first-line intravenous agent in the therapy of status epilepticus, with an efficacy of greater than 60%. However, the anticonvulsant effect is only temporary and administration of another longer-acting AED is required. Peak brain concentration following intravenous administration is reached within 12 minutes. Diazepam distributes quickly in lipoid tissues and rapidly crosses the blood-brain barrier, resulting in a rapid anticonvulsant action. After the peak concentration is reached, a bi-exponential decline of the plasma concentration is observed. A short distribution half-life of approximately 1 hour determines the rapid initial decline. Correspondingly, the plasma concentration may drop below therapeutic values within 15–20 minutes after intravenous injection, depending on the initial peak concentration. The subsequent slower decline results mainly from the elimination of the drug; its slope determines the elimination half-life.

The usual dosage is 0.2–0.4 mg/kg intravenously, with a maximum dose of 10 mg. It should be administered at a rate of approximately 1–2 mg per minute. When the initial administration does not stop seizures completely, a second or third intravenous injection may be effective. An interval between injections of 10–20 minutes is recommended. Diazepam may also be administered rectally at a dose of 0.5 mg/kg. As would be expected from the pharmacokinetics of the drug, diazepam is quick acting. Because its distribution is so rapid, its effective half-life is short and another AED, usually phenytoin or phenobarbital, should be administered to avoid recurrence of the status.

Diazepam is widely known to lead to respiratory depression and hypotension. Many patients who developed those complications had received large doses of barbiturates prior to intravenous administration of diazepam or had evidence of severe acute brain lesions that could also lead to respiratory distress. Although it is likely that the dangers of using diazepam are overemphasized, the physician must he aware that respiratory depression and hypotension may occur. These risks may be decreased by a slow infusion rate. Extreme care must be used in administering the drug to patients with pulmonary disease or those who have previously received a sedative drug such as phenobarbital. Because diazepam depresses consciousness, it should be avoided in situations in which neurologic signs must be followed closely, such as head trauma.

Lorazepam

Lorazepam is another benzodiazepine that is effective in the treatment of status epilepticus in children and adults. It has a half-life of 13–15 hours, rapidly penetrates the CNS, and appears to produce minimal cardiovascular depression and less respiratory depression than diazepam. Although lorazepam has a shorter half-life than diazepam, its longer distribution phase gives it a longer duration of action. Lorazepam can also be used safely in patients on high doses of chronic barbiturates. The major side effect is sedation. An initial dose of 0.05–0.1 mg/kg should be given at 1 mg/min, with the dose repeated up to two times. The mean time to seizure control is about 10 minutes. Its prolonged anticonvulsant effect and limited respiratory depressant effect make lorazepam the preferred initial agent in status epilepticus in many centers.

TABLE 8.29

Properties of Five AEDS Used for the Intravenous Treatment of Status Epilepticus

Property	Diazepam	Lorazepam	Fosphenytoin	Phenobarbital	Midazolam
Dose	0.2–0.4 mg/kg (maximum dose 20 mg)	0.05–0.1 mg/kg	15–20 mg/kg	15–20 mg/kg	Bolus: 0.15–0.3 mg/kg Drip: 0.75–10 µg/kg/min
Time to stop seizure	3–10 min	1–20 min	5–30 min	10–30 min	15 min
Half-life	50 hours	15 hours	10–15 hours	80–100 hours	1.7–4.0 hours
Duration of action	Minutes	Hours	12–24 hours	Days	30–80 min
Side effects	Hypotension Apnea Somnolence	Hypotension Apnea Somnolence	Cardiac arrhythmias Hypotension	Hypotension Apnea Somnolence	Hypotension Apnea Somnolence

Phenytoin

Phenytoin, and its new formulation fosphenytoin (Table 8.29), is an excellent first-line drug for the treatment of generalized status epilepticus. It reaches the brain rapidly, effectively stops GTC seizures in more than 60% of patients, and can be safely given with minimal depression of consciousness or respiration.

Phenytoin loading for status epilepticus is achieved with a dose of 15–20 mg/kg administered at a rate of 0.5–1.0 mg/kg/minute. Phenytoin enters the brain within minutes and reaches a peak brain concentration in 15–30 minutes. The anticonvulsant effect of phenytoin was evident as early as 10 minutes after the start of the infusion, with 30% of the status having stopped by this time. Seizures stop within 20 minutes in more than 80% of patients. This loading dose results in a peak level greater than 10 mg/dL for over 24 hours. Intravenous phenytoin may be used for status epilepticus even if the patient is on chronic phenytoin therapy. Fosphenytoin, given intravenously or intramuscularly, produces effective blood levels much more quickly, as it can be infused faster; it can also be administered via an intravenous line containing glucose solution (whereas phenytoin cannot).

With proper administration, side effects with phenytoin are unusual. Hypotension and cardiac arrhythmias have been reported, primarily in older patients. It is necessary to monitor both the electrocardiogram and blood pressure during the infusion of phenytoin. Contraindications to phenytoin include a prior history of allergic response to phenytoin, porphyria, sinus bradycardia, sinoatrial block, second- and third-degree atrioventricular block, hypotension, and myocardial insufficiency.

Phenobarbital

Phenobarbital continues to be extensively used in some institutions for the treatment of childhood status epilepticus. The popularity of this drug is due to its efficacy, safety, and familiarity to pediatricians and family physicians. Phenobarbital should be given as an intravenous bolus in a dosage of 15–20 mg/kg at a rate no faster than 50 mg/min. Like phenytoin, phenobarbital enters the brain quickly but does not reach brain peak levels for approximately 30–60 minutes. Therapeutic responses, therefore, are usually slower than those achievable with diazepam or phenytoin. Major side effects include sedation, hypotension, and respiratory depression. The combination of diazepam and phenobarbital is particularly likely to lead to respiratory depression.

Like phenytoin, phenobarbital is long lasting, and if the seizures stop with the loading dose, maintenance drugs do not need to be started for 12 hours. Because phenobarbital may depress consciousness, it should be avoided when neurologic signs must be closely monitored.

Refractory status epilepticus

When status epilepticus fails to respond to the medications described previously, more drastic treatment must be initiated. Until recently, the first step in stopping refractory status has been induction of coma using pentobarbital. The depth of coma can be assessed using EEG monitoring; the appearance of burst suppression on the EEG suggests that the brain's metabolic rate is slowed and that ongoing status epilepticus should be suppressed. However, distinguishing burst suppression from epileptic discharges can be difficult, and some authorities recommend pushing the medication until the EEG is completely flat, since any persistence of EEG activity predicted recurrence of status epilepticus when the infusion is stopped (Treiman 2001).

The patient must be intubated and mechanically ventilated before pentobarbital coma is induced. Although it is often effective at stopping status, pentobarbital coma is associated with significant hypotension and myocardial depression. Furthermore, there are few guidelines as to the use of pentobarbital coma in children, such as the most efficacious duration of coma, optimal interburst interval, and best approach if seizures recur.

A recent alternative to pentobarbital coma is continuous infusion of the water-soluble benzodiazepine midazolam (Versed; see Table 8.29). Midazolam has a rapid onset of action and excellent effectiveness. In one large series of children, midazolam promptly stopped status (usually in less than 1 hour) and was associated with a very low morbidity (Rivera *et al.* 1993). In critical care units, the anesthetic agent propofol is becoming more widely used, especially for refractory status (Claassen *et al.* 2002). It has a rapid onset and minimal hemodynamic side effects. Some authorities recommend general anesthesia by inhalation of halothane or enflurane, but these agents must be administered in the controlled environment of an operating suite, which poses practical problems for a child in an intensive care unit. Future studies will clarify the role of these and other agents in the management of status in children.

Prognosis of childhood epilepsy

It is difficult to ascribe an overall prognosis to childhood epilepsy, because the outcome is very dependent upon the epilepsy syndrome and several other factors, including preexisting neurologic impairment, duration of epilepsy, and ease with which seizures are controlled (Sillanpaa *et al.* 1998; Arzimanoglou *et al.* 2004c). Many childhood epilepsies do remit over time (Berg *et al.* 2002).

It has been emphasized that in epilepsy, seizures are often just "the tip of the iceberg" (Bax 1999). Children with

epilepsy often have significant psychological, social, and educational challenges that, in many cases, outweigh the burden of the seizures themselves. When discussing prognosis, seizure control (i.e. with AEDs) must be distinguished from seizure remission. Psychosocial adjustment and AED side effects play a prominent role in a child's self-image.

Prognosis related to individual syndromes was discussed above. Generally, the idiopathic benign epilepsies of childhood (BCECTS, BEOP) have a favorable prognosis, with seizure resolution and continuance of normal neurologic function once the seizures remit in adolescence. Generalized epilepsy syndromes such as childhood absence epilepsy and GEFS+ have an intermediate prognosis: seizures resolve in many cases but a significant proportion persists. Some epilepsy syndromes are considered "catastrophic" (Camfield & Camfield 2002). Catastrophic epilepsy syndromes include infantile spasms, Lennox–Gastaut syndrome, and Landau–Kleffner syndrome, in which seizures persist, become refractory to medical treatment, and are accompanied by severe cognitive impairment. It is an intriguing but unanswered question whether "seizures beget seizures," i.e. the occurrence of a seizure increases the chance that a subsequent seizure will occur. There is considerable experimental investigation into determining whether epilepsy is a progressive disorder and whether this phenomenon is age-related (Pitkanen & Sutula 2002).

Finally, some children with epilepsy die unexpectedly, without an obvious cause determined either historically or by postmortem examination. Sudden unexplained death in epilepsy (SUDEP) has been seen in both adults and children (Breningstall 2001; Donner *et al.* 2001). Definitive risk factors have not been established, but children with severe, intractable generalized epilepsies may be at greater risk.

TABLE 8.30 Some Nonepileptic Disorders that May Mimic Epilepsy

Apnea
Benign paroxysmal vertigo
Breath-holding spells (cyanotic and pallid)
Cardiac arrhythmias (e.g. prolonged QT syndrome)
Cataplexy
Daydreaming
Episodic dyscontrol (rage attacks)
Gastroesophageal reflux
Hyperekplexia (startle disease)
Hyperventilation
Jitteriness
Migraine
Narcolepsy
Night terrors
Pediatric autoimmune neuropsychiatric disorder after streptococcus (PANDAS)
Paroxysmal choreoathetosis
Pseudoseizures (psychogenic seizures)
Sandifer syndrome
Shuddering attacks
Spasmus nutans
Syncope
Tics, Tourette syndrome

Nonepileptic disorders that may mimic epilepsy

Differentiating epileptic seizures from the wide variety of nonepileptic paroxysmal alterations of motor activity or behavior is a challenging task for the primary care physician and seasoned epilepsy specialist alike (Bleasel & Kotogal 1995; Prensky 2001). Many nonepileptic disorders may mimic epilepsy by history or clinical presentation (Table 8.30). Here, only a few of the more common disorders are described. From a therapeutic point of view, it is important to distinguish epileptic from nonepileptic behaviors, because some nonepileptic phenomena respond to medications other than AEDs and others require no specific treatment other than reassurance or avoiding circumstances that precipitate the spell.

Benign paroxysmal vertigo

Benign paroxysmal vertigo (BPV) manifests as sudden, brief overwhelming sensations of vertigo that cause a child to stagger, lose balance, and sometimes fall to the ground. The child appears very distressed and frightened and often becomes pale, diaphoretic, and nauseated. Nevertheless, consciousness is maintained. An episode may last from a few minutes to several hours, and episodes may occur once every few months to several times per week. BPV is thought to be a migraine variant; there is often a family history of migraine. The disorder usually affects preschool-age children and usually resolves by 7 years of age, although most affected children go on to develop more typical migraine symptoms later in life. As opposed to other causes of vertigo, in BPV there is no accompanying tinnitus, hearing impairment, or other brainstem dysfunction, though nystagmus is often present. Diagnosis is aided by a normal EEG and neurologic examination. The lack of rhythmic movements or alteration of consciousness further differentiates BPV from epilepsy. The attacks typically fail to respond to anticonvulsant or antimigraine medications, and the only treatment is to reassure the parents of the benign nature of the spells.

Breath-holding spells

Despite their name, breath-holding spells (BHSs) are involuntary reflex responses with a benign prognosis. They are age related and are typically outgrown by school age. Two types of BHSs occur: cyanotic (often called cyanotic infantile

syncope) and pallid (often called pallid infantile syncope or reflex anoxic seizures). Features of each type are listed in Table 8.31. Their nomenclature, pathophysiology, and differentiation can be complex (Stephenson 1990; Arzimanoglou *et al.* 2004b).

Cyanotic BHSs, the more common type, are precipitated by upset, anger, or frustration. The hallmark is crying, during which the child will stop breathing (usually in expiration), become cyanotic, then loses consciousness. At that point the child may become rigid, limp or even shake, raising the concern about a seizure. The unconsciousness lasts from seconds to a minute. The pathogenesis of cyanotic BHS is complex, probably involving an interaction between hyperventilation, Valsalva maneuver, expiratory apnea, and intrinsic pulmonary mechanics (Stephenson 1990; Breningstall 1996).

Pallid BHSs are similar to cyanotic BHSs in some respects but are more likely to be provoked by fright or a mild unpleasant stimulus (such as a mild head bump or even stubbing a toe). There will be a gasp but little or no cry, followed by loss of consciousness, pallor, diaphoresis, and limpness. Pallid BHSs result from vasovagally mediated cardiac inhibition, causing diminished cerebral blood flow. During an attack, the pulse slows significantly. Such spells are very frightening to an observer, who may initiate cardiopulmonary resuscitation, thinking the child has died.

Neither type of BHS is associated with an increased predisposition to epilepsy, although seizure activity can occur at the end of a cyanotic or pallid BHS. These so-called "seizures" manifest as tonic stiffening of the extremities, sometimes followed by brief clonic jerking. Such seizures are not epileptic in nature, however, and merely represent a response of the brain to acute, mild hypoxia. These seizures terminate spontaneously and do not require anticonvulsant treatment. Notably, in a BHS, cyanosis occurs before the seizure, whereas in an epileptic seizure, cyanosis usually occurs during or after the seizure.

Evaluation with an EEG is usually not needed. An electrocardiogram can rule out the possibility of prolonged QT syndrome, which can mimic epilepsy. In addition, anemia can worsen BHS and should be excluded; some authors have recommended iron therapy even in the absence of anemia (Daoud *et al.* 1997). Management of BHS consists mainly of reassuring the parents that the spells will be outgrown, usually by school age, and that the BHS will not lead to future epilepsy or brain damage. Children with the pallid type may develop syncope later in life. Parents of children with BHS may be reluctant to discipline their child in an age-appropriate manner for fear of provoking an attack. Counseling the parents about limit setting may be indicated. Medical therapy is advised only in exceptional circumstances. A child followed by the author had pallid BHS and leukemia; he was treated with a small dose of atropine before his frequent blood draws, which predictably precipitated attacks.

Syncope (fainting)

Syncope, seen commonly in older children and adolescents, can often be differentiated from an epileptic seizure by history. Attacks may be preceded by warning (presyncopal) signs such as lightheadedness, blurring of vision, pallor, nausea, or diaphoresis. These warning signs are followed by a gradual loss of consciousness and a slow slump to the ground, as opposed to the more violent fall seen with a myoclonic or atonic seizure. Late in the syncopal spell, there may be a brief tonic or clonic seizure secondary to cerebral hypoperfusion and hypoxia; these are not epileptic seizures. Consciousness is regained rapidly, compared with a more prolonged epileptic postictal state. A child may be tired after syncope but is not ordinarily confused for more than a few seconds. Seizure is further differentiated from syncope in that a seizure is not associated with cold, clammy skin.

Syncope is caused by transiently diminished cerebral blood flow, due to an irregular heart rate (an arrhythmia causing decreased cardiac output), decreased venous return (orthostasis or Valsalva), a vasovagal mechanism (fright, pain, emotional upset), or, rarely, cough- or micturition-

TABLE 8.31

Clinical Differentiation of Cyanotic and Pallid Breath-Holding Spells

Clinical data	Cyanotic BHS	Pallid BHS
Onset of spells	0–18 months	12–24 months
Remission	Most by 4–6 years	Most by 4–6 mo
Percent of total*	60	20
Precipitant	Anger, frustration, fright	Sudden unpleasant stimulus, e.g. minor injury
Sequence of events	Cry → apnea, cyanosis → loss of consciousness and tone (or rigidity) → ± brief tonic–clonic seizure	Gasp or weak cry → pallor → loss of consciousness and tone → ± brief tonic–clonic seizure
Duration of unconsciousness	Usually less than 1 minute	May be longer than 1 minute
Mechanism	Multifactorial (see text)	Vasovagal
Therapy	Reassurance	Reassurance; rarely, atropine

*The remaining 20% consists of mixed types or indeterminate spells.

induced reflex syncope. Vasovagal attacks often occur in a hot, crowded environment. Orthostasis is most commonly precipitated by rising from a sitting or recumbent position.

A child who has an arrhythmia or who faints from any position other than standing requires a cardiac evaluation. A cardiac workup might include an electrocardiogram, echocardiogram, Holter monitor and perhaps a tilt-table test. Orthostatic blood pressures should be taken in the office; upon standing, a drop in pulse of more than 20 points or systolic blood pressure of more than 15 points is abnormal. The EEG is usually normal.

The hallmark of treatment is prevention. The child should avoid precipitating factors as much as possible. During a syncopal event, the observer should allow the child to lie horizontally or with the head at a lower level than the body; lifting or raising the head can delay return of consciousness by prolonging the duration of cerebral hypoperfusion.

PEARLS & PERILS

Pseudoseizures

- In most cases, prolonged video-EEG monitoring is necessary to diagnose pseudoseizures.
- Epileptic seizures and pseudoseizures often coexist in the same patient.
- Urinary incontinence is an unsatisfactory discriminating feature, because it occurs in up to 20% of patients with nonepileptic seizures.
- Some frontal lobe epileptic seizures present with ictal manifestations similar to classic pseudoseizures (e.g. bilateral motor activity with preserved consciousness, pelvic thrusting).
- Pseudoseizures are real in the sense that they are the symptom of real (psychiatric) disease. Therapy is aimed at uncovering the underlying psychological etiology and teaching the child effective new coping skills. In evaluating pseudoseizures, always rule out physical and sexual abuse.

Pseudoseizures

Pseudoseizures, also referred to as psychogenic seizures, psychogenic nonepileptic seizures, or simply nonepileptic seizures (to avoid a presumption of etiology or any pejorative connotations), are paroxysmal changes in motor activity or behavior that resemble epileptic seizures clinically but have no EEG correlate. The diagnosis of pseudoseizure should be considered in any child with seizures refractory to anticonvulsants or with consistently normal EEGs (awake, asleep, and with activation procedures). A history of strong emotional overlay or psychiatric disturbance in the child or family may suggest pseudoseizures. Clinically, it may be very difficult to differentiate between epileptic seizures and pseudoseizures (Table 8.16), and simultaneous video-EEG monitoring can be most helpful. A single routine EEG is not usually useful, because even if a spell is captured, it is likely to be obscured by muscle artifact. Diagnosis relies on prolonged monitoring and careful correlation of clinical and electrographic findings. To complicate the diagnostic evaluation, pseudoseizures and epileptic seizures often coexist in the same child.

Pseudoseizures are no less serious and disabling than epileptic seizures, in that they reflect major underlying psychopathology that necessitates proper diagnosis and treatment. As with many psychosomatic illnesses, pseudoseizures can arise because of unresolved psychological conflicts and anxiety that are converted into a physical symptom. In children with pseudoseizures, one must always be suspicious of physical or sexual abuse. As noted above, many children with pseudoseizures have epilepsy. Others may have witnessed a real seizure, either first-hand or in the media.

Pseudoseizures present with a variety of clinical forms. Many resemble generalized tonic–clonic seizures, although the two sides of the body are more likely to be jerking *out of phase* with each other. Pseudoseizures can also simulate complex partial, atonic, myoclonic, and even absence seizures. Sometimes the behavioral manifestations of the spell are a clue to its nonepileptic nature. For example, GTC activity in the setting of preserved consciousness favors a nonepileptic event. However, caution is warranted, as it is becoming increasingly apparent that some behaviors previously thought to be pseudoseizures are, in fact, epileptic events generated by brain areas distant from scalp EEG electrodes. For example, seizures arising from the frontal lobe may give rise to behavioral ictal manifestations that were formerly thought to be characteristic of pseudoseizures. Seizures originating in the supplementary area (SMA) of the frontal lobe involve bilateral motor activity with preserved consciousness. Compared with pseudoseizures, SMA seizures are briefer, more stereotyped, frequently occur during sleep, and initially manifest with arm abduction (fencer's pose). Seizures originating in the orbitofrontal region are now recognized to include nonspecific screaming, affective changes such as intense fear, bilateral nonrhythmic leg or arm movements, and even sexual automatisms such as pelvic thrusting. Such behaviors were previously considered to be the *sine qua non* of pseudoseizures. These observations underscore the difficulty of differentiating between epileptic seizures and pseudoseizures on clinical grounds.

A child with pseudoseizures must be approached with a great deal of sensitivity. It is usually best to avoid confronting the child directly with the diagnosis, and one's suspicions should be discussed with the family in a supportive fashion. Therapy must involve both the child and family and might include psychotherapy (occasionally requiring inpatient management), stress management strategies, relaxation techniques, or biofeedback. Management is best instituted with the assistance of a psychiatrist experienced in this field. The family members must be counseled to reduce

secondary gain engendered by the child's behavior. They should be assured that the symptom (pseudoseizure) is real but does not involve epileptic neuronal discharges, and that therapy is designed to address the underlying cause of the symptom. Pseudoseizures are a learned behavior, and the main therapeutic goal is to teach the child alternative coping skills, so that anxiety or psychological stress does not need to manifest in such a maladaptive fashion.

The psychopathology that causes a child to manifest pseudoseizures is varied and complex; it may simply be a reaction to death or illness in a family member or it may indicate subconscious repression of a serious insult such as physical or sexual abuse. There have been several methods described to induce or terminate a pseudoseizure, but interpretation of such procedures is difficult and produces many false-positive results. Therefore, provocative methods should be used with extreme caution if at all, ideally with concurrent EEG monitoring. Serum levels of prolactin, cortisol, and other substances have been reported to correlate with an epileptic seizure, thereby providing a way to differentiate epileptic seizures from pseudoseizures. In practice, interpretation of such levels is fraught with difficulty, and these are not routinely recommended in children for the diagnosis of pseudoseizures.

The outcome of pseudoseizures in children varies but may be more auspicious than in adults. In one study, 81% of children and adolescents were free of pseudoseizures 3 years after diagnosis, compared with only 40% of adults with pseudoseizures (Wyllie *et al.* 1991). Another group reported that all children with pseudoseizures resumed regular school attendance after treatment (Gudmundsson *et al.* 2001).

KEY CLINICAL QUESTIONS

- Was it an epileptic seizure?
  Differentiation of an epileptic seizure from a nonepileptic event is critical, and is based largely on obtaining a careful history of the event. An EEG may be helpful but can be normal in cases of epilepsy. A video-EEG also yields important information, but is most useful if spells are frequent. A home video recording of the event in question can also assist in the diagnosis.
- If so, what kind of seizure was it?
  The seizure semiology is important for classification and treatment choice.
- Does the seizure, in conjunction with other clinical information (e.g. age, EEG findings, family history, etiology) conform to an epilepsy syndrome?
  This information is crucial for discussion the treatment options and natural history of the epilepsy.
- What diagnostic workup is necessary and sufficient for a given patient?
  An efficient diagnostic evaluation should be tailored to the individual child, based on associated findings and potential for a treatable etiology.

Episodic dyscontrol (rage attacks)

Rage attacks are episodes of aggression and loss of control that are out of proportion to the precipitating event and the social context (Gordon 1999). They are common in school-aged children and adolescents, especially boys. Children often come to neurologic attention when the primary caregiver or psychiatrist becomes concerned that a child's temper tantrum is out of character with his or her usual personality. The attacks may appear suddenly and explosively and consist of uncontrolled behaviors such as hitting, kicking, biting, spitting, and throwing objects around the room. After an attack, the child may be completely or partially amnestic for the event or show signs of remorse. Some fatigue may follow an episode, but not usually the prolonged postictal confusional state that follows an epileptic seizure. Guidelines to differentiate rage attacks from epileptic seizures are provided in Table 8.15. Some children with complex partial seizures exhibit episodic dyscontrol interictally. Rage attacks often occur in children who are mildly impaired neurologically, including those with such conditions as autism, attention deficit disorder or following traumatic injury to the temporal or frontal lobe. Children who experience rage attacks sometimes respond to propanolol, carbamazepine, or selective serotonin reuptake inhibitors.

Spasmus nutans

Spasmus nutans is a condition usually seen in infants between 6 and 12 months of age. The child presents with a

Episodic Dyscontrol

PEARLS & PERILS

- Rage attacks are usually provoked, although the provocative stimulus may seem minor or trivial to the parent or other observer.
- In a rage attack, the violence is not random but goal-directed; violence during an epileptic seizure is usually very brief and not directed at a specific target.
- In rage attacks, the behavioral manifestations are varied and change with time. In an epileptic seizure, rhythmic or nonpurposeful behaviors are seen throughout the event.
- Rage attacks last minutes to hours, while seizures usually last seconds to minutes.
- The response to AEDs does not discriminate between the two conditions. A positive response may reflect a placebo effect, and some AEDs (especially carbamazepine and valproate) have antidepressant, calming actions independent of their antiepileptic mechanism.

triad of symptoms including nystagmus, torticollis, and most commonly, horizontal but at times vertical head movements. The congenital nystagmus can be pendular and mistaken for the nystagmus seen as a consequence of impaired vision. Impaired vision and lesions of the optic tract should be excluded before this diagnosis is made. The condition is often self-limited and disappears by 3–4 years of age.

Sandifer syndrome

Sandifer syndrome is an episodic movement disorder that may mimic tonic seizures. It is associated with tilting or lateral flexion of the head and associated extension of the neck; limbs are rarely involved. Spells usually occur with feeding, and are due to gastroesophageal reflux with or without an associated hiatal hernia.

Night terrors

Night terrors (pavor nocturnas) are a common parasomnia that are often confused with seizures. Night terrors occur in children from about 18 months to 8 years of age, with a peak around 4–5 years of age. They occur in the early stages of sleep (non-REM, stages 3 and 4). The child will awaken with inconsolable, frantic screaming, sweating and other signs of sympathetic activation, and flailing of all extremities in a nonrhythmic fashion for several minutes, then fall back to sleep without memory of the episode in the morning. There is often a family history of night terrors. The diagnosis is a clinical one; video-EEG recording is rarely needed. The main differential diagnosis is nightmares (which occur out of REM sleep) and nocturnal epileptic seizures such as frontal lobe seizures. The only treatment is reassurance.

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Although somewhat dated with regard to syndromes and new AEDs, this book contains superb introductory chapters on the basics of EEG and on pharmacokinetic principles.

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This comprehensive book is an invaluable resource for physicians treating children with epilepsy.

CONSIDER CONSULTATION WHEN...

- Initial anticonvulsants do not control seizures.
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- Seizures are associated with regression in language, cognition, or motor function.
- Seizures are associated with a focal neurologic deficit.

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CHAPTER 9

Movement Disorders in Childhood

Kenneth J. Mack, MD, PhD and Steven M. Shapiro, MD

OUTLINE

Description of movements
Evaluation of the child
Ancillary testing
Functional anatomy of the extrapyramidal section
Chorea and athetosis
Dystonia
Tremor
Tics
Myoclonus
Paroxysmal movement disorders
Ataxia

Description of movements

Abnormal movements in children are typically classified as chorea, hemiballismus, athetosis, dystonia, tremors, tics, myoclonus or ataxia. The word *chorea* has been derived from the Greek word for "dance," and originally referred to the epidemic dancing manias of the Middle Ages (Hallett 1993). Choreic movements are single, quick, isolated muscle movements that result in uncoordinated jerks of the face, trunk, or extremities. Patients at times may attempt to conceal abnormal movements that occur distally by converting a sudden purposeless movement of the upper extremity into a purposeful act, such as pretending to straighten a tie. Often choreic movements occur in combination with athetosis, in which case the term *choreoathetosis* is used.

Hemiballismus is characterized by large amplitude, wild, and irregular limb movements. This movement often occurs after an infarct of the subthalamic nucleus opposite the side of the movements. Often the movements will fade into chorea after a period of days (Hallett 1993).

Athetosis is characterized by slow, sinuous, writhing, and purposeless involuntary movements, which may flow into one another. The wrists are usually held in a flexed position, and the fingers, the shoulders, and much of the lower extremities are held in extension. Athetotic movements are exaggerated by voluntary activity and are not noted during sleep.

Dystonia refers to an abnormal maintenance of a posture, a result of sustained muscle contraction. This abnormal tone may last for seconds to minutes in an affected muscle group. Patients with torsion dystonia (dystonia musculorum deformans) display contortions of the trunk and pelvic and shoulder girdles.

A recent consensus agreement workshop defined terms used to describe the clinical features of hypertonia (Sanger *et al*. 2003). *Dystonia* was defined as hypertonia in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both (Sanger *et al*. 2003).

Spasticity was defined as hypertonia in which resistance to externally imposed movement increases with increasing speed of stretch, varies with the direction of joint movement, and/or rises rapidly above a threshold speed or joint angle (Sanger *et al*. 2003).

Rigidity was defined as hypertonia in which resistance to externally imposed joint movement is present at very low speeds of movement, does not depend on imposed speed, and does not exhibit a speed or angle threshold. With rigidity, simultaneous co-contraction of agonists and antagonists may occur and manifest as an immediate resistance to a reversal of the direction of movement about a joint. In contrast to dystonia, the limb does not return toward a particular fixed posture or extreme joint angle; and voluntary activity in distant muscle groups does not lead to involuntary movements about the rigid joints, although rigidity may worsen (Sanger *et al*. 2003).

Tics are brief, involuntary contractions of a muscle or muscle group. Children with Tourette syndrome have multiple tics, including vocal tics (throat clearing), shoulder shrugging, and grimacing. More often, however, tics are localized to the face and shoulder.

Tremors are involuntary, rhythmic, oscillatory movements caused by the alternate contractions of agonist and antagonist muscles. Typically, these movements oscillate around a fixed point. Intention tremor refers to the decomposition of movement that occurs during motion, such as finger-to-nose testing. In contrast, the static tremor of adult Parkinson's disease occurs during rest.

Ataxia refers to a poor coordination of motor function. When a child with cerebellar disease is asked to touch his or her nose with the tip of an index finger, the movement is performed in an unsteady, halting manner. Ataxic movements may occur in the extremities (appendicular) and/or in the axial musculature (truncal).

Although multiple terms are used to describe abnormal movements, we think of these abnormal movements as flowing along a continuum, rather than as discrete entities. A dystonic child will exhibit an abnormal maintenance of posture in space. Dystonia may flow into the slow, writhing, snake-like movements of athetosis. Chorea is described as sudden jerk-like movements, but many of the disorders described in this chapter appear as a "chorea-athetosis" or "choreoathetosis." In the most severe form of jump-like movements, ballismus (or more typically, hemiballismus), the movements will be strong enough to knock a child off a chair. Many abnormal movements do not readily fit into a single descriptive category. Hence, it may be more informative to describe the actual movements, than to attempt to label the movements.

While these classifications are descriptively useful, some diseases are manifested by multiple movement abnormalities. For instance, patients with ataxia-telangiectasia may have both ataxic and choreiform movements. Wilson's disease patients may exhibit tremor, dystonia and/or rigidity. Similarly, patients with juvenile Parkinsonism may have dystonia, tremor, bradykinesia, and rigidity.

Evaluation of the child

In the evaluation of a child with abnormal movements, the history and physical exam will be the most important factor in making the diagnosis. Historically, it is useful to determine whether the movements represent an acute or a slowly progressive process. Sudden onset of movements suggests some recent insult to the brain. Did the child recently have varicella (as in post-infectious varicella ataxia) or a streptococcal infection (as in Sydenham's chorea)? Do certain activities trigger the movements, as in a paroxysmal movement disorder? Are there co-morbid features, such as symptoms of attentional problems or obsessive-compulsive traits, as in tic disorders?

The past medical history and review of systems can be most helpful. A history of liver disease certainly raises concern about Wilson's disease, although neurological symptoms usually present later in life, they may present before liver abnormalities are identified. Huntington's disease in childhood may first present as a difficult to control seizure disorder. A history of significant jaundice may suggest a bilirubin encephalopathy. Patients with ataxia-telangiectasia are subject to frequent sino-pulmonary infections.

A thorough family history is often crucial in making the diagnosis. Some movement disorders are inherited as a simple recessive or autosomal dominant trait. However, in other disorders the genetics are more complex. Huntington's disease shows anticipation in succeeding generations, so that newer generations may be symptomatic earlier and have a more severe course than their parents. The genetics of Tourette syndrome are poorly understood, although parents and siblings may show a subset of comorbid symptoms (attention deficit disorder, obsessive compulsive symptoms, or tics) and the tics may be inherited as an autosomal dominant trait with variable penetrance.

KEY CLINICAL QUESTIONS

- Describe the movements that your child is experiencing?
- Did the symptoms come on suddenly, or slowly progress over time?
- Does anyone else in the family have similar movements?
- What other symptoms has your child experienced?

A complete physical exam is often the most cost-effective diagnostic study and the most significant segment of the evaluation of a child with a movement disorder. Some diseases have notable changes on the general exam, such as the bulbar conjunctival telangiectasias in ataxia-telangiectasia. The mental status exam will be of note in several disorders. Because of the behavioral, cognitive and personality alterations that may occur in Huntington's or Wilson's disease, patients may be misdiagnosed with a psychiatric disorder. Patients with Sydenham's chorea often display an emotional lability. In the opsoclonus-myoclonus syndrome, severe random chaotic eye movements will be noted. Ataxia is noted by observing the incoordination of the eye movements (nystagmus), trunk (titubation) and extremities (decomposition of movements during finger to nose testing). Many choreoathetotic movement disorders have an associated hypotonia. In choreoathetotic disorders, it is helpful to have the patients try to rest their hands on their legs. Often the patient is unable to maintain this position, eliciting the movements. Alternatively, the patient can stand with their hands outstretched and eyes closed, in which case quick jerking movements of the fingers may be noted. Some abnormal movements in the affected extremity appear following a hemiplegia, in which case weakness can also be detected. Reflexes are diminished or absent in several disorders, such as ataxia-telangiectasia. In the choreas, reflexes are often described as being "hung up." This has the appearance of a prolonged contraction in a muscle whose tendon has been tapped with a reflex hammer. Gait is a critical part of the exam. Parkinson patients will show a slow, shuffling gait. Hereditary dystonic disorders often show tonic posturing of the feet, often brought out by walking.

During the exam, it is more useful to see the abnormal movements than to rely on the patient's or another individual's labeling of these movements. When the movements are complex, it is often useful to describe the dyskinesia, rather than trying to force the movement into a descriptive catego-

ry. The accessibility of camcorders has made photographic documentation of the severity, duration, and frequency of the movements more readily available for later study. This is particularly useful for movements that are not readily observed in the office, and parents can often bring in a videotape of a movement disorder that occurs infrequently.

Ancillary testing

The history and physical exam should direct which ancillary tests should be ordered. Not every patient with a movement disorder needs all or any of the following tests. Some of the diseases that manifest movement disorders have specifically defined pathophysiology and are described in other chapters of this book. Ataxia-telangiectasia, Wilson's disease, thyroid dysfunction and other conditions are discussed elsewhere, and the reader should also consider these sources of information.

Oftentimes it is useful to ask if there is a structural abnormality predisposing the child to the movement disorder. This is particularly true in an acute onset disorder, in the choreoathetoses, or in the dystonias. Magnetic resonance imaging (MRI) is the most helpful test, and characteristic MRI abnormalities have been noted in Huntington's (caudate atrophy), Sydenham's (increased T2 signal in the basal ganglia) and neurodegeneration with brain iron accumulation (NBIA; "eye-of-the-tiger" MRI abnormality secondary to iron deposition in the basal ganglia). The MRI findings in kernicterus (bilateral globus pallidus lesions with or without lesions in the subthalamic nuclei) can distinguish it from hypoxic-ischemic encephalopathy.

The EEG can sometimes be abnormal, although EEG abnormalities in these disorders tend to be nonspecific, and therefore of limited use in making an etiologic diagnosis. The EEG is of most benefit when trying to differentiate abnormal movements from seizure activity. Video-EEG documentation of the abnormal movements is often helpful.

Blood tests can help confirm a diagnosis. ASO titers for Sydenham's, ceruloplasmin for Wilson's, IgA levels for ataxia-telangiectasia, and thyroid studies to rule out thyroid abnormalities are easily performed. Specific genetic testing is now available for many genetic disorders, such as Huntington's disease, although counseling must be done before the test is performed. In some of the intermittent ataxia syndromes, measurement of serum amino acids, short chain fatty acids, and urine organic acids may detect some forms of metabolic causes.

Nerve conduction studies have not been useful in identifying specific abnormalities associated with these diseases except for ataxia. Some forms of ataxia are associated with peripheral neuropathies, and nerve conduction studies may be of help in delineating the etiology.

Functional anatomy of the extrapyramidal system

The extrapyramidal system plays an important role in the control and execution of motor movements. It consists of the basal ganglia, thalamus, subthalamic nuclei, substantia nigra, red nuclei, and brainstem reticular formation. The basal ganglia are composed of the corpus striatum and the amygdaloid nuclear complex. The amygdala is not involved in movement and is not usually considered as part of the extrapyramidal system. The term *corpus striatum* refers to caudate, putamen, and globus pallidus. *Neostriatum,* or just *striatum,* refers to the caudate and putamen; *palladium* refers to globus pallidus. *Lenticular nucleus,* a descriptive term, refers to the combination of the putamen and globus pallidus. The neostriatum and palladium are phylogenetically, cytologically, and functionally distinct. The neostriatum receives fibers from the cerebral cortex, the intralaminar nuclei of the thalamus nuclei, the substantia nigra, and the globus pallidus, and it sends fibers to the substantia nigra and globus pallidus (Fig. 9.1).

The extrapyramidal system can be thought of as a complex series of interconnected feedback loops that ultimately, through modulation of the direct corticospinal pyramidal pathways, influence movement. One example is a loop that connects cerebral cortex to striatum to globus pallidus to

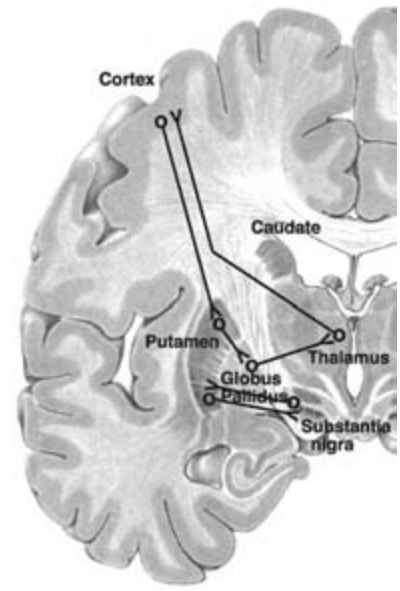

Fig. 9.1 A coronal brain section showing some of the connections involving the basal ganglia. From *Color Atlas of the Brain and Spinal Cord* by Marjorie A. England and Jennifer Wakely.

thalamus and back to cerebral cortex; another loops from striatum to substantia nigra and back again to striatum.

Striatal neurons discharge prior to the onset of movement, suggesting that the basal ganglia participate in the initiation of movement. The extrapyramidal system also participates in control of ongoing movement, posture, and automatic and skilled volitional movement.

A functional equilibrium exists between the excitatory acetylcholine and the inhibitory dopamine systems of the extrapyramidal system. The reduction of dopamine in the striatum and substantia nigra in Parkinson's disease, and a relative increase in the cholinergic neurotransmitter system, are associated with akinesia or bradykinesia. The functional equilibrium between the acetylcholine and dopaminergic systems is paralleled by pharmacotherapeutic effects on symptoms. Parkinsonian symptoms respond favorably to dopaminergic or anticholinergic drugs; an excess of these agents produces chorea and other hyperkinesias. The chorea of Huntington's disease is exacerbated by L-dopa, and treated with cholinergic agonists, or dopamine receptor blockers.

To understand the anatomy of these abnormal movements, one may think of two classes of movement disorders, *hyperkinetic* and *hypokinetic*. The *hyperkinetic* disorders, e.g. tics, chorea, athetosis, and ballismus, are characterized by an excess of movement, with uncontrollable and relatively rapid motor acts intruding into the normal flow of motor activity (Albin *et al*. 1989, for review). In addition to shared anatomy, some of these movements will share a common pharmacology. These abnormal movements tend to be exacerbated by dopamine agonists (e.g. methylphenidate) and attenuated by dopamine antagonists (e.g. haloperidol).

The most clearly understood anatomical substrate of a movement disorder is for ballismus. Ballismus, characterized by violent, flinging motions of the extremities, is usually seen after an infarction or damage to the subthalamic nucleus of Luys (see Fig. 9.1).

Choreoathetosis is seen in a variety of neurological diseases. Because of the association of Huntington's disease with abnormalities in the striatum (i.e. the caudate and putamen), choreoathetosis has been assumed to be caused by a striatal lesion. However, traumatic, ischemic, or ablative lesions of the striatum in humans infrequently produce choreoathetosis. In Huntington's disease, the degeneration of GABA and cholinergic striatal neurons with relatively preserved dopaminergic function, is associated with chorea.

Tics, a third category in this hyperkinetic movement disorder group, have not been consistently associated with specific neuropathological lesions of the basal ganglia.

In contrast, hypokinetic movement disorders are characterized by akinesia (lack of movement), bradykinesia (slow movement), and/or rigidity. Parkinson's disease is the best understood movement disorder. Parkinson's disease results from impaired dopaminergic transmission from the substantia nigra (in the midbrain) to the striatum. This may be caused either pharmacologically (e.g. by phenothiazines), by toxin exposure (e.g. MPTP), or by cell loss in the region of the substantia nigra. Pharmacologically, Parkinson's disease is the inverse of hyperkinetic movement disorders in that dopaminergic agonists (and cholinergic antagonists) will relieve symptoms, whereas dopaminergic antagonists (and cholinergic agonists) will exacerbate symptoms.

Dystonia occurs when the patient spontaneously and uncontrollably assumes an unusual, fixed posture that lasts from seconds to minutes. Radiographic studies of patients with hemidystonia, in whom symptoms are confined to one side of the body, have implicated the putamen, globus pallidus, or the thalamic target regions of the globus pallidus (Marsden *et al*. 1985).

Chorea and athetosis

As mentioned above, this group of disorders presents with quick, jerk-like movements (chorea) that can at times seem to flow into the writhing snake-like movements of athetosis. Some of these disorders have dystonic movements as well. Ataxia-telangiectasia (AT; discussed later in this chapter) should be in the differential diagnosis of an individual with chorea, since the choreoathetoid movements of AT are as prominent as the ataxia. Some of the more frequent disorders seen in children with choreoathetosis are described below.

Sydenham's chorea

> The child with Sydenham's chorea is punished three times before a diagnosis is made: Once for general fidgetiness, once for breaking crockery, and once for making faces at his grandmother. The unending profusion of quick purpose-like little movements, appearing at random mainly in distal segments and disfiguring the facies of childhood by a series of smirks or frowns, is pathognomonic.
>
> (Wilson & Bruce 1955)

Sydenham's chorea (St Vitus' dance) was first described by Sydenham in 1684. It was recognized as the major neurological manifestation of rheumatic fever a century later. St Vitus was originally designated as "protector" of the faithful from the dancing manias of the middle ages. St Vitus later lost his protector status as his name became synonymous with the chorea of acute rheumatic disease (Park & Park 1990). Rheumatic fever, an inflammatory disease that may affect heart, joint, central nervous system, and subcutaneous tissue, follows a group A β-hemolytic streptococcal pharyngitis. The chorea is characterized by quick, uncoordinated motions (often occurring unilaterally), while the athetosis

is writhing in nature. Hypotonia and emotional lability are also characteristics of this disorder. The symptoms are often short-lived (typically regress over a period of weeks to months), but can be quite debilitating.

The pathology of Sydenham's chorea involves the caudate and subthalamic nuclei, cerebral cortex, trigeminal nerve, geniculate ganglion, and medullary hypoglossal nucleus. Arteritis of small meningeal and cortical vessels, embolism, and rarely, meningoencephalitis with perivascular and diffuse round cell infiltration of gray and white matter may occur.

There is experimental evidence that Sydenham's chorea is due to an autoimmune response. Serum immunoglobulins from patients with Sydenham's chorea binds to caudate and subthalamus brain tissue in direct proportion to the clinical severity of the chorea (Husby *et al.* 1976; Swedo 1994). There is cross-reactivity between these central nervous system tissues and the bacteria, because serum-binding activity can be abolished by preabsorption with group A streptococcal membranes. Antibasal ganglia autoantibodies that cross-react with streptococcal, caudate, and subthalamic nuclei antigens can be identified by Western immunoblotting and immunofluorescence in both acute and persistent Sydenham's chorea (Church *et al*. 2002). Recent evidence of increased cytokines and interleukins suggest that cell-mediated mechanisms may also be involved (Church & Dale *et al*. 2003; Teixeira *et al*. 2004).

Functional overactivity of the dopaminergic system in Sydenham's chorea is suggested by several observations: (1) the finding of increased homovanillic acid (a dopamine metabolite) in cerebrospinal fluid (Naidu & Narasimhachari 1980); (2) patients have an increased reaction to dopamine-active drugs (Nausieda *et al.* 1983); and (3) drugs that release dopamine or sensitize postsynaptic dopamine receptors (e.g. amphetamines, L-dopa, decongestants, phenytoin, thyroid hormones) increase chorea; drugs that block dopamine receptors (e.g. haloperidol) decrease chorea.

Recent reports have suggested that a broader spectrum of poststreptococcal hyperkinetic movement disorders exists and includes tics, dystonia and myoclonus, in association with behavioural sequelae, particularly emotional disorders such as obsessive-compulsive disorder, anxiety and depression (Hartley *et al*. 2002).

MRI studies have been inconsistent and may be normal or may show increased signal intensity on T2-weighted images in the basal ganglia or cerebral white matter after symptoms appear (Robertson & Smith 2002; Kienzle *et al.* 1991). Signal abnormalities may occur contralateral to the affected extremities in children with hemichorea, and gradually resolve after the movements cease.

The onset of Sydenham's chorea is usually subtle, beginning with clumsiness, restlessness, fidgetiness, and fatigue. The abnormal movements begin in the face. Unlike Huntington's disease, Sydenham's chorea affects the upper extremities more than the lower extremities, and the distal muscles are more affected than the proximal. Speech is dysarthric and patients may even become mute. Onset occurs between 5 and 15 years of age and the sex ratio is about 50:50 until puberty, when females become affected twice as often as males. There may be a positive family history for rheumatic fever. The chorea can lag behind the etiologic streptococcal infection by 1–6 months; so antistreptococcal titers may be negative (Ayoub & Wannamaker 1966).

The physical signs associated with Sydenham's chorea are summarized in Table 9.1.

Chorea is most often generalized, but one out of five patients has hemichorea (Nausieda *et al.* 1980). Hemiparesis, seizures, or EEG abnormalities may occur rarely. Psychological disturbances may occur before, during, or after the onset of the illness. These manifestations include emotional lability, nightmares, poor attention span, and obsessive-compulsive symptoms (Swedo 1994).

The natural history of the disorder is that one-quarter to one-third of patients who present with chorea, but no other signs of rheumatic fever, will eventually develop rheumatic heart disease. If other manifestations of rheumatic fever occur at any time, the risk of heart disease is greatly increased (Aron *et al.* 1965).

The course of the disease is *subacute.* Often chorea and associated findings disappear by 1 month, and invariably are gone by 2 years. About 20% of patients develop a second episode of chorea, usually within 2 years of the first attack (Nausieda *et al.* 1983).

Uncomplicated Sydenham's chorea is usually a benign self-limited disorder of the central nervous system, though minimal neurological sequelae may remain. Mild motor abnormalities, such as choreiform movements, hypotonia, intention tremor, and impaired fine and gross motor abili-

TABLE 9.1 Physical Signs Associated with Syndenham's Chorea

Sign	Explanation
Milkmaid's grip	Inability to maintain a sustained handgrip contraction
Darting tongue	Inability to maintain tongue protrusion
Pronator sign	External rotation of the hands when arms are held over head
Choreic hand	So-called dishing hand or spoon hand
"Hung up" deep tendon reflexes	Evoked choreic movement when deep tendon reflexes (e.g. knee jerk) are elicited, resulting in a slow return to original position
Pendular knee jerks	Antagonist hypotonia
Diffuse hypotonia	Floppy muscular tone
Abnormal speech	Indistinct, jerky, explosive, and irregular speech

ties, have been found 20 years after the initial episode (Bird *et al.* 1976; Nausieda *et al.* 1983). Psychiatric symptoms are more frequent in patients evaluated two or three decades after the onset of Sydenham's chorea (Freeman *et al.* 1965).

Commonly prescribed drugs – such as phenytoin, female sex hormones and thyroid hormones (which sensitize postsynaptic striatal dopamine receptors), decongestants (sympathomimetic or anticholinergic), and *d*-amphetamine – may induce chorea at low doses in patients with a previous history of Sydenham's chorea. Nausieda *et al*. (1983) found dopaminergic hypersensitivity (adverse choreic reactions to these drugs) in about half of patients who had had Sydenham's chorea an average of 22 years earlier. These patients also had elevations in their Minnesota Multiphasic Personality Inventory scores, indicative of a potential for psychotic thought processes. These findings are consistent with the notion of chronic hypersensitivity of the dopaminergic system with effects on both motor and mental function in some patients following episodes of Sydenham's chorea.

Treatments for Sydenham's chorea have included bed rest, diazepam, haloperidol, carbamazepine, valproate, baclofen, and steroids, but their efficacy has not been well established. Many of these medications may be more useful in attenuating the chorea, and are less successful in dealing with the psychological symptoms. Currently, a randomized trial of plasmapharesis, intravenous immunoglobulins, and prednisone is being conducted at the NIH (Swedo 1994). Because of the high incidence of associated serious heart disease, penicillin or other antibiotic prophylaxis is indicated until at least adulthood, and during childbearing years (Table 9.2).

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Table 9.2 Sydenham's Chorea

Discriminating feature

1. Chorea

Consistent features

1. Generalized chorea
2. Subacute in onset
3. Usually chorea disappears by 2 months

Variable features

1. Insidious onset
2. Distal more affected than proximal
3. Hemichorea
4. Mental and emotional disturbances
5. Recurrence within 2 years in 20% of cases

Huntington's disease

Huntington's disease is an autosomal dominantly inherited, neurodegenerative disease. Huntington's disease is the result of a trinucleotide (CAG) expansion in the gene IT15 on chromosome 4 (4p16.3) (Huntington's Disease Collaborative Research Group 1993), which encodes a protein known as huntingtin, found throughout the brain. Individuals with the disease generally have >39 repeats, normal being 20. Repeats >80 are often associated with the juvenile form. Complete (100%) penetrance has been described with CAG repeats ≥42, while only some with CAG repeat lengths of 36–41 showed signs or symptoms within a normal lifespan (Brinkman & Mezei *et al*. 1997).

The CAG expansion occurs during meiosis, so that children will tend to have a larger expansion (and therefore worse disease) than their parents. The size of the expanded CAG repeat is inversely associated with the age of onset of the disease (Brinkman & Mezei *et al*. 1997). However, only 70% of the variation in the onset of Huntington disease is accounted for by repeat size (Djousse & Knowlton *et al*. 2003; Li & Hayden *et al*. 2003). Recent evidence is that the unexplained variation is strongly heritable, suggesting that several other genes modify the age of onset (Li & Hayden *et al*. 2003).

The tendency of CAG repeats to expand from generation to generation underlies "genetic anticipation," a worsening of the disease in subsequent generations, and paternally derived CAG repeats seem more unstable (Ranen & Stine *et al*. 1995).

The juvenile form is more likely to be inherited from the father. Juvenile-onset Huntington's disease, with onset at or before 10 years of age, accounts for about 5% of reported cases (Jervis 1963; Osborne *et al.* 1982). The onset, presentation, and course of Huntington's disease differ in juveniles and adults.

Adult-onset Huntington's disease may present as (1) abnormal movements, especially chorea, (2) intellectual decline and dementia, (3) emotional instability, or (4) some combination of the foregoing. The course is slowly progressive, and unaffected by current treatment. Juvenile-onset Huntington's disease most often presents with rigidity (the Westphal variant), speech defects, intellectual abnormalities, chorea or choreoathetosis, and tremor (Markham & Knox 1965; Hansotia *et al.* 1968). Cerebellar signs and seizures are also frequent. In contrast to patients with adult-onset Huntington's disease, seizures occur in up to 50% of children; the seizures are either grand mal or grand mal in combination with absence, myoclonic, astatic, or photosensitive seizures. The juvenile-onset disease progresses about twice as rapidly as the adult-onset version, with an average duration of 9.3 years (Osborne *et al.* 1982). Table 9.3 presents a comparison of juvenile- and adult-onset Huntington's disease.

TABLE 9.3

Comparison of Juvenile and Adult-Onset Huntington's Disease

Symptoms of juvenile-onset	Symptoms of adult-onset
Rigidity	Chorea
Speech disorder	Dementia
Behavioral abnormality	Emotional effects
Seizures	
Cerebellar signs	
Inheritance from father in 90%	Inheritance from mother in 55–70%

The pathologic findings include atrophy of the corpus striatum and, in contrast to adult-onset cases, severe gliosis of the globus pallidus and cerebellar atrophy. Involvement of the vestibular nuclei and the lateral corticospinal tracts has also been described. The damage to the globus pallidus has been proposed to be responsible for the prominence of rigidity in children (Byers & Dodge 1967).

Clinical diagnosis can be difficult in the absence of a family history. However, if suspected, DNA testing is now available (see below) and diagnosis is made by analysis of the number of trinucleotide repeats in a patient's IT15 gene. CT scan and MRI may show atrophy of the caudate nuclei, which often precedes clinical symptoms (Terrence *et al.* 1977; Sax & Menzer 1977). In mild Huntington disease, atrophy of putamen may be detected before obvious changes in the caudate (Harris & Pearlson *et al*. 1992), especially in children (Harris & Codori *et al*. 1999). In early to midstages, morphometric MRI studies show volume reduction in almost all brain structures, including total cerebrum, total white matter, cerebral cortex, caudate, putamen, globus pallidus, amygdala, hippocampus, brainstem, and cerebellum (Rosas & Koroshetz *et al*. 2003). In children, cerebellar atrophy may be seen. Positron emission tomographic scans show decreased glucose use in the caudate and putamen, which appears even earlier than the tissue loss demonstrable by CT (Kuhl *et al.* 1982; Antonini & Leenders *et al*. 1996).

Genetic testing is now available through direct mutation analysis using polymerase chain reaction (PCR) testing to estimate the number of CAG repeats in the IT15 gene. Children under the age of 18 years are generally not tested unless symptomatic.

Concern has been raised regarding the potentially damaging psychological effects of presymptomatic testing for this devastating disease. However, studies show that 75–80% of people at risk for Huntington's disease wish to know this information in order to cope, plan, and prepare for the future (Koller & Davenport 1984). Specific guidelines are available for the testing of patients at risk (Hersch *et al.* 1994).

Management consists of symptomatic treatment and genetic counseling. The chorea may respond to such dopamine receptor blockers as haloperidol, dopamine depletors, e.g. reserpine or tetrabenazine, or benzodiazepines. Medical management of comorbidities such as depression, anxiety or obsessive-compulsive disorder, and supportive management by members of a multidisciplinary team may be helpful.

Benign familial chorea

The condition of benign familial chorea was initially described in 1967 by Haerer *et al*. Several authors have stated that more cases of benign familial chorea exist than have been reported, so that it is difficult to estimate the prevalence of this syndrome (Chun *et al.* 1973; Sleigh & Lindenbaum 1981). The syndrome is characterized by the early onset of nonprogressive chorea and is unassociated with intellectual deterioration. Lack of progression of the chorea, and the absence of dementia distinguishes it from Huntington's disease. However, a recent case report of an abnormal IT15 gene in a family of "benign hereditary chorea" points out the diagnostic difficulty (MacMillan *et al.* 1993) in distinguishing between Huntington's and benign hereditary chorea. The persistence of involuntary movements for many years distinguishes this condition from Sydenham's chorea. A history of familial occurrence makes the diagnosis of a choreic form of cerebral palsy unlikely.

The abnormal movements usually have their onset early, during infancy or childhood, and are often first noted when the child begins to walk. The gait of children with the syndrome is noticeably more lurching and halting than that of other children learning to walk. The abnormal movements persist throughout adulthood, and after the initial presentation show little or no progression. On reaching middle age, some individuals use walking implements such as canes for greater gait stability. The severity of the choreic movements varies from mild jerking of the extremities to gross sudden jerks that interfere with ambulation and writing. Movements persist during the waking hours and invariably cease during sleep. As with other individuals with movement disorders, the chorea is aggravated by tension and anxiety. Some patients suffer varying degrees of dysarthria, the severity of which may be related to the extent of the chorea. The involuntary movements impair smooth air production during speech.

Affected children are often delayed in walking, and may present to a physician for evaluation of delayed motor milestones (Wheeler *et al.* 1993). Cognitive and academic skills may be impaired; however, progressive dementia is not a feature of this disorder. One kindred was assessed for intellectual function; affected members were noted to have lower verbal intelligence and greater deficits in verbal abstract concept formation than unaffected family members (Leli *et al.* 1984). Some affected children have significant difficulty in learning to write legibly due to the severity of the involuntary movements.

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Disorders Presenting with Chorea, Athetosis, or Both

- Persistence of choreic movements over a 6-month period is uncommon in Sydenham's chorea.
- In the assessment of a child who presents with chorea, a positive family history distinguishes Huntington's and benign familial chorea from Sydenham's chorea.
- MRI, metabolic studies and drug screening tests should be considered in all children with a new acute-onset movement disorder.

Virtually all of the reported pedigrees suggest autosomal dominant inheritance. It has been suggested that penetrance of the gene is nearly 100% in males, but only 75% in females (Harper 1978). Genetic probes have excluded the Huntington's locus as the gene for benign hereditary chorea (Quarrell *et al.* 1988). Obligate but unaffected carriers will transmit the syndrome. Examination of antecedents is important to assess accurately the inheritance pattern. There have been no complete neuropathologic studies reported.

No medication has been consistently effective in relieving the abnormal movements of these patients. It was discovered serendipitously that the movements were lessened by steroids in one instance (Robinson & Thornett 1985). Some of our patients felt better while on short-term courses of haloperidol or other dopamine receptor blockers. Genetic counseling, occupational and speech therapy, and educational guidance are important management measures (Table 9.4).

Kernicterus a.k.a. bilirubin encephalopathy

Bilirubin encephalopathy is caused when brain tissue is exposed to toxic levels of free (unbound) unconjugated bilirubin. The clinical features of bilirubin encephalopathy range from severe to mild. The severity of bilirubin encephalopathy depends on the amount and duration of bilirubin exposure, the maturational state of the exposed brain, and factors that favor the net transfer of bilirubin into brain tissue, such acidosis and hypoalbuminemia.

Autopsies of infants with severe bilirubin toxicity reveal the pathologic syndrome of kernicterus with bright yellow staining of fresh brain tissue, and neuronal necrosis of the basal ganglia, hippocampus, and brainstem nuclei, including oculomotor, cochlear, and inferior colliculi (Gerrard 1952; Malamud 1961). One large and often cited series (Haymaker & Margles *et al*. 1961) included many patients with hypoxia-ischemia and other neonatal conditions, and the pathology ascribed to hyperbilirubinemia in that study is excessively broad.

Kernicterus is mistakenly believed to be a disease of the past, owing to the decline of its best-known cause, Rh disease of the newborn. However, the prevalence of kernicterus in newborns with other conditions (e.g. prematurity, low birth weight, and associated conditions) is a continuing concern (Gartner *et al.* 1970), particularly in the preterm population. Recent reports of kernicterus in term and near-term infants due in part to early discharge of newborns from hospitals (Brown & Johnson 1996; 2001; Johnson & Bhutani *et al*. 2002; Braveman *et al*. 1995; Seidman & Stevenson *et al*. 1995; Maisels & Newman 1998) have prompted new warnings to hospitals in the United States and a new Practice Parameter on Hyperbilirbinemia from the American Academy of Pediatrics (2004).

Kernicterus in current usage refers to both the clinical as well as the neuropathological syndrome. The clinical symptoms of bilirubin toxicity can be classified into acute and chronic bilirubin encephalopathy. Acute bilirubin encephalopathy in a neonate initially manifests with lethargy, decreased feeding, poor suck, and may include variable abnormal tone (hypotonia and/or hypertonia). As toxicity evolves, high-pitched cry, the "setting sun" sign, hypertonia, retrocollis and opisthotonos occur and may progress to fever, seizures, and death.

Laboratory evidence ranges from prolonged brainstem auditory evoked potential (BAEP) interwave intervals I–III and I–V and decreased amplitude waves III and V, to absent BAEPs, which may improve with exchange transfusion (Wennberg *et al*. 1982; Nwaesei *et al*. 1984). Giant cochlear microphonic responses, present with stimulation at high intensity, must not be confused with true BAEP responses (Berlin *et al*. 1998). The MRI shows acute abnormalities in the globus pallidus and subthalamic nucleus (Penn *et al*. 1994; Johnston & Hoon 2000; Govaert *et al*. 2003).

After the first year of life, infants who survive significant bilirubin toxicity gradually develop the syndrome of chronic postkernicteric bilirubin encephalopathy.

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Table 9.4 Benign Familial Chorea

Discriminating features

1. Nonprogressive chorea
2. No intellectual deterioration or dementia
3. Persistence of involuntary movements for many years

Consistent features

1. Family history; autosomal dominant
2. Early onset
3. Lurching walk

Variable features

1. Dysarthria
2. Mildly impaired cognitive skills

Classic kernicterus or chronic bilirubin encephalopathy is characterized by (1) a movement disorder consisting mainly of dystonia and/or athetosis, but also including spasticity and hypotonia, (2) auditory dysfunction consisting of deafness or hearing loss and auditory neuropathy or dys-synchrony, (3) oculomotor impairments especially impairment of upgaze, but also of lateral gaze including strabismus (impaired upgaze of kernicterus may be difficult to appreciate clinically and may improve with age), and (4) dental enamel hypoplasia of the deciduous teeth. The extrapyramidal abnormalities are the most striking feature of this syndrome, occurring in over 90% of patients with severe neonatal jaundice (Perlstein 1960). Athetosis is the principal manifestation, involving all limbs but usually with the upper limbs affected more than the lower. Abnormal swallowing, phonation, and facial movements are also present, and chorea, ballismus, dystonia, and less often, tremor or rigidity may occur. In some cases, the extrapyramidal abnormalities may be apparent only during attempted skilled movements. These neurological findings correspond to neuropathological lesions in (1) basal ganglia, specifically the globus pallidus, subthalamic nucleus, cerebellum and brainstem nuclei involved with truncal tone and posture, (2) auditory brainstem nuclei and perhaps the auditory nerve, (3) brainstem oculomotor nuclei.

In the "athetoid" cerebral palsy due to kernicterus, the dystonia does not usually lead to fixed postures and contractions, and sparing of cortex and subcortical white matter tracts usually results in normal intelligence. However, specific learning disorders, abnormal sensory or sensorimotor integration may occur from involvement of auditory pathways and proposed sensorimotor integration areas of globus pallidus integration may occur from involvement of auditory pathways (Boecker *et al*. 1999). In severe cases, individuals may appear severely mentally retarded but in fact may have normal or superior intelligence.

The auditory system is the neural system that is most sensitive to clinically overt bilirubin injury (Connolly & Volpe 1990); it can be assessed electrophysiologically with brainstem auditory evoked potentials in infants and children too young for reliable behavioral assessment. Auditory disturbances consist of bilateral high-frequency sensorineural loss with recruitment that is often severe, as well as central auditory disturbances, e.g. auditory agnosia, and "deafness" to normal pure tone audiograms (Matkin & Carhart 1966). The auditory disturbances correlate with lesions of the cochlear nuclei and inferior colliculi.

Kernicterus may occur as a comorbidity in children with other illnesses, often dramatic life-threatening illnesses, e.g. cyanotic congenital heart disease or necrotizing enterocolitis, when treatment for hyperbilirubinemia is stopped or interrupted perioperatively during emergency surgery.

The less severe type of bilirubin encephalopathy may produce subtle cognitive disturbances, neurological abnormalities, and hearing loss (Hyman *et al.* 1969; Odell *et al.* 1970; Johnson & Boggs 1974; Naeye 1978; Rubin *et al.* 1979), and may occur in premature infants without marked hyperbilirubinemia (Connolly & Volpe 1990). Choreoathetosis and impaired upgaze are uncommon findings in this group of patients – about 60% having hearing loss as their only manifestation (Bergman *et al.* 1985). Thus, auditory dysfunction may be the principal manifestation of bilirubin neurotoxicity in the premature infant without marked hyperbilirubinemia (Connolly & Volpe 1990). Auditory system abnormalities with hyperbilirubinemia have recently been reviewed and are characterized by absent or abnormal BAEPs with normal tests of inner ear function such as cochlear microphonics or otoacoustic emissions (Shapiro & Nakamura 2001) consistent with dysfunction in the pons and possibly the spiral ganglia, and described by the newly coined terms, "auditory neuropathy (AN)" (Starr *et al*. 1996; Deltenre *et al*. 1997), also known as "auditory dys-synchrony"(Berlin *et al*. 1998; Berlin *et al*. 2003), functionally defined as absent or abnormal BAEPs with normal tests of inner ear function. These electrophysiological findings were first reported in 1979 in children with hearing loss due to hyperbilirubinemia (Chisin *et al*. 1979).

Measures of free bilirubin, i.e. unconjugated bilirubin that is not bound to albumin, predict these outcomes better than conventional total or conjugated bilirubin (Odell *et al*. 1970; Johnson & Boggs 1974) (Table 9.5).

Athetotic cerebral palsy

Cerebral palsy refers to a set of static motor impairment syndromes that occur from insults acquired before, at, or immediately after birth. Extrapyramidal disorders are rarely observed before the end of the first year of life, possibly because the pyramidal tracts, which are necessary for the expression of movement disorders, have not yet fully myelinated. One fifth of children with static encephalopathy caused by developmental defect or a brain injury acquired

FEATURES

Table 9.5 Bilirubin Encephalopathy

Discriminating feature

1. Unconjugated hyperbilirubinemia

Consistent features

1. Athetosis
2. Impairment of upgaze
3. Hearing loss

Variable features

1. Dental enamel hypoplasia
2. Impaired extraocular movements
3. Dysarthria

in the perinatal period develop movement disorders (Lagregran 1983). Both athetoid and dystonic forms of cerebral palsy have been identified, primarily in full-term infants (Kuban & Leviton 1994). Chorea or choreoathetosis may also occur. Pyramidal tract signs (spasticity, paresis) are usually seen in combination with the movement disorder. Oromotor difficulties, speech dysarthria, and drooling are particularly prominent in this group.

In some cases of athetotic cerebral palsy, no etiology is discovered. In a few cases, calcifications of the basal ganglia are seen on CT scans (Billard *et al.* 1989). In one study, abnormalities in the basal ganglia, thalamus, and/or white matter were seen on MRI imaging of 14 of 16 children with athetotic cerebral palsy (Yokochi *et al.* 1991). The association of prematurity, hypoxia, ischemia, acidosis, and subependymal and intraventricular hemorrhage with increased susceptibility to bilirubin neurotoxicity may explain the frequent intermingling of pyramidal and extrapyramidal symptoms.

Two causes of athetoid, dystonic CP have now been recognized, hypoxia-ischemia and bilirubin neurotoxicity (kernicterus, see description above). In hypoxia-ischemia, areas of abnormal, hyperintense MRI signal are identified in the putamen, thalamus, and motor strip, whereas in kernicterus, hyperintense signal are seen in the globus pallidus and, occasionally, subthalamus (Penn *et al*. 1994; Johnston & Hoon 2000; Govaert *et al*. 2003).

Postpump chorea

Postpump chorea occurs in about 1% of children who undergo open cardiac surgery. The chorea begins 3–12 days after surgery, and may be either transient or permanent. Imaging studies reveal diffuse atrophy. Many patients have additional cognitive deficits. During surgery, affected patients seem to have spent more time on the pump, and at temperatures under 36°C, compared to unaffected controls (Medlock *et al.* 1993). Other authors have hypothesized that hypothermia and respiratory alkalosis during the rewarming period may have contributed to this insult (Curless *et al.* 1994).

Systemic illness involuntary movements

Chorea and other movement disorders, e.g. athetosis, myoclonus, tremor, and dystonia, are occasionally associated with systemic illness, presumably by altering basal ganglia function through a variety of mechanisms, e.g. hypoperfusion of subcortical vascular watershed regions secondary to ischemia, cytotoxic or inflammatory reactions or vasculopathy caused by infections or autoimmune processes (Janavs & Aminoff 1998).

Chorea associated with systemic diseases such as systemic lupus erythematosus and anaphylactoid (Henoch–Schönlein) purpura may resemble Sydenham's chorea (Herd *et al.* 1978). Chorea may be a manifestation of hyperthyroidism or its treatment, hypocalcemia, or hypoparathyroidism with cerebral calcification, processes which may influence neurotransmitter balance in the basal ganglia (Janavs and Aminoff 1998). Infections such as *Mycoplasma pneumoniae* (Beskind & Keim 1994) or Epstein–Barr virus (Tachi *et al.* 1993) have also been associated with the onset of chorea. In patients with severe pre-existing brain damage, valproate may also provoke choreiform movements (Lancman *et al.* 1994). Conditions that increase estrogen concentration, such as the taking of oral contraceptives, may be associated with chorea, presumably based on an estrogen-induced increase in dopamine receptor activity (Nausieda *et al.* 1979).

Involuntary movements with systemic illnesses are not exclusively due to basal ganglia involvement. Contralateral involuntary limb shaking movements and chorea have been reported secondary to moyamoya disease or radiation-induced middle cerebral artery stenosis with MRI and PET findings of hypoperfusion or small infarcts in the frontal corona radiata (Im *et al*. 2004).

Chorea may also be sequelae of brain injury caused by head trauma or vascular disease. Various chronic, progressive, metabolic and neurodegenerative disorders of childhood may be associated with chorea. These include infantile Leigh's syndrome, Pelizaeus–Merzbacher disease, Lesch–Nyhan disease, juvenile Niemann–Pick disease, ataxia-telangiectasia, and glutaric aciduria. Tumors of the basal ganglia are very rarely a cause of chorea, but should be considered in cases of unilateral chorea, even though other conditions are much more likely. Thus – in addition to the taking of clinical and family histories – a physical examination; tests such as blood and urine amino acid chromatography; measurements of lactate and pyruvate, uric acid and IgM, calcium, phosphorus, and thyroid and parathyroid hormones; lysosomal enzyme assays; and neuroradiologic imaging studies, especially MRI, may be useful.

Dystonia

Dystonia, as a symptom, is characterized by slow sustained contortions of axial and appendicular muscles producing twisting, often repetitive movements and abnormal positions and postures, and is found in a number of disorders. Dystonic syndromes may be classified into primary and secondary disorders. The primary dystonic states, currently termed torsion dystonias, are familial and in the past have been identified by such names as dystonia musculorum deformans, spasmodic torticollis, and progressive torsion spasm of childhood.

Secondary dystonias may be found in other familial or acquired disorders, including Wilson's disease and neurodegeneration with brain iron accumulation (NBIA), and as a sequela following perinatal brain injury, encephalitis, head injury, and other conditions (McGeer & McGeer 1988). Of particular note is that some patients, initially believed

to have cerebral palsy, may instead have a dopa-responsive dystonia (Boyd & Patterson 1989), which may represent 10% of all childhood dystonias (see hereditary progressive dystonia with marked diurnal variation, below).

The differential diagnosis of disorders that present with chronic and progressive dystonia include torsion dystonia, NBIA and other metabolic disorders, e.g. glutaric aciduria. However, more than one type of abnormal movement may regularly occur in specific disorders. Wilson's disease and torsion dystonia may manifest tremors as well as dystonic symptoms. The nature, course, and association of other types of movements, along with the presence or absence of significant dementia, provide significant differential diagnostic information. The diagnosis of a specific disorder is based on clinical and laboratory findings.

Idiopathic torsion dystonia

Idiopathic torsion dystonia (formerly dystonia musculorum deformans) is a familial disorder most frequently transmitted as an autosomal dominant or as an autosomal recessive. A smaller number of cases may be X-linked recessive. While certain factors are more often noted in the recessive form (e.g. Jewish ancestry, consistent age of onset), and other factors are more frequently noted in the dominant form (e.g., non-Jewish ancestry), the differences are not sufficient to differentiate clinically between these forms in individual cases. A gene for idiopathic torsion dystonia has been found to lie on chromosome 9q34 and is called DYT1 (Ozelius *et al*. 1992), however the frequency of detecting a DYT1 mutation without a family history of dystonia is less than 6%. DYT1 encodes a protein called torsinA, and the defect deletes a glutamate residue from the protein. Other gene loci are responsible for the different subtypes (Spinella & Sheridan 1994), including an X-linked form and dystonia with the spinocerebellar ataxia-6 gene.

The average age of onset in the recessive form is 10 years, while it varies in the dominant form from 1 to 40 years of age. The initial major symptom is dystonic posturing of the axial muscles, particularly the neck muscles, thus starting as a focal dystonic disorder. Coactivation of antagonistic groups of muscles leading to impairment of reciprocal inhibition has been demonstrated in idiopathic torsion dystonia (Rothwell et al. 1988). In some cases, torticollis is the only manifestation of the disorder. Initial symptoms may be misdiagnosed as hysteria. Many other patients will have a variably progressive course in which dystonia affects other axial and limb muscles resulting in segmental or generalized dystonia with contortions of the trunk, appendicular dystonia, and tortipelvis. Peripheral injuries my precipitate dystonia in genetically predisposed – in one study of 104 patients, 17% had a history of injury within days or up to 12 months before the onset of dystonia, which began in the injured part of the body before becoming generalized (Fletcher *et a*l. 1991). Dysphonia may develop in some cases. Mental retardation is not a consistent associated finding. There is no convincing evidence of a decreased lifespan in individuals with torsion dystonia (Table 9.6).

The diagnosis is based on clinical findings, and laboratory studies help exclude the secondary forms of dystonia. Currently, genetic testing for a DYT1 gene mutation in conjunction with genetic counseling is recommended for patients with onset before 26 years of age (Bressman *et al*. 2000).

Management of the patient with torsion dystonia requires attention to the physical and emotional aspects of the disorder. Severe emotional stress may impede the therapeutic progress of rehabilitation. The patient with generalized dystonia needs support from members of a multidisciplinary team, including physicians, counselors, physical and occupational therapists. No medications provide dramatic relief of the symptoms. L-Dopa has had limited success in controlling dystonia. High doses of anticholinergics (trihexyphenidyl) have been successful in some patients and well tolerated in children. If the symptoms of dystonia are paroxysmal, then patients may respond to phenytoin or carbamazepine. Diazepam has been recommended but has not been universally beneficial. Recent experience has shown that deep brain stimulation of the internal globus pallidus is over 70% effective for the primary generalized dystonias (Cif *et al*. 2003; Kupsch *et al*. 2003).

Neurodegeneration with brain iron accumulation

Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of disorders differentiated by clinical, radiographic, and molecular features (Hayflick 2003). The autosomal recessive disorder known as pantothenate kinase-associated neurodegeneration (PKAN) accounts for most patients diagnosed with NBIA, and is caused by mutations in the gene encoding pantothenate kinase 2 (PANK2) located on chromosome 20p13-p12.3 (Hayflick 2003). PKAN is characterized by dystonia and pigmentary retinopathy in

FEATURES

Table 9.6 Torsion Dystonia

Discriminating features

1. Dystonia
2. Familial

Consistent features

1. Commonly autosomal dominant or recessive
2. Dystonic posturing of the neck and axial muscles
3. Abnormality of DYT1 gene

Variable features

1. Can be X-linked recessive
2. Dysphonia

Disorders Presenting with Dystonia

PEARLS & PERILS

- Chronic progressive dystonia is a symptom complex that may be seen in children with a number of movement disorders. Treatable diseases such as dopa-responsive dystonia and Wilson's disease should be carefully ruled out.
- As in other neurodegenerative diseases, extraneural tissue may provide supporting histologic evidence of neurodegeneration with brain iron accumulation (NBIA) when the presence of sea-blue histiocytes and cytosomic inclusions can be demonstrated.
- Early dystonia may be misinterpreted as a hysterical mannerism.

children, speech and neuropsychiatric defects in adults, and a specific pattern of abnormality on MRI of the brain (Hayflick 2003; Hayflick *et al*. 2003).

The clinicopathologic findings were initially described by Hallervorden and Spatz in 1922, who found pathologic amounts of iron stored in the globus pallidus and reticular zone of the substantia nigra of five siblings. The term Hallervorden–Spatz disease has been replaced by NBIA due to the subsequent unethical activities of these German neuropathologists during World War II (Shevell 1992; Hayflick *et al*. 2003; Shevell 2003). The clinical features include occurrence at a young age, a motor disorder of the extrapyramidal type, dementia, and a progressive course. The pathologic features are symmetric lesions of the globus pallidus and pars reticulata of the substantia nigra with loss of myelinated fibers and neurons, dissemination of round nonnucleated swollen axons (spheroids) in the central nervous system, and accumulation of iron-containing pigments in the affected regions (Dooling *et al*. 1974).

The onset of symptoms typically occurs by 10 years of age. A small number of cases may begin in adulthood. Posturing or movement abnormalities are the most frequent presenting symptoms. These changes lead to gait disorders. Motor symptoms include rigidity, dystonic posturing, choreoathetoid movements, and tremors. Dysarthria is present in most of the cases. The deep tendon reflexes tend to be hyperactive and the toe reflexes upgoing. Progressive intellectual deterioration (dementia) is often present and the rate of its progression is variable. Seizures may occur, but were absent in 66 patients recently reported with PANK2 mutations (Hayflick *et al*. 2003).

In a recent genetic, clinical and radiographic delineation of this disorder, 123 patients were classified as having either classic disease (66 patients) or atypical disease (57 patients). In the classic disease, symptoms were early-onset with 88% before 6 years of age. The disease was rapidly progressive, manifested by dystonia progressing to severe disability by 20 years of age, and MRI indicated high iron content in the basal ganglia. Atypical disease included patients with extrapyramidal dysfunction and radiographic evidence of iron accumulation in the basal ganglia, had a later onset and a more slowly progressive course.

In *classic* NBIA or PKAN disease, early dystonia often involved the cranial and limb musculature. Acanthocytosis was found in 8%; 68% had clinical or electroretinographic evidence of retinopathy; only 3% had optic atrophy; and 85% became nonambulatory within 15 years after onset.

Clinical features of *atypical* NBIA and PANK2 mutations were heterogeneous with patients older at onset (mean about 14 years), extrapyramidal defects were less severe and more slowly progressive, and retinopathy was less common. Speech difficulties, palilalia and dysarthria, were often a presenting or early feature in contrast to no speech difficulties in patients with the classic disorder (Hayflick *et al*. 2003).

The nearly pathognomonic MRI abnormality, is the "eye-of-the-tiger" sign, and consists of bilateral areas of hyperintensity within a hypointense medial globus pallidus on T2-weighted images. A striking correlation is found between the MRI findings and the presence or absence of PANK2 mutations in patients with NBIA syndrome. MRI scans from patients with *PANK2* mutations show the eye-of-the-tiger sign and no *PANK2*-mutation – positive patients lacking the eye-of-the-tiger sign have been found (Hayflick *et al*. 2003). In addition, no mutation-negative patients with NBIA had the eye-of-the-tiger sign; MRIs from these patients showed only a region of hypointensity in the medial globus pallidus (Table 9.7).

The authors suggest that the eye-of-the-tiger pattern may reflect tissue necrosis and edema (hyperintensity on T2-weighted MRI) within a region of iron deposition (T2 hypointensity), and have suggested that cysteine, which would normally condense with phosphopantothenate, and cysteine-containing compounds might form complexes with iron and exacerbate oxidative damage in this brain structure (Zhou *et al*. 2001).

Extraneural evidence of the disease can be found when the presence of sea-blue histiocytes was demonstrated in the bone marrow cells and cytoplasmic inclusions of circulation lymphocytes (Swaiman *et al.* 1983; Zupanc *et al.* 1990) in children with HSS.

Hypoprebetalipoproteinemia, acanthocytosis, retinopathy, and pallidal degeneration (HARP) refers to a disorder that falls within the phenotypic spectrum of PKAN and was recently shown to be caused by mutations in the pantothenate kinase 2 gene and is thus no longer distinguished from PKAN.

Pantothenate kinase is a key enzyme which regulates the biosynthesis of coenzyme A (CoA). Hayflick has postulated that the mechanism of disease may be a combination of product deficit and secondary metabolite accumulation (Hayflick 2003). Since the globus pallidus and retina have

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Table 9.7 Neurodegeneration with Brain Iron Accumulation (NBIA)

Discriminating features

1. Symmetric pathologic lesions of the globus pallidus and pars reticularis of the substantia nigra
2. Autosomal recessive

Consistent features

1. Occurs at young age
2. Extrapyramidal motor disorder; rigidity, dystonia, choreoathetosis, and tremor
3. Dementia
4. Progressive course
5. MRI findings of cortical atrophy, "eye-of-tiger" abnormality

Variable features

1. Abnormal EEG, visual evoked potentials (VEP)
2. Sea-blue histiocytes and cytoplasmic inclusions in lymphocytes
3. Seizures
4. Increased radioactive uptake of iron in basal ganglia
5. Late (adult) onset

high metabolic demands and are among the tissues most sensitive to oxidative stress, their destruction in PKAN may result from either increased oxidative damage or a defect in lipid metabolism. Based on an association of PANK2 with mitochondria, Hayflick hypothesizes that defects of PANK2 lead to CoA deficiency and metabolic consequences, especially insufficient energy production leading to generation of reactive oxygen species, which damage membrane phospholipids via peroxidation and lead to apoptosis. Since the product of pantothenate kinase, phosphopantothenate, normally condenses with cysteine in CoA synthesis, Hayflick also speculates that the basal ganglia iron deposition could be explained by the accumulation of cysteine, which chelates iron.

Supportive and symptomatic therapy should be provided to children and their families. Emotional support and genetic counseling are important components of the management program. Systemic administration of iron chelators does not lower CNS iron in NBIA. Baclofen and trihexyphenidyl may help to relieve some of the extrapyramidal symptomatology of disabling dystonia and spasticity, and patients generally do not denefit from L-dopa (Hayflick 2003).

Dopa-responsive dystonia

Dopa-responsive dystonia (Calne 1994) is also called progressive dystonia with diurnal variation, Segawa syndrome. It is caused by mutations in the guanosine triphosphate cyclohydrolase 1 (DYT-5) gene responsible for conversion of guanosine triphosphate to tetrahydrobiopterin (BH4), an essential cofactor for tyrosine hydroxylase, which in turn is the rate-limiting enzyme for dopamine synthesis. This gene has been mapped to chromosome 14q22.1–22.2. The disease is an autosomal dominant disorder with reduced penetrance and variable expressivity, though an autosomal recessive and another autosomal dominant (DYT-14) variant have been described.

Symptoms begin in childhood, usually before the age of 10 years, with dystonic manifestations and respond rapidly to L-dopa (Nygaard & Duvoisin 1986). Females are more frequently affected than males by at least a 2:1 ratio. A patient's presenting sign is often a gait disorder, with dystonia of the legs or with equinovarus posturing of a foot. As the disorder progresses, dystonia becomes more generalized and features of parkinsonism may appear. There may be flexor and extensor posturing of the upper extremities and trunk musculature. Parkinsonian features include cogwheel rigidity, bradykinesia, and tremors. The deep tendon reflexes are often brisk with extensor toe responses. Diurnal variation, in which symptoms become more severe during the day and improve after sleeping, is a prominent feature especially noted in the cases reported from Japan (Segawa *et al.* 1976), though some do not experience these fluctuations (Table 9.8).

The diagnosis is based on clinical assessment. Routine laboratory studies are used to rule out such treatable disorders as Wilson's disease. Cerebrospinal fluid homovanillic acid and 5-hydroxyindoleacetic acid levels have been reported as normal or low. Autopsy studies have revealed poorly pigmented cells in the substantia nigra (Yokochi *et a*l. 1984) and a reduction in tyrosine hydroxylase without the dramatic cell loss seen in juvenile parkinsonism (Rajput *et al*. 1994). Oral phenylalanine loading can identify presymptomatic individuals and asymptomatic carriers (Hyland *et al*. 1999). Pharmacologic challenge with low-dose L-dopa separates dopa-responsive dystonia from idiopathic torsion dystonia

FEATURES

Table 9.8 Progressive Dystonia with Diurnal Variation (Dopa-Responsive Dystonia)

Discriminating features

1. Progressive dystonia
2. Diurnal variation

Consistent features

1. Gait disorder
2. Marked and rapid response to L-dopa
3. Caused by mutations in guanosine triphosphate cyclohydrolase 1 (DYT-5)

Variable features

1. Brisk deep tendon reflexes
2. Posturing

and the secondary dystonias and it is recommended that an empiric trial of levodopa be considered in any child with dystonia.

The reduction of dystonic and parkinsonian features after the administration of L-dopa is rapid and marked. Function is often normalized within a day of initiation of medication. Small dosages of medication sometimes result in dramatic changes. Dosages should be individualized. Control with L-dopa is sustained, in some cases for more than 10 years. There has been no deterioration of the parkinsonian or dystonic symptoms while on medication. Anticholinergics (Allen & Knopp 1976) are also beneficial in reducing the symptoms; however, the response is not as striking. Carbamazepine has also produced favorable therapeutic responses (Garg 1982). Treatment with tetrahydrobiopterin may raise CSF levels of biopterin and 5-hydroxyindoleacetic acid and improve dystonia.

Childhood Tremor

PEARLS & PERILS

- Benign essential tremor is the most common persistent tremor in childhood.
- Stress and tiredness will increase tremor in benign familial or essential tremor.
- Shuddering attacks in infancy and childhood should prompt a careful history for the presence of familial tremor.
- "Wing-beating tremor," in which arms are abducted and elbows flexed, suggests Wilson's disease.
- A Kayser–Fleischer ring (a brown to yellow to green discoloration in Descemet's membrane at the limbus of the iris) is pathognomonic of Wilson's disease. This can be seen more readily in persons with blue eyes. It is definitively diagnosed by slit-lamp examination.

Focal dystonias

Focal dystonia is a descriptive rather than etiologic term. Focal dystonias express themselves when the eyes screw shut (blepharospasm), the jaw is forced open or shut (oromandibular dystonia), the neck is twisted (torticollis), or the arm adopts a posture of hyperpronation with flexed wrist and extended fingers, particularly during the act of writing (writer's cramp). Professional musicians are known to develop their own peculiar cramps or dystonic reactions. Although many of these syndromes are more typical in the adult population, occasionally focal dystonias can be seen in children. Some of the primary dystonias first present as a focal dystonia (Marsden 1986). About 30% of people with "focal dystonia" carry an abnormal DYT1 gene (Spinella & Sheridan 1994) and other genes including DYT6, DYT7, DYT13, and PANK2 (Nemeth 2002).

Most of the focal dystonias respond poorly to medications (Marsden 1986). Local injection of botulinum toxin, a neuromuscular blocking agent, is effective therapy for temporary relief of focal dystonias (American Academy of Neurology 1994). Occasionally these injections may have the side effect of local weakness; however, the dystonia is typically improved.

Tremor

Tremor can be defined as an involuntary, rhythmic oscillation. Tremor may be worse with trying to maintain a posture or with action, as in essential tremor, or worse at rest as in a parkinsonian tremor. The presence or absence of other symptoms and signs helps to differentiate the various conditions.

Essential tremor

Benign familial or essential tremor is the most common persistent childhood tremor. Essential tremor is a monosymptomatic disorder. The mean age of onset is 7 years. The tremor primarily involves the arms. It may involve both a postural tremor and an action tremor. Tremor is absent at rest. The characteristic tremor is rapid (5–8 Hz) and exacerbated by stress, anxiety, and antigravity posture. Characteristically the tremor in adults responds dramatically to alcohol. There is a positive family history in about 70% of cases (Louis *et al.* 2001) (Table 9.9).

This can be inherited as an autosomal dominant disorder, with approximately 5% of cases presenting in childhood. A positive family history is present in about 50% of patients. The pathophysiology is unknown in hereditary cases. However, there may be as yet unidentified environmental factors that contribute to the tremor (Louis 2001).

The condition is not usually debilitating, although slow progression with prolonged plateaus may occur. Proprano-

FEATURES

Table 9.9 Benign Familial Tremor

Discriminating features

1. Intention or postural tremor
2. Most often affects the hands and arms
3. Autosomal dominant

Consistent features

1. Positive family history
2. Worse after caffeine ingested and with stress; better after alcohol ingestion

Variable features

1. Shuddering

lol (1–3 mg/kg/day), or primidone (starting at 25 mg at bedtime, titrating up to a dose of 250 mg per day) may be therapeutically useful in some cases. Other medications such as benzodiazepines, gabapentin, and topiramate may also be helpful in select patients (Pahwa & Lyons 2003).

Infantile movements

Chin trembling occurs in infants, and is characterized by episodes of involuntary quivering of the chin. These episodes can be induced by emotional stimuli. The episodes are hereditary, and may inherit as an autosomal dominant disorder. The frequency decreases with age (Danek 1993; Grimes *et al.* 2002).

Head rolling or head tremor can also present in young children between the ages of 5 and 10 months. Patients with this "yes-yes" or "no-no" tremor have an otherwise normal neurological exam and laboratory studies. A family history of tremor or shuddering spells can be obtained in some children. Spontaneous remission occurs (DiMario 2000).

Spasmus nutans is a benign syndrome of infancy that consists of a triad of head nodding, pendular nystagmus and a head tilt. Spontaneous remissions of the head nodding typically occur by 2 years of age, although some cases persist up to 6 years of age (Doummar *et al.* 1998). Subclinical nystagmus may still persist until 5–12 years of age (Gottlob *et al.* 1995). There have been case reports of spasmus nutans being associated with an optic chiasm or third ventricle glioma, however the prevalence of tumors in spasmus nutans is estimated to be less than 2% (Arnoldi & Tychsen 1995).

Shuddering spells

Brief shuddering attacks of variable frequency, sometimes with posturing, may be seen in infancy or childhood in families with essential tremor (Vanasse *et al.* 1976). These attacks may start during infancy and continue during early childhood. The episodes appear as a "shudder" or a shivering movement, lasting for seconds, and without loss of consciousness. The shuddering attacks may be precipitated by emotional stimuli and disappear with time. These attacks are often confused with epileptic seizures. When severe, propanolol has been useful in attenuating the episodes (Barron & Younkin 1992).

Wilson disease

Hepatolenticular degeneration, or Wilson disease, results in the deposition of copper in the central nervous system, liver, cornea and other organs. 95% of patients with Wilson's disease will have low ceruloplasmin levels. However, the gene for Wilson disease, ATP7B, encodes a copper-transporting ATPase, and not ceruloplasmin (Thomas *et al.* 1995). The reduced or absent function of ATP7B leads to decreased liver excretion of copper into the bile, and this in turn leads to increased hepatic accumulation of copper. After the liver has been saturated with copper, the elevated copper enters the blood stream and results in copper deposition in other tissues, including the brain.

Patients may present with hepatic, neurologic, or psychiatric symptoms. Young children may present with dystonia followed by tremor and other findings. In such children, the onset of Wilson disease is often rapid, presenting with tremor, coarse "flapping," or fine rhythmic tremor, whereas in adults the onset is usually insidious. Half of patients are symptomatic by age 15 years, and rarely do patients present before the age of 6 years. Cerebellar and pseudobulbar signs, such as drooling, difficulty in swallowing, and dysarthria often occur. Rigidity develops later in the course of the disease. Dementia is not prominent in juvenile presentations. A Kayser–Fleischer ring (a brown to yellow-green discoloration in Descemet's membrane at the limbus of the iris) is frequently seen.

Early diagnosis and treatment of Wilson disease may prevent permanent neurological damage. Because it is treatable, the diagnosis of Wilson disease should be considered in all children with new onset of tremor or dystonia. A search for low ceruloplasmin levels is a good initial screen for this disease. However, ceruloplasmin levels are subject to false positives and false negative results. Twenty-four hour urinary copper excretion or measurement of serum nonceruloplasmin-bound copper concentration are helpful to confirm the diagnosis. In cases where the diagnosis is in doubt, hepatic parenchymal copper concentration can be measured (Roberts & Schilsky 2003).

Treatment with the chelating agent penicillamine, trientine, and/or zinc can result in symptomatic improvement.

PEARLS & PERILS

Wilson's Disease

- Wilson's disease is rare and has no specific early manifestations. Physicians should think of Wilson's disease when confronted with children with unexplained hepatic dysfunction or disease, hepatomegaly, acute hemolysis, acute dystonia, and recent onset of school or behavioral problems.
- Wilson's disease is not a cause of mental retardation.
- A golden brown Kayser–Fleischer ring near the limbus of the eye is seen only by slit-lamp examination until late in the course. Kayser–Fleischer rings are more frequent in neurologic or psychiatric forms of the disease.
- Most patients with Wilson's disease have a low serum ceruloplasmin and an increased concentration of loosely bound, nonceruloplasmin copper in the serum.

Liver transplantation can also be considered for select cases (see El-Youssef 2003 for review).

Juvenile Parkinson disease

Parkinson disease affecting individuals over 40 years old is a common disorder. However, parkinsonism in children is rare. In 1917, Hunt, and subsequently others (Martin *et al.* 1971), described a condition in which symptoms of parkinsonism appeared early in life. Juvenile Parkinson disease shares some but not all of the clinical, pathological, and pharmacological properties of adult Parkinson's disease. Pathological studies show a loss of cells in the substantia nigra, similar to the major pathologic findings in Parkinson's disease (Takahashi *et al.* 1994). Lewy bodies may be absent, however (Shimura *et al.* 2000).

The most common form of Parkinson disease is the idiopathic form. The clinical syndrome consists of tremor, rigidity, bradykinesias, and impaired postural stability. Other symptoms (e.g. oculogyric crisis, hyperhidrosis, and gait abnormalities) are often present. In children, the disorder is characterized by the early appearance of symptoms similar to those of the idiopathic form. Tremor, rigidity, and bradykinesia are also prominent in the juvenile form of the disorder. Facial masking, resting tremor, loss of associated movements, and cogwheel rigidity of the neck and limb muscles are prominent findings. The gait may be either dystonic or shuffling. Deep tendon reflexes are frequently brisk.

The disorder in children and in some adults is familial. The mode of inheritance of juvenile Parkinson disease is autosomal recessive, although sporadic cases have been reported. The gene responsible in some patients with juvenile Parkinson disease is parkin, and is involved in protein degradation in the neuron (Shimura *et al.* 2000).

Drug therapy in juvenile Parkinson disease is similar to therapy for idiopathic Parkinson disease. The cases reported in the literature have had dramatic response to relatively low doses of L-dopa/carbidopa. Other potential causes of juvenile parkinsonism include dopa-responsive dystonia, Wilson disease, Huntington disease, neuroacanthocytosis, medications (neuroleptics and valproate), and mitochondrial disorders (Paviour *et al.* 2004).

Secondary causes of tremor

Hyperthyroidism is associated with tremor that is rapid, mainly involves the extremities, and is more prominent with the arms outstretched. Tremor secondary to hyperthyroidism can be diagnosed by appropriate thyroid function tests. Drugs, such as the α-adrenergic agonists, valproic acid, lithium, heavy metals, alcohol, and "street drugs" can all produce tremor. The tremor stops when the drug is withdrawn, or (as in the case with valproate) when the levels of the drug are decreased. Finally, up to 45% of severely head injured children will manifest a tremor within the first 18 months after injury (Johnson & Hall 1992).

Tics

Tics are rapid, brief involuntary darting movements. Tics can be primarily motor such as eye blinking or facial grimacing, or the tics can be vocal such as throat clearing or sniffing. Transient tic disorder is defined by tics which last for at least 4 weeks, and less than a year in duration. Motor or vocal tics that persist over 1 year are defined as a chronic tic disorder. Patients with Tourette syndrome will have multiple motor tics and vocal tics that persist for longer than a year. Transient tic disorder and chronic motor tics may be part of a spectrum with Tourette syndrome, since all three disorders may be seen within the same family (Kurlan *et al.* 1988).

Tics are common in children. Up to 5% of all children will experience a single transient tic lasting a few weeks to months (Solomon 1991). In a classroom situation, 6% of regular students and 26% of special education students were observed to have tics during the school day (Kurlan *et al.* 1994). Often these involuntary movements are manifested in only one muscle group and occur transiently.

Tourette syndrome

Gilles de la Tourette syndrome (TS) is a disorder characterized by the early onset (2–15 years of age) of chronic motor and vocal tics. The tics involve multiple motor groups and will vary in intensity, waxing and waning over a period of months to years. The motor tics may be simple or complex, with manifestations changing over time. Eye blinking and facial grimacing may occur in one period, more complex movements in the next. Vocal tics include simple sniffling sounds, barking, grunting, and throat-clearing sounds, and also more complex echolalia and coprolalia. However, coprolalia (explosive production of obscene words) is uncommon in children with TS (Table 9.10).

Tics may appear in preschool or early grade school years, and have an average age of onset of 6 years. Often tics seem

PEARLS & PERILS

Tics

- Children with attention-deficit/hyperactivity disorder (ADHD) on stimulant medications should be monitored for the onset of tics.
- Because of the high incidences of behavioral disorders in children with TS, psychological or psychiatric consultation may be helpful.
- Tourette syndrome, chronic motor tics, ADD or ADHD, and obsessive-compulsive disorder may be commonly seen within the same family.

to increase in severity during childhood, reaching a peak period of tic severity at 10 years of age. Many patients will show fewer tics, or a complete disappearance of tics, by the time they reach late adolescence or early adulthood (Erenberg *et al.* 1987). The improvements in tic disability with age do not appear to relate to medication use, as many patients never treated with medications will often show improvements (Pappert *et al.* 2003).

The lifetime prevalence of TS is estimated to be 1% (Robertson 2003). Tourette syndrome is probably inherited as an autosomal dominant with incomplete penetrance and variable expressivity. There are likely modifier genes that affect expression (Paul 2001). Although there is evidence to suggest a strong genetic contribution, nongenetic factors (such as a history of prematurity, anxiety, head injury, infections, medications) also play a role in the expression of tics.

There are medications that can effectively reduce the symptoms of TS. However the program of management of the children and their families can be quite complex. Typical target symptoms for treatment include the tics, problems with attention, obsessive-compulsive disorder, anxiety, depression, oppositional behavior and learning disabilities. The severity of the symptoms and the extent to which these symptoms affect the development, self-image, and performance of the child in school and at home should be addressed. Parents need to be educated about the disorder, and counseled about its possible transmission. To reduce the frequency of the tics, several medication groups have been used. Often patients are started on an alpha-2-adrenergic agonist, such as clonidine. It is started at 0.05 mg/day and slowly titrated to 0.15–0.3 mg/day. Tiredness and hypotension are dose-limiting side effects. Neuroleptics may be the most effective group of medications for the control of the tics. Older generation neuroleptics such as haloperidol or pimozide are now being replaced with the "atypical antipsychotics" such as risperidone, olanzapine and ziprasidone. These atypicals appear to be equally efficacious, and may have an advantage with a lower rate of tardive dyskinesia (Sallee *et al.* 2000; Budman *et al.* 2001; Gilbert *et al.* 2004). Risperidone may be started at 0.5 mg per day, and titrated up to 3 mg per day. Weight gain is a significant problem. The concurrent use of nizatidine may attenuate the neuroleptic-induced weight gain (Atmaca *et al.* 2003). Other agents, including baclofen, some anticonvulsants (topiramate and leveitracetam), benzodiazepines, pergolide, and tetrabenazine have been used less frequently to treat patients with TS. In the future, deep brain stimulation may show promise in severe cases (Temel & Visser-Vandewalle 2004).

Over half of the children with this syndrome may have symptoms of attention deficit disorder (ADD), obsessive-compulsive symptoms, or other behavioral disorders. Typically the attentional problems are evident before the onset of the tics. The use of stimulant medications (methylphenidate, dextroamphetamine, and pemoline) may be associated with the first appearance of, or an increased incidence of, tics. However, a recent multicenter clinical trial showed a benefit of stimulants on both attention and tics (Tourette Syndrome Study Group 2002). Tricyclics, such as desipramine, may be a useful alternative for the treatment of attentional symptoms and impulsivity in Tourette syndrome (Singer *et al.* 1995). Recently atomoxetine has been used to improve attention in patients with tics. Early experience seems to suggest that atomoxetine does not aggravate the tic frequency. Anxiety or obsessive-compulsive symptoms can also be quite troubling and may respond to selective serotonin reuptake inhibitors or cognitive behavioral therapy (Miguel *et al.* 2003).

The pathogenesis of this syndrome is incompletely understood. A number of neurotransmitter alterations have been implicated. The dramatic response of symptoms to dopamine receptor-blocking agents like haloperidol suggests a dopaminergic involvement. Baseline cerebrospinal fluid levels of homovanillic acid have been low, with levels increasing after the administration of haloperidol. Noradrenergic mechanisms have been implicated because symptoms of the syndrome are reduced after the administration of clonidine, a drug that inhibits noradrenergic functioning. However, more information is needed to understand adequately these complex mechanisms.

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Table 9.10 Tourette Syndrome

Discriminating features

1. Motor and vocal tics greater than 1 year in duration
2. Involves multiple motor groupings
3. Waxing and waning of symptoms
4. Onset before 18 years

Consistent features

1. ADD or ADHD in 70% of patients
2. Obsessive compulsive features
3. Response to dopamine receptor antagonists

Variable features

1. Coprolalia
2. Remission in late adolescence or early adulthood in some patients

Pediatric autoimmune neuropsychiatric disorder (PANDAS)

As early as 1929, it was noted that some children with obsessive-compulsive disorder (OCD) and/or tics have symptom exacerbations triggered by group A beta-hemolytic streptococcal (GBHS) infection or other infections (Garvey *et al.* 1999; Singer 1999). A proposed mechanism is that the GBHS triggers antibodies which cross-react with the basal ganglia

of genetically susceptible hosts, leading to OCD and/or tics (Garvey *et al.* 1998).

In PANDAS, symptom onset of tics or OCD is believed to be triggered by GABHS infection or pharyngitis. In addition to tics and OCD, many of the described patients in the literature have emotional lability, separation anxiety, nighttime fears and bedtime rituals, cognitive deficits, oppositional behaviors and motoric hyperactivity (Swedo *et al.* 1998). However, abrupt tic onset or an exacerbation of tics associated with a streptococcal infection (11%) or any infection (18%) is not uncommon in patients with tic disorders (Singer *et al.* 2000).

One controlled study of penicillin prophylaxis failed to prevent either the exacerbation of symptoms or the frequency of infections (Garvey *et al.* 1999). An open label trial of plasma exchange has failed to show benefit in a group of five patients with OCD without streptococcal exacerbations (Nicolson *et al.* 2000). In contrast, either plasma exchange or IVIG benefits the symptoms of patients with severe infection-triggered exacerbations of OCD or tic disorders (Perlmutter *et al.* 1999). Since these studies have limited controls and utilize highly select populations, many authors suggest that treatment be given to patients only as part of controlled double-blind protocols (Singer 1999).

To date, PANDAS is a controversial hypothesis rather than a proven clinical disorder. Clinical diagnostic criteria have not yet proven to be reliable nor valid. Similarly, there are no convincing data for the routine use of immunologic or antibiotic therapy in patients with tics (Kurlan 2004).

Stereotypies

Stereotypies occur in normal children as well as in children who are delayed in their development or autistic. These movements are repetitive, nonpurposeful, rhythmic, and the child can exert some degree of volitional control over the movements. Common examples can include head banging, rocking, jumping, or flapping of the hands and arms. Often times they occur more frequently when the child is excited or bored (Mitchell & Etches 1977). In the nonautistic child with normal intelligence, the stereotypies may also be associated with obsessive-compulsive symptoms and perfectionism (Niehaus *et al.* 2000).

The movements can be transient or they may persist for years. The movements are resistant to either behavioral therapy or to medications. An occasional child may respond to one of the neuroleptics, or a selective serotonin reuptake inhibitor.

Myoclonus

Myoclonic movements are sudden, brief, shock-like and involuntary. These movements can be the result of muscle contractions (positive myoclonus) or inhibitions (negative myoclonus). Myoclonus is a sign that can be seen in a variety of neurological conditions. For instance, myoclonus may be seen in a patient after a severe hypoxic-ischemic injury. Myoclonus may also be seen in neurodegenerative diseases, such as neuronal ceroid lipofuscinosis. Myoclonic movements may also have an epileptic etiology, and an EEG should be considered in a patient who shows a new onset of daytime myoclonus. In contrast, most children will exhibit sleep myoclonus, a totally normal movement. This occurs as the child is falling asleep, or just prior to awakening (Butler 1992).

PEARLS & PERILS

Myoclonus

- Myoclonic movements occur commonly in sleeping infants and are frequently misinterpreted as seizures.
- Predominantly front-to-back head movements, with the head appearing like a doll's head on a spring, occur in the "bobble head doll" syndrome, which should prompt a search for neuroblastoma and for third ventricle cyst, dilatation, or tumor.
- The occurrence of myoclonus with abnormal eye movements (opsoclonus) and ataxia should prompt an investigation for a neuroblastoma.

Opsoclonus-myoclonus-ataxia

This rare syndrome has generated great interest because of its association with neuroblastoma. It consists of myoclonus, opsoclonus ("dancing eyes") and ataxia (OMA) in infants with sudden onset. It appears in the literature with the name myoclonic encephalopathy of infancy, Kinsbourne's syndrome, infantile polymyoclonia, and "dancing eyes" syndrome. The initial report of six cases (Kinsbourne 1962) has been supplemented by over 100 additional case reports (Lott & Kinsbourne 1986), some with long-term follow-up. A comparison of OMA with mycoclonic epilepsy is shown in Table 9.11.

The syndrome may be idiopathic, viral, or neuroblastoma-related. Idiopathic and neuroblastoma-related OMA may be distinct entities, or may represent immunologic reactions of varying effectiveness against neuroblastoma formation. In the published literature the incidence of neuroblastoma associated with OMA is about 50%; however, because of a selection bias in favor of reporting cases associated with neuroblastoma, the true incidence of associated neuroblastoma is probably much lower (Lott & Kinsbourne 1986).

Patients with opsoclonus-myoclonus generate an immune response against a variety of brain antigens (Pranzatelli 1992; Connolly *et al.* 1997). It is probable that neuroblastoma (or viral antigens) and the cerebellum are joint targets of an immunologic attack. In adults with paraneoplastic OMA,

TABLE 9.11

Opsoclonus-Myoclonus-Ataxia vs. Myoclonic Epilepsy

Criteria	Opsoclonus-myoclonus-ataxia	Myoclonic epilepsy & infantile spasms
Character of myoclonus	Asymmetric, arrhythmic, asynchronous	Bilateral, symmetric, synchronous, rhythmic
Dependence on stimuli	Induced by voluntary movement	Not induced by movement
EEG	Normal	Abnormal (hypsarrhythmia, atypical absence)

some patients develop antibodies to the RNA-binding protein Nova-1 (Jensen *et al.* 2000). To date, this antibody has not been found in the childhood version of OMA. Other as yet unidentified antibrain antibodies can be seen in childhood cases of OMA (Autunes *et al.* 2000).

Onset usually occurs between the ages of 6 and 18 months but can occur at up to 36 months of age. The onset of myoclonus is acute, often occurring after a nonspecific respiratory or gastrointestinal illness, and reaches maximal intensity in 2–7 days. The myoclonic movements are intense and brief with continual shock-like muscular contractions, irregularly timed, and of variable amplitude. They are widely distributed across muscle groups, asymmetric, increased by startle, present at rest, and abolished only by deep sleep. Rarely, choreoathetosis may also be seen.

Abnormal eye movements (opsoclonus) temporally unrelated to the myoclonus consist of rapid (up to eight displacements or rotations per second), irregular, conjugate ocular movements, mainly horizontal but also vertical and diagonal. The eye movements are exacerbated by the same stimuli as the myoclonus, and some authors consider opsoclonus to be the ocular equivalent of myoclonus.

Patients may also exhibit cognitive and mood changes as well, which persist past the myoclonic stages of this illness.

When OMA is associated with a neuroblastoma, neurological symptoms may occur months before a tumor if found. Fifty per cent of reported tumors are localized to the thorax. Imaging of the chest has the highest diagnostic yield, followed by abdominal films. Urinary catecholamines are rarely diagnostic. Electroencephalogram is normal. Anti-Hu antibodies were seen in 10 of 64 patients with neuroblastoma, but were not specific for the development of OMA (Antunes *et al.* 2000).

Success of treatment ranges from complete recovery in 3 months to persistence over several years, and the latter course is more frequently noted. Incomplete recovery may be followed by relapse related to infection or discontinuation of effective therapy. Most cases show a remarkable response to adrenocorticotropic hormone (ACTH) or corticosteroid therapy. Usually 20–40 units/day of ACTH, or 5–20 mg of prednisolone have been needed for therapeutic benefit, with the dose titrated downward to a level below which symptoms appear.

More than half of patients are left with sequelae: mental retardation, dysarthria, learning disabilities, or ADHD. Patients with neuroblastoma have slightly less serious sequelae. Neuroblastoma associated with myoclonic encephalopathy has a more favorable prognosis for survival than neuroblastoma without the neurological syndrome (Altman & Bachner 1976).

Paroxysmal movement disorders

The movement disorders discussed thus far in this chapter have been persistent. However, some movement disorders only occur paroxysmally or intermittently. Paroxysmal movement disorders are characterized by sudden attacks of involuntary movements of the body without loss of consciousness. The movements may be choreic, athetotic, tonic, dystonic, or ataxic, or may occur in any combination. They may be unilateral or bilateral, or they may start in one extremity and then gradually spread to others. There is no loss of awareness during the episode. However, many patients are unable to speak because of the severity of the movements. Paroxysmal movement disorders may be classified into (1) paroxysmal kinesigenic choreoathetosis, (2) paroxysmal dystonic choreoathetosis of Mount and Reback, (3) acquired forms of paroxysmal movement disorders, with neurological disorders or metabolic disorders, and (4) familial periodic ataxia.

The differentiation of paroxysmal dyskinesia and tonic seizures induced by movements is not always readily discernible. Some cases of paroxysmal choreoathetosis are initially misdiagnosed as seizures. In reflex epilepsy, when the seizures are induced by movements, the differentiation may be particularly difficult. The state of consciousness is the most helpful distinguishing feature. When there is alteration or loss of consciousness the episode is more consistent with seizures. However, it may be necessary to obtain an electroencephalogram during the attack to confirm the diagnosis.

Paroxysmal kinesigenic dyskinesia

A frequently reported familial paroxysmal movement disorder is the kinesigenic one, in which the episodes are precipitated by movement. The abnormal movements may be

dystonic, choreic, athetotic, ballistic or mixed forms of movement occurring unilaterally or bilaterally (Goodenough *et al.* 1978). Dystonia is generally the predominant symptom. Characteristically, the movements are brief, with durations on the order of seconds to minutes, and may occur several times a day. The lower limbs may be primarily affected. Individuals with these episodes have noted the ability to abort some of the attacks by various maneuvers, such as grasping the involved extremity. Occasionally there is an aura of tightness or other vague sensation prior to the episode.

The precipitating movement is often a brisk and sudden event, such as a quick head turn, or suddenly moving the leg. Attacks may be induced in the examination room by having the individual hop in place on one foot for a short period, or perform other movements which the patient reports to induce the problem.

The attacks usually start in childhood and may increase in frequency during adolescence. The neurological examination and history are otherwise normal. In most instances, electroencephalograms obtained during the episode are normal. Epilepsy and migraines may coexist in some patients. There have been no consistent pathologic findings at autopsy. When the diagnosis is uncertain, video recordings of the event may provide additional diagnostic information.

An autosomal dominant mode of inheritance with incomplete penetrance is described by a number of authors. Sporadic cases have been reported. However, a woman previously described as a sporadic case had a daughter 10 years later who not only inherited the disorder, but was more severely affected (Bird *et al.* 1978). Two separate loci on chromosome 16 have been proposed for this entity, but the causative genes have not been found. A third locus may exist as well (Spacey *et al.* 2002; Lotze & Jankovic 2003). Patients may also exhibit these symptoms secondary to other underlying neurological disorders, such as a previous history of kernicterus, encephalitis, trauma, or multiple sclerosis (Blakeley & Jankovic 2002).

The response to anticonvulsant medication is dramatic in most instances. Phenytoin or carbamazepine are the medications most commonly prescribed. The serum concentration necessary for control of the attacks is lower than that employed when phenytoin is prescribed for seizure control (Wang & Chang 1985). Other anticonvulsants used include phenobarbital, valproic acid, primidone, levetiracetam, lamotrigene, and clonazepam. Some cases have responded to medications not ordinarily used for seizure control (e.g. L-dopa).

The episodes can start or increase in frequency during adolescence, and may decrease in frequency in the early adult years (Goodenough *et al.* 1978). Spontaneous remission can occur (Table 9.12).

FEATURES

Table 9.12 Paroxysmal Kinesigenic Dyskinesia

Discriminating feature

1. Movement-induced paroxysmal episodes

Consistent features

1. Induced by specific movements
2. Brief duration of episodes
3. Choreoathetotic, dystonic, tonic, or mixed forms
4. Dramatic response to anticonvulsant medication
5. No EEG changes during episode
6. Often involve the lower extremities

Variable feature

1. Often positive family history

Paroxysmal dystonic choreoathetosis of Mount and Reback

Paroxysmal dystonic choreoathetosis, initially described in 1940, occurs less frequently than the kinesigenic form (Mount & Reback 1940). Following the initial publication only a few case reports appeared until 1977, when Lance described four families (Lance 1977). Since then a number of other families have been reported.

The attacks in many of the cases begin in infancy; a smaller number of patients do not exhibit attacks until adulthood. The paroxysmal attacks have been manifested as choreoathetotic or dystonic movements. They are often bilateral, and may involve the face and laryngeal muscles or extremities. Episodes invariably last longer than 5 minutes, and can last for more than an hour. The attacks can occur daily, or the patients may go for months without one. The attacks are not precipitated by movement. More commonly, episodes are induced by intake of alcohol, coffee, tea, fatigue, hunger, or emotion. The attacks could be relieved by a short period of sleep in some patients (Jarman *et al.* 2000). As in the kinesigenic form, there is no loss of consciousness during the attack. Muscle stiffness without involuntary movement may be a forme fruste of this disorder (Matsuo *et al.* 1999).

Paroxysmal dystonic choreoathetosis is clearly transmitted through an autosomal dominant mode of inheritance with linkage to chromosome 2q (Fouad *et al.* 1996). As in the kinesigenic form, more males are affected than females. Routine laboratory studies, including electroencephalograms during the attacks, have been normal. There have been no pathologic findings in the central nervous system. The pathophysiology of this disorder, like that of the kinesigenic form, is unknown.

Unlike the kinesigenic form, the frequency of the attacks has not been reduced by many different anticonvulsants. Benzodiazepines have been an effective therapeutic agent

in eliminating or significantly reducing the frequency of the episodes (Lance 1977; Mayeux & Fahn 1982). Alternate-day oxazepam therapy provided sustained relief of the attacks in another study (Kurlan & Shoulson 1983), as did acetazolamide (Mayeux & Fahn 1982), or neurontin (Chudnow *et al.* 1997) (Table 9.13).

Paroxysmal exertional dystonia

In this disorder, patients will have attacks precipitated by continuous exercise such as walking or running. Stress and cold may also be precipitating factors. The episodes last minutes to hours in duration, often involving the lower limbs, although it may spread to other body parts. The attacks are frequently unilateral (Lance 1977; Demirkiran & Jankovice 1995; Bhatia *et al.* 1997).

The onset occurs in childhood or as a young adult. There have been families reported with an autosomal dominant pattern of inheritance, but many cases are sporadic. Exertional cramping without dystonia may also occur in family members (Kurlan *et al.* 1987).

Clonazepam, levodopa, carbamazepine, trihexyphenidyl, and acetozolamide have been tried as therapy (Demirkiran & Jankovice 1995; Bhatia *et al.* 1997).

Acquired forms of paroxysmal movement disorders

Acquired forms of paroxysmal disorders occur in association with an underlying disease and are not the result of a genetic defect. Underlying processes include trauma, multiple sclerosis, stroke, endocrinopathies, or a history of CNS infection. The nature of the involuntary movements during the attacks can be similar to that in the kinesigenic or nonkinesigenic form of paroxysmal movement disorders (Blakeley & Jankovic 2002).

FEATURES

Table 9.13 Paroxysmal Dystonic Choreoathetosis of Mount and Reback

Discriminating features

1. Paroxysmal episodes of choreoathetosis or dystonia
2. Not induced by movement
3. Autosomal dominant

Consistent features

1. Typically has an early onset
2. Episodes of long duration
3. Inconsistent response to medication
4. May involve the face or arms

Variable features

1. Adult onset

Paroxysmal movement disorders, particularly in children diagnosed with a static encephalopathy, are often misdiagnosed as seizures or hysteria. Because of their length, the episodes can be very painful and distressing to patients, families, and teachers. The paroxysmal episodes that occur in individuals with a static encephalopathy syndrome often begin in childhood (Rosen 1964). The attacks are usually brief, measured in minutes; however, in a number of cases the attacks have lasted for hours (Erickson & Chun 1987). The movements can be dystonic, tonic, or choreoathetoid; occurrences range from several a day to once every several months. Neurological examination reflects the findings of the past encephalopathy. Some individuals have signs of spasticity or hemiparesis; others are severely hypotonic or have persistent choreoathetosis. Electroencephalograms during the episode are no different than those recorded during the interictal period. The response to anticonvulsants is variable. Botulinum toxin injections may also be helpful in select cases.

The paroxysmal episodes of patients with multiple sclerosis are primarily flexor spasms (Miley & Forster 1974). Because of the intensity, the attacks are often painful. They may be the initial symptoms of multiple sclerosis. The attacks are short, lasting minutes, and frequently stop after 1 or 2 months of symptoms. They respond to anticonvulsants.

Paroxysmal choreoathetotic episodes occur in individuals with endocrine diseases such as hyperparathyroidism (Arden 1953), thyrotoxicosis (Fischbeck & Layzer 1979), and diabetes during periods of hypoglycemia (Newman & Kinkel 1984). The attacks consist of tonic metabolic defect leads to cessation of the episodes. The etiology of the dyskinesia is unknown. It is postulated that striatal dysfunction may result from a neurotransmitter defect.

Nocturnal paroxysmal dystonia

These are complex motor attacks that arise abruptly during sleep, especially during non-rapid eye movement sleep. The typical patient displays attacks lasting 15 seconds to 2 minutes in length. There may be a sudden opening of the eyes, followed by dystonic postures or by disordered violent movements. The episodes may occur several times during the night. Nocturnal paroxysmal dystonia may respond to carbamazepine, but not to other agents (Montagna 1992). These attacks often represent a form of seizure activity and this can be verified by overnight video EEG recording.

Ataxia

Ataxia may be caused by a heterogeneous group of diseases. Patients with recessively inherited errors of metabolism such as Hartnup's disease, Leigh's disease, and maple syrup urine disease may intermittently be ataxic. Individuals with

acquired diseases could possibly manifest ataxia as part of the clinical spectrum. Stroke or mass lesion can present with ataxia when the lesions involve the posterior fossa. Acute onset of ataxia, particularly when other focal neurological signs are present, warrants consideration of an MRI or CT scan. Some peripheral neuropathies, especially those occurring in families, also present with ataxia, either because the underlying disease directly affects cerebellum, or because of posterior column damage (and loss of position sense input). Medications can cause ataxia, and not infrequently patients taking anticonvulsants will become ataxic at higher levels of these medications. Weakness can also appear as indistinguishable from ataxia (Stumpf 1985; 1987).

Acute cerebellar ataxia

Acute cerebellar ataxia most often presents as a sudden disturbance of gait and balance. Although the ataxia of gait is the most prominent sign, appendicular ataxia and nystagmus also occurs.

ACA usually develops days to weeks after a viral illness, particularly chickenpox. In the largest series (Connolly *et al.* 1994), 26% of patients had chickenpox, 3% had Epstein–Barr virus infection, 49% had other viral illnesses, 19% had no prodrome, and 3% developed ACA after immunizations. Other preceding infections include measles, mumps, herpes simplex virus, cocksackievirus, echovirus, poliovirus, *M. pneumoniae*, and *Legionella pneumophila*.

ACA usually occurs in children between 2 and 5 years of age and is rare in adolescents and adults. Epstein–Barr virus infection and immunizations are the most common causes in these older patients (Connolly *et al.* 1994). Some ataxia is seen in all children who have ACA, and 20–50% of patients are unable to walk. Finger dysmetria is seen in two-thirds of these children but is strikingly mild compared with the gait ataxia (Connolly *et al.* 1994). Nystagmus was present in less than 20% of Connolly's (1994) patients, whereas 45% of Weiss and Carter's patients had nystagmus (1959). Transient behavioral alterations and school difficulties are seen in at least one-third of children with ACA.

Laboratory studies reveal a mild CSF pleocytosis. Neuroimaging studies are typically normal, although occasionally abnormal signal can be seen in the cerebellum.

Given the variety of antecedents, it is likely that a common immunoinflammatory process mediates ACA. Antineuronal antibodies in ACA follow Epstein–Barr virus infection (Ito *et al.* 1994). CSF pleocytosis occurs in 25–50% of children, almost always with a lymphocytic predominance (Weiss & Carter 1959; Connolly *et al.* 1994). The CSF IgG index is elevated in 50% of these children, and oligoclonal bands are present in 10–17%.

Ninety per cent of children will completely recover from the ataxia, typically within the first few months after the onset of disease. Supportive therapy is needed. One-fifth of children experience transient behavioral or intellectual problems (see Connolly *et al.* 1994, for extensive review). In rare cases without complete recovery, atrophy of the cerebellar hemispheres or other conditions, such as cerebellar tumor, opsoclonus-myoclonus-ataxia, or intoxication should be expected (Table 9.14).

Ataxia-telangiectasia

Ataxia-telangiectasia (AT) is a multisystem disease, affecting both the nervous system and the immune system. Soon after beginning to walk, the children will present with a progressive ataxia, as well as choreoathetotic movements of their extremities. There is typically also a loss of deep tendon reflexes, dysarthria and an oculomotor apraxia. Besides their neurological symptom, these children will also show prominent telangiectasias that can be most prominently seen in the conjunctiva and skin. These children become wheelchair-bound during their second decade.

The gene responsible for AT, called ATM, is a kinase that may be involved in cell cycle control, DNA repair, and prevention of programmed cell death (Savitsky *et al.* 1995). *In vitro*, the cells derived from AT patients have defective DNA repair capability when exposed to irradiation. Heterozygotes for the ataxia-telangiectasia gene (about 1% of the general population) may be at increased risk for cancer, particularly female breast cancer.

The cerebellar and extrapyramidal systems of the brain are the most severely affected. Macroscopically, the cerebellum is usually grossly atrophic (Gatti *et al.* 1991), most prominently throughout the vermis. Microscopically, atrophy affects all layers of the cerebellar cortex. Other pathologic changes include cortical atrophy, diffuse gliosis, and degeneration of anterior horn cells.

Care should be taken to avoid radiographs in these patients, since their cells are hypersensitive to ionizing radiation. Neuroimaging shows atrophy of the cerebellar hemispheres and vermis, although white matter abnormalities mimicking a leukodystrophy or primary demyelinating

FEATURES

Table 9.14 Acute Cerebellar Ataxia

Discriminating features

1. Acute onset of ataxia

Consistent features

1. Follows viral infection
2. Typically occurs in young children
3. Recovery over the first few months

Variable features

1. CSF pleocytosis
2. Abnormalities on MRI scan

disease have been described (Ciemins & Horwitz 2000). These patients also have nearly a 100-fold increased risk for malignancy, and should be carefully monitored for malignancies. Heterozygotes for the AT gene will carry nearly a seven-fold risk of increased malignancies (Swift *et al.* 1981).

Serum studies reveal a decrease in the IgA and IgE levels and elevated alpha-fetoprotein levels. Alpha-fetoprotein levels are highly elevated, although difficult to interpret prior to the age of 2 years. The diagnosis is often a challenge to make before the age of 5 years, and many children will experience symptoms for several years before a definitive diagnosis is made.

The treatment is supportive. Infections can be treated with antibiotics and IVIG. Live-virus vaccines should not be used after the diagnosis of AT is made. Genetic counseling should be provided for the families of this autosomal recessive disorder.

Prognosis is poor, and the progression is relentless. Children lose the ability to walk independently in their second decade. Death may occur in adolescence or early adulthood due to malignancy or pulmonary infection.

Episodic ataxia

The syndrome of episodic ataxia (EA) results in episodes of vertigo and ataxia, often triggered by stress, fatigue or exercise. EA has been called by a variety of other names, including periodic ataxia. It was initially described in 1946 (Parker 1946). Since that time, multiple families have been reported. It is an autosomal dominantly inherited disorder. Episodic ataxia type 1 (EA-1) is caused by mutations in the potassium channel gene KCNA1, whereas episodic ataxia type 2 (EA-2) is caused by mutations in the calcium channel gene CACNA1A (Baloh & Jen 2002).

The episodes usually begin in infancy or childhood, but infrequently may start in adulthood (Tibbles *et al.* 1986). The attacks of cerebellar incoordination are characterized by paroxysmal bouts of ataxia, dysarthria, and nystagmus. The frequency is variable; episodes may occur daily or may be separated by weeks or months. The duration of the episodes may be brief, but more often the episodes last for hours and sometimes days. Ataxia of the trunk and extremities is frequently so severe during the episodes that the patient cannot stand without assistance. Speech becomes dysarthric and difficult to understand, although receptive language function remains intact. Vertical or horizontal nystagmus may be present during the attack.

Slight cerebellar signs are often noted during interim neurological examination. Horizontal and sometimes vertical nystagmus and mild ataxia on finger-to-nose and heel-to-shin testing are typical findings. Although some authors found no progressive neurological involvement, others reported a slow progression of ataxia. EA-1 is more likely to have interictal myokymia and EA-2 often has interictal nystagmus (Jen 2000).

CT and MRI studies are usually unremarkable in young children; however, in individuals whose symptoms persist over a prolonged period, neuroimaging will frequently reveal cerebellar atrophy, especially of the vermis.

Acetazolamide in many cases completely eliminates or greatly reduces the number of episodes within 24 hours of its administration (Griggs *et al.* 1978). Some patients on medication have remained attack-free for many years. Other authors report a less complete response to this drug. Anticonvulsants such as phenytoin and phenobarbital have no effect on these paroxysmal attacks (Table 9.15).

FEATURES

Table 9.15 Episodic Ataxia

Discriminating features

1. Periodic episodes of ataxia or vertigo
2. Autosomal dominant

Consistent features

1. Difficulty walking during ataxia or vertiginous attacks
2. Precipitated by physical or emotional stress
3. Cerebellar signs on neurologic examination
4. Responds to acetazolamide

Variable features

1. Cerebellar degeneration

CONSIDER CONSULTATION WHEN...

- The child has a family history of chorea or dystonia.
- The symptoms of a child suspected of having Sydenham's chorea continue for more than 2 months.
- Dystonia involves the legs and/or is progressive.
- Tremor is associated with rest or with an increase in muscle tone.
- The symptoms of ataxia have no defined cause and are persisting over 1 month.

Annotated bibliography

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Additional resources

The website "We Move" is a not-for-profit organization that maintains an up-to-date pediatric section, "Kids Move" (http://www.wemove.org/pediatric/) that provides current information for both physicians and patients. Many of the disorders discussed in this chapter are discussed in depth at this website.

CHAPTER 10

Infections of the Central Nervous System

William E. Bell, MD and Frederick W. Henderson, MD

OUTLINE

Bacterial infections of the central nervous system
Viral infections of the central nervous system
Fungal infections of the central nervous system
Parasitic diseases of the central nervous system
Schistosomiasis
Spirochaetal diseases of the central nervous system
Rickettsial infections

Bacterial infections of the central nervous system

Acute bacterial meningitis

Acute bacterial meningitis in most cases is a septic-borne, rapidly progressive infection which occurs in an anatomical area of impaired host resistance. This local physiologic immunodeficiency is because cerebrospinal fluid contains very low contents of immunoglobulins and complement compared to plasma, components required for effective phagocytosis and intracellular bacterial killing. For this reason, eradication of bacteria in cerebrospinal fluid requires the attainment of high cerebrospinal fluid levels of bactericidal antibiotics.

Pyogenic meningitis can affect any age but, among children, the disorder has a decided predisposition to occur in the younger age groups including the neonate and those less than 4 years of age. Peak incidence of meningococcal meningitis is under age 2 years and that of pneumococcal meningitis is under age 4 years. When *Haemophilus influenzae* meningitis was far more common before 1990, this illness peaked in incidence between 6 and 9 months of age and most cases occurred in children below 3 years of age. Currently, the most common causes of meningitis in the neonatal period are group B *Streptococcus* and *Escherichia coli* followed less often by *Listeria monocytogenes*. In older infants and children, *Streptococcus pneumoniae* and *Neisseria meningitidis* now account for the great majority. As pneumococcal conjugate vaccine becomes more widely acceptable for use in infancy, it can be expected that invasive pneumococcal infections in children will sharply decrease leaving meningococcal meningitis to become the leading type in this age group.

It is now known that the inflammatory reaction to invading bacterial organisms is not primarily from the pathogens themselves. Bacterial cell death within the cerebrospinal fluid as well as in the systemic circulation leads to release of endotoxin known as lipopolysaccharide from Gram-negative bacteria and teichoic acid-peptidoglycans from Gram-positive organisms. These substances stimulate the production from macrophages, monocytes, and brain cellular elements of cytokines which activate the complement cascade resulting in meningeal and meningovascular inflammatory responses. Cytokine-induced meningeal inflammation provokes a cerebrospinal fluid cellular response while that affecting the microvasculature of the brain and cerebrospinal fluid alters the blood-brain barrier increasing vascular permeability causing brain swelling. The degree of cerebrospinal fluid pleocytosis and vascular inflammation has been found to correlate with the magnitude of cytokine production. The recognition that cytokine production can be curtailed by the administration of corticosteroids given before or at the time of initiation of antibiotic therapy has led to the consideration of use of dexamethasone in patients over 1 month of age with acute pyogenic meningitis. Except for certain unusual instances with rapid onset of high-grade cerebral swelling, this therapeutic approach remains controversial and was studied most extensively only in infants with *Haemophilus influenzae* meningitis.

Clinical manifestations of bacterial meningitis are outlined in the following sections and are more determined by age of the affected infant or child than the causative organism. Except in the neonate, fever is customary and in all age groups, the illness tends to result in decline in responsiveness unless treatment is begun early. Lethargy is often preceded by headache, vomiting, confusion, and disorientation. Seizures occur in up to 50% of cases of meningitis and can be the first suggestive event in the febrile infant or child. Although brain swelling usually rapidly becomes a component of the illness, well-established papilledema is not usually found and if present, suggests an alternative diagnosis. Meningeal signs including neck stiffness, Kernig's signs, and Brudzin-

ski's sign are not usually found in neonates but begin to be common signs in infants beyond a few months of age with acute meningitis.

The indication for cerebrospinal fluid examination is determined by the clinical suspicions from history and physical examination. In the neonate, it is often on the basis of signs of bacterial sepsis, especially when complicated by seizures, lethargy, or a full fontanel. On gross observation, infected cerebrospinal fluid may range from clear to purulent. Cerebrospinal fluid with the rare and unusual examples of meningitis caused by the anthrax bacillus and *Clostridium* species is often hemorrhagic due to the intense necrotizing vasculitis with these infections. Characteristic cerebrospinal fluid abnormalities with pyogenic meningitis include a neutrophilic pleocytosis, reduced glucose content, and increase in the protein level. Meningitis in older patients caused by *Listeria monocytogenes* has been notable for the occasional occurrence at a lymphatic pleocytosis and a normal cerebrospinal fluid glucose content. On rare occasions, the cerebrospinal fluid in suspected meningitis will contain fewer than 10 cells/mL, normal other findings, but a positive culture. Preliminary antibiotic therapy can alter the cerebrospinal fluid abnormalities although not usually to the degree that precludes establishing the diagnosis of meningitis. A controversial issue concerns the need in older children for neuroimaging before lumbar puncture when signs of meningitis include those indicative of intracranial hypertension. Certain findings listed in Table 10.1 warrant preliminary computed tomography (CT) scanning, although in many other cases performing a lumbar puncture as soon as possible is highly desirable.

Neonatal meningitis

Bacterial meningitis in the first month after birth is considered separately from that occurring later in infancy and childhood because the predisposing factors are different, the clinical signs of the illness are different, and the causative organisms are usually different. Except for lethargy and the common occurrence of seizures, the clinical signs in the neonate with pyogenic meningitis reflect the presence of sepsis, present in almost all with neonatal meningitis. Temperature instability, poor feeding, vomiting, irritability, and respiratory abnormalities are hallmarks of neonatal bacteremia. The association with meningitis is usually documented by cerebrospinal fluid examination in the infant suspected or known to be septic. Meningeal signs, including neck stiffness and Kernig's sign, are not usually seen in the neonate but begin to correlate with meningeal inflammation later in infancy. Fullness of the anterior fontanel in the septic neonate suggests the possibility of meningitis but is often not present, at least early in the illness. In the infant with signs indicative of sepsis, the occurrence of a seizure should immediately indicate the probability of meningitis.

Group B *Streptococcus* (*S. agalactiae*) is the most common cause of neonatal meningitis in this country, followed by *Escherichia coli* and other Gram-negative pathogens. Less common causes include *Listeria monocytogenes*, *Salmonella* species, and *Citrobacter koseri*, the latter being complicated by periventricular abscess formation in the majority of cases (Table 10.2).

Group B *Streptococcus* neonatal infection occurs in two clinical forms. The early-onset form is more common and describes onset of illness between birth and age 7 days with most showing overwhelming signs of infection with respiratory distress, cardiovascular collapse, and neutropenia within hours after birth. The early-onset form is caused by vertical transmission from the maternal anogenital tract. Meningitis is found in about 20% of such cases. The late-onset form has onset of illness between 7 and 90 days after birth and usually presents with clinical evidence of meningitis, most often between 2 and 4 weeks of age. Unlike infants with the early-onset form, those who present later do not usually experience severe respiratory compromise although many have intense signs of central nervous system infection. In only about 50% of late-onset cases is the organism derived from the mother. Studies by Sundell *et al*. in 2000 suggest that the more virulent early-onset form of illness with prominent respiratory compromise is due to an exotoxin termed CM101 liberated from group B *Streptococcus*

TABLE 10.1 Indication for CT Examination before Lumbar Puncture in a Child Suspected of Pyogenic Meningitis

Papilledema
Dilated or poorly reactive pupils
Focal (simple partial) seizures
Hemiparesis
Bradycardia
Decerebrate posturing
Tonic attacks
Immunosuppressive disease
Bradycardia or hypertension with neck flexion

TABLE 10.2 Most Common Causes of Bacterial Meningitis from Birth to 4 Weeks

Group B *Streptococcus*
Escherichia coli
Listeria monocytogenes
Klebsiella species
Proteus species
Pseudomonas aeruginosa
Citrobacter koseri
Salmonella species

which binds to immature pulmonary vascular receptors. Rapid maturation of pulmonary vascular receptors after 1 week of age supposedly explains the less severe septic components of the late-onset form of the illness. As a result of maternal screening with vaginal and anal cultures at approximately 36 weeks of gestation with intrapartum penicillin given to culture-positive mothers, the incidence of early-onset group B *Streptococcus* invasive disease in the neonate has sharply decreased from 2–4 per 1000 live births in 1993 to 0.61 per 1000 in 1998. Factors that predispose to neonatal invasive disease with group B *Streptococcus* include a heavy inoculum of the fetus at delivery with organisms from the maternal anogenital tract, low birth weight and obstetrical complications, and deficiency of maternal type-specific antibodies directed against group B *Streptococcus*.

Among Gram-negative enteric bacilli causing neonatal meningitis, *Escherichia coli* is the most common offender. In older children and adults, *E. coli* is well known as a cause of meningitis complicating neurosurgical procedures, following open craniocerebral injuries, and in the immunosuppressed. Low birth weight sick neonates requiring persistent intubation or those with indwelling intravascular catheters are also susceptible to sepsis and meningitis with *Pseudomonas aeruginosa*, *Klebsiella* species, *Proteus* species, *Serratia marcescens*, as well as *Candida* species, a yeast-phase fungus.

Escherichia coli meningitis can present soon after birth but most become symptomatic near the end of the first week after birth or 1–2 weeks later. In perhaps 20% of cases of *E. coli* meningitis in the neonate, a predisposing cause will be apparent, including urinary tract malformations, neurosurgical closure of an open neural tube defect, necrotizing enterocolitis, or complicating sepsis in a child with galactosemia or hereditary tyrosinemia. Usual presenting manifestations are seizures, lethargy, poor feeding, vomiting, and temperature instability. Blood leukocyte counts are variable, some being elevated and others being suppressed and associated with thrombocytopenia. Cerebrospinal fluid is diagnostic in the majority of the cases. Blood cultures are frequently positive and urine culture may reveal the same organism. Among a large series of neonates with Gram-negative bacillary meningitis, Unhanand *et al*. (1993) found a case fatality rate of 17%. Among survivors, 61% had long-term sequelae such as seizures, deafness, long tract signs, visual loss, developmental and mental retardation, and hydrocephalus.

Haemophilus influenzae type B meningitis

Following the widespread use of *Haemophilus influenzae* conjugate vaccine in early infancy in 1990, the incidence of invasive disease including meningitis caused by this organism dramatically declined by well over 95%. Prior to that time, *H. influenzae* type B accounted for approximately 70% of all cases of acute pyogenic meningitis in children. The disease is now rarely seen in large medical centers but before effective immunization given in early infancy, the peak age at occurrence of the illness was 6–9 months and the great majority occurred before age 3 years. Most cases would begin with fever and irritability for 1–3 days when vomiting, lethargy, seizures, and variable neurologic signs evolve, indicating blood-borne cerebrospinal fluid invasion. Less often, the illness will be more fulminating with rapid evolution of high fever, deep coma, respiratory compromise, evidence of consumption coagulopathy and shock, and rapidly progressive intracranial hypertension. Meningitis can be complicated by pneumonia, otitis media, or suppurative pericarditis. In 5–8% of cases either septic or reactive arthritis will be found. About 30% of children with *H. influenzae* meningitis will have the illness complicated by sterile subdural effusion which resolves spontaneously in most cases. Infected subdural effusions or subdural empyemas are less common but more symptomatic and require surgical drainage.

Haemophilus influenzae was originally highly sensitive to ampicillin until 1974 when ampicillin-resistant strains emerged and eventually became common. Thereafter, cefotaxime became the standard mode of therapy. Most studies revealed that *H. influenzae* meningitis had a mortality of about 3% and neurologic sequalae would occur in over 30% of survivors, with hearing loss being the single most common deficit.

Meningococcal meningitis

Invasive meningococcal infections have been categorized as primarily meningitis in presentation or primarily in the form of meningococcemia. Schuchat and colleagues (1997) state that in all age groups, about 48% of cases of meningococcal disease present predominantly as meningitis and 48% are manifested with signs of meningococcemia. In 3%, pneumonia is the primary form of illness. In this review, the overall case fatality rate was 11%. Among those presenting as meningococcal meningitis, the fatality rate was 3% while those in the meningococcemia group had a case fatality rate of 17%. Among persons with fulminating meningococcemia with early onset of hypotension and purpura fulminans, the case fatality rate is considerably higher.

At least 13 serogroups of *Neisseria meningitidis* have been described with most human infections being caused by serogroups A, B, C, Y, and W-135. Serogroup A has been known since the early 20th century to cause periodic epidemics of meningococcal disease occurring roughly at intervals of 8–12 years. Serogroup A is now infrequent in the United States but continues to be a serious public health problem in sub-Saharan Africa and Asia. Most cases of meningococcal disease in the United States are caused by serogroups B or C and occur sporadically or in localized outbreaks. Serogroups Y and W-135 are less common causes of invasive disease and are better known as causes of pneumonia.

Invasive disease with *N. meningitidis* has two peaks in age incidence. The first is among infants younger than 2 years of

age who commonly lack protective antibodies. The second affects adolescents and young adults. These illnesses can occur any time of year but are more frequent in late winter and early spring. During winter months, 5–10% of the population have nasopharyngeal colonization with *Neisseria* species, most being nonpathogenic strains. Of those colonized with pathogenic *N. meningitidis*, on infrequent occasions organisms become transferred from the mucosal surface to the vascular compartment and invasive disease follows in some fashion. Presentation of meningococcal meningitis, like that with other common offenders, is usually with abrupt onset of fever, chills, and headache, soon followed by lethargy, confusion, and the development of meningeal signs. Approximately 60–70% will develop skin lesions, sometimes initially with a maculopapular rash but more characteristically with multiple petechial lesions indicative of either vascular wall disruption due to infectious vasculitis or thrombocytopenia. In some, the illness will rapidly resolve with antibiotic therapy while others will experience rapidly progressive disease reflecting sepsis, endotoxemia with consumption and hypotension leading to shock and multiple organ failure.

Among children presenting with meningococcemia, most will exhibit petechiae and when fulminant, the rash may proceed to purpura fulminans which becomes associated with systemic hypotension, shock, and multiple organ failure with visceral hemorrhages. This condition is called the Waterhouse–Friderichsen syndrome and although adrenal hemorrhage along with hemorrhage in other organs is commonly found at autopsy, the fulminate nature of the illness is due to massive endotoxemia with consumption coagulopathy. Acquired protein C and protein S deficiency appears to play a role in the severity of the coagulopathy and may be a component of the illness amenable to treatment.

Diagnosis of invasive meningococcal disease is often suspected clinically when fever occurs with a petechial rash, with or without meningitis. Because of the potential for invasive meningococcal disease to progress rapidly with the development of cardiovascular instability within hours after onset of first symptoms, intravenous antibiotic treatment should be started as soon as possible. When the illness is suspected on the basis of fever and the characteristic rash, if transport to a medical facility will require more than a short time period and if cerebrospinal fluid examination cannot be done locally, treatment should be initiated before transport even though this might diminish the value of subsequently obtained specimens for culture. Etiologic diagnosis is confirmed by cultures of blood, cerebrospinal fluid, and urine. Latex agglutination can also be useful where available. In children with meningitis, Gram stain shows intracellular Gram-negative diplococci in most. Cerebrospinal fluid may be cloudy or purulent and includes findings typical of acute bacterial meningitis in the majority. Exceptions do occur and in a large series of pediatric meningococcal meningitis cases reported by Wong *et al*. (1989), cerebrospinal fluid which was ultimately culture positive for meningococci in 11% did not have a neutrophilic pleocytosis and had normal cerebrospinal fluid glucose contents and negative Gram stains. It is probable that the cerebrospinal fluid specimens in these atypical cases were obtained soon after entrance of bacteria from blood into cerebrospinal fluid and before an inflammatory reaction could occur. Infants with meningococcal meningitis are more likely to have sequelae than are adolescents. Findings early in the illnesses that predict a poor or fatal outcome include neutropenia, hypothermia, hypertension or shock, and evidence of coagulopathy including purpura fulminans.

Penicillin is the antibiotic of choice for treatment of meningococcal disease. Isolates in this country have been found to be sensitive to penicillin although decreasing sensitivity to penicillin has recently been found in some foreign countries. For children intolerant to penicillin, cefotaxime or ceftriaxone can be used. Antibiotic therapy is usually given for 7–10 days although recent studies suggest that 3 days is probably sufficient, an approach not yet adopted in this country. Management of complicating features such as endotoxic shock, thrombocytopenia, cardiac or respiratory compromise, and the indications for corticosteroids requires intensive care and consultation with the appropriate medical specialties.

Most meningococcal infections are acquired by contact with respiratory secretions from an asymptomatic NP carrier rather than from a patient with clinical disease. Household members and those with close contact with an infected patient are usually advised to receive prophylactic therapy. This was done in earlier times with rifampin given orally for 4 days but currently most give a single IM dose of ceftriaxone.

Meningococcal quadrivalent vaccine protects against serogroups A, C, Y, and W-135 but not against serogroup B which is not immunogenic. The vaccine is not believed to be effective for children less than 2 years of age and routine immunization is not recommended for children. The vaccine is useful to curtail local outbreaks of serogroup C meningococcal infections and for certain high-risk groups. These include persons with asplenia or those scheduled for splenectomy for certain disorders such as hereditary spherocytosis or immune thrombocytopenia. It is also advised for those susceptible to recurrent meningococcal infections because of late complement component deficiency. The vaccine is given to military recruits and to travelers going to certain endemic regions, such as sub-Saharan Africa. It is now recommended to provide information to freshman college students about the vaccine and is made available to those who elect to take it.

Streptococcus pneumoniae meningitis

Streptococcus pneumoniae is a Gram-positive diplococcus that is now considered to be the leading cause of pyogenic men-

ingitis in infants and children. Among the common cases of bacterial meningitis in children, the pneumococcus causes the highest mortality and provokes the most abundant meningeal inflammatory response. The mortality rate of pneumococcal meningitis occurring in infants and children is generally stated to be approximately 10% and is higher when the illness occurs in early infancy. Pneumococcal meningitis in children has its highest incidence in the first 4 years of life, indicative of the common occurrence and high bacterial density of nasopharyngeal colonization at this age. By age 2 years, the majority of children have had at least one occasion of NP colonization with this organism. Invasive pneumococcal infections have only rarely been described in the first days after birth but infrequent cases occur between 2 and 4 weeks of age, probably by vertical transmission from the mother.

Most cases of *Streptococcus pneumoniae* meningitis occur in previously normal children. Studies suggest that about 10–15% occur in children with a predisposing factor which includes functional or anatomical asplenia, sickle cell disease, agammaglobulinemia, and intracranial cerebrospinal fluid fistula. With post-traumatic or congenital defects associated with cerebrospinal fluid rhinorrhea or otorrhea, in approximately 70% of children who develop meningitis *S. pneumoniae* will be the cause. In addition, the pneumococcus is the most common cause of community-acquired pneumonia in children and in adults, the most common cause of acute otitis media and sinusitis, and by far the most common cause of so-called occult bacteremia in infancy, an illness with fever without localizing signs which sometimes will be complicated by localized disease if not treated with antibiotics.

Aspects of pneumococcal meningitis suggestive of a poor prognosis include age of onset, a very low cerebrospinal fluid glucose content and a markedly elevated cerebrospinal fluid protein, coma, respiratory distress, shock and seizures early in the course of the illness, and its development in the asplenic patient which is frequently associated with a fulminating septic course, with or without meningitis.

A major factor which has affected the management of children with pneumococcal meningitis has been the rapid rise in penicillin-resistant strains in the past decade. Resistance has also risen among the cephalosporins but to a less degree that with penicillin. While penicillin resistance has been found in a high percentage of isolates in many foreign countries, the incidence of resistant strains continues to vary from community to community in this country. It is sufficiently prevalent, however, to account for the therapeutic use of vancomycin in combination with cefotaxime or ceftriaxone for unspecified bacterial meningitis in children over 1 month of age and the continuation of this regimen when *S. pneumoniae* is found to be the cause. The concern of the possibility of antibiotic resistance of the pneumococcus has led to the common practice of repeating the cerebrospinal fluid examination after 48 hours of treatment if the organism is then known to be a resistant strain and if clinical signs have not improved or have worsened.

Heptavalent pneumococcal vaccine is FDA approved for routine immunization of children beginning at 2 months of age and provides protection against seven of the most common pneumococcal strains which cause invasive disease in children. Following its availability in year 2000, the vaccine has already had a substantial impact on the occurrence of pneumococcal infections, including meningitis. More widespread acceptance of the vaccine is expected in the future to further control the illness in children.

Treatment of acute bacterial meningitis

The best chance of a favorable outcome among infants and children with acute pyogenic meningitis is with the initiation in the early stage of the illness of high-dose, intravenous bactericidal antibiotics. In most cases, antibiotics will be started before the causative organism is isolated. The current recommendations for selection of antimicrobials are outlined in Table 10.3. In the neonate, ampicillin is included because some strains of *E. coli* remain sensitive to the drug and because *Listeria monocytogenes* is resistant to the cephalosporins. Should group B streptococcus be proven to be the cause, either ampicillin, with or without an aminoglycoside, or penicillin is usually chosen. With less common enteric bacilli cerebrospinal fluid infections, changes in the regimen will be determined by *in vitro* sensitivity studies. In those over 1 month of age, vancomycin is now included because the pneumococcus has become the most common isolate from cerebrospinal fluid and is now known to have a significant rate of increased resistance to penicillin. Invasive meningococcal infections are treated with single drug therapy with penicillin or with cefotaxime or ceftriaxone.

Control of fever, control of seizures, control of increased intracranial pressure, and fluid and electrolyte management are additional important aspects of care of the infected child. Among children with meningitis who are not dehydrated, a modest reduction in the fluid volume administered in the first 24 hours of treatment can be useful relative to cerebral

TABLE 10.3 Empirical Antibiotic Therapy for Unspecified Bacterial Meningitis

Under Age 1 Month
Cefotaxime or ceftriaxone Ampicillin
Over Age 1 Month
Vancomycin Cefotaxime or ceftriaxone

edema. When clinical signs or laboratory findings suggest vascular volume depletion, not less than maintenance fluid needs must be given. It is critical to maintain vascular volume to protect tissue and cerebral perfusion during an acute febrile illness, especially so in more severe cases in which cerebral autoregulation may be disturbed.

Use of dexamethasone to diminish cytokine production thereby curtailing the inflammatory response has become a popular topic in the past decade but remains controversial. In children, most studies evaluating the affect of dexamethasone have been among young children with *H. influenzae* meningitis. Early studies did show their use reduced the inflammatory response and decreased the incidence of sequelae, especially hearing loss. It is generally agreed that if dexamethasone is to be used, it should be given before or at the time of initiation of antibiotics. Concerns of the possible adverse effects of dexamethasone in children with meningitis include their possible adverse effect on neutrophil phagocytic function as well as the possibility of decreasing penetration of antibiotics, especially vancomycin, into cerebrospinal fluid. If one chooses to use dexamethasone, the dose for this purpose is 0.6 mg/kg/day given in four divided doses for the first few days of the treatment regimen.

Recurrent bacterial meningitis

Recurrent attacks of bacterial meningitis are not common but certainly not rare and the underlying cause can be identified in most, outlined in Table 10.4. The majority are secondary to an abnormal communication between the external environment and the cerebrospinal fluid. Specific localization of the defect can often be difficult and requires help from consultants in neurosurgery and ENT in many instances, for both diagnosis and treatment. The most common causes are traumatic injuries with dural lacerations through frontal or ethmoidal sinuses, the base of the skull, or the tegmen tympani of the temporal bone leading to cerebrospinal fluid leakage into the middle ear. The next most common causes are congenital defects, especially at the cribiform plate, with or without a basilar encephalocele, and, as infectious complication of a ventricular shunt for hydrocephalus. Congenital dermal sinuses which penetrate into the cerebrospinal fluid can be located along the midline in the occipital region or anywhere along the spine. A dermal sinus is suspected in any child with recurrent meningitis not secondary to craniocerebral trauma and without cerebrospinal fluid rhinorrhea. Dermal sinus presents as a small, midline orifice in the skin often surrounded by a surface capillary hemangioma or a tuft of hair. A dermal sinus in the occipital region sometimes terminates in a posterior fossa dermoid, a non-neoplastic lesion that predisposes to bacterial meningitis due to transmission of bacteria via the dermal sinus into the cerebrospinal fluid or to aseptic meningitis secondary to spontaneous leakage of material from the dermoid into the cerebrospinal fluid.

TABLE 10.4 Causes of Recurrent Bacterial Meningitis in Children

- Post-traumatic craniocerebral injuries
- Postsurgical defects with dural lacerations
- Ventricular shunt infections
- Congenital defects
  - Basal encephaloceles
  - Congenital defects of the cribiform plate
  - Congenital inner ear defects
  - Congenital dermal sinuses
  - Neuroenteric fistula
- Chronic increased intracranial pressure
- Empty sella syndrome
- Parameningeal suppurative foci
- Immunosuppression and late complement component deficiencies

Additional causes of abnormal cerebrospinal fluid communications include erosion of the skull base from chronic increase in intracranial pressure, the empty sella syndrome, and postneurosurgical dural defects, especially as a complication of pituitary surgery by a trans-nasal, trans-sphenoidal approach. Congenital defects affecting the inner ear such as the Mondini defect with a perilymphatic fistula through the oval window or a malformation affecting the stapes footplate allowing cerebrospinal fluid and perilymph to be transmitted into the middle ear likewise can cause recurrent meningitis. These conditions are suspected in a child with unilateral deafness, sometimes with episodes of ataxia or vertigo, who develops acute pyogenic meningitis.

Cerebrospinal fluid rhinorrhea is a finding indicative of an intracranial defect predisposing to recurrent meningitis and can present almost immediately after cranial injury or a neurosurgical operative procedure or can be delayed for weeks, months, or even years thereafter. Nasal discharge of cerebrospinal fluid is often abundant when the dural laceration is anteriorly placed but may be scanty or absent when the source is from inner ear pathology in which case cerebrospinal fluid is transmitted into the middle ear, down the Eustachian tube, and into the posterior nasopharynx where the majority may be swallowed. Should the injury or pathology disrupt the tympanic membrane, cerebrospinal fluid otorrhea will occur. It cannot accurately be documented that the clear fluid dripping from the nostrils is cerebrospinal fluid by testing the fluid for glucose by dipstick methods or by testing for chloride content, as these substances can be similar in fluid generated by the nasal mucosa or in tears. That the fluid *is* cerebrospinal fluid can sometimes be shown by the presence of B-transferrin on protein electrophoresis.

TABLE 10.5

Predisposing Factors Associated with Brain Abscesses in Children

Congenital cyanotic heart disease
Suppurative sinusitis
Chronic otitis media and mastoiditis
Dental infections
Penetrating cranial injury
Immunocompromising conditions
Large animal bites to the cranium
Complication of acute pyogenic meningitis
Pulmonary arteriovenous fistula

Precise localization of a cerebrospinal fluid fistula is highly desirable before surgical correction is undertaken. There have been numerous techniques proposed and the least invasive methods are usually first attempted. High resolution CT is useful for defects anteriorly along the cribiform plate, and especially for temporal bone fractures and congenital defects, including the Mondini defect. Conventional magnetic resonance imaging (MRI) and also MRI cisternography performed with heavily weighted T_2 sequences can be helpful in the demonstration of abnormal cerebrospinal fluid communications. Additional studies sometimes resorted to include CT cisternography with iohexal as a contrast agent and intrathecal radioactive technetium with placement of cotton pledgets in the nostrils. The latter, when positive, indicates that cerebrospinal fluid is gaining entrance into the nasal region but does not specifically localize the site of pathology. Both are invasive techniques and are only considered when other methods have failed.

With intracranial cerebrospinal fluid leaks causing bacterial meningitis, about 80% are caused by *S. pneumoniae*. Other causative organisms include the meningococcus, *Haemophilus* species, and *Staphylococcus aureus*. With intraspinal defects such as dermal sinuses, meningitis is more often caused by Gram-negative bacilli or *St. aureus*. *Staphylococcus aureus* meningitis in a child without a ventricular shunt or immunosuppression is so unusual that it should always provoke a search for a neurocutaneous fistula such as a dermal sinus.

The use of prophylactic antibiotics during the investigation to find the site of a cerebrospinal fluid leak is controversial. Most do not recommend their use because the effectiveness has not been proven and they may lead to the occurrence of meningitis from resistant organisms. Dural lacerations with cerebrospinal fluid fistulae from basilar skull fractures heal spontaneously within days to weeks in the majority. Cerebrospinal fluid leaks that accompany congenital defects including those with cribiform plate defects, anterior encephaloceles, inner ear anomalies, or congenital dermal sinuses are expected to persist until surgically corrected. Meningitis complicating an acquired intracranial cerebrospinal fluid fistula can occur within days after the injury or surgical procedure or can be delayed for years. For this reason, the history from any patient with meningitis, and especially recurrent meningitis, should include questions pertaining to possible previous craniofacial injuries, history of deafness, and whether cerebrospinal fluid rhinorrhea has been observed.

Recurrent meningitis caused by *N. meningitidis* is an infrequent but well-established disorder associated with hereditary late complement deficiency, predominantly C5 through C8. It is estimated that about 1% of persons with their first attack of invasive meningococcal disease have this familial deficiency. The condition should be suspected and searched for by complement measurement when a child or adolescent has acute meningococcal meningitis and there is a history of a previous attack with the same organism in a direct family member remote in time from the current patient's illness. It should also be considered when one has repeated attacks of meningococcal invasive disease. The mean age of onset of meningococcal infection with this familial disorder is approximately 15 years, thus considerably later than the mean age of onset of meningococcal meningitis in immunologically normal children. Clinical features and cerebrospinal fluid findings are similar to those without late complement deficiencies although in most, the illness is less severe, sequelae are milder, and mortality rate is lower. It has been proposed that the lesser intensity of meningococcal disease in persons with deficiency of late complement components is indicative of a more abundant inflammatory response with greater immune attack on peripheral blood cells and vascular endothelium in complement normal persons. Patients identified to have predisposition to invasive meningococcal disease due to late complement component deficiencies are maintained on prophylactic penicillin and are also given meningococcal vaccine.

Cerebrospinal fluid shunt infection

In the mid-1960s, ventriculoperitoneal (VP) shunts largely supplemented ventriculoatrial (VA) shunts for cerebrospinal fluid diversion in persons with hydrocephalus. This was mainly because of the diverse complications of VA shunts such as pulmonary vascular micro emboli and immune-mediated glomerulonephritis, among others. While the incidence of shunt infection is approximately the same with the two types of shunts, bacteremia is common with VA shunt infection and occurs only occasionally with VP shunt infections. Most workers claim the incidence of VP shunt infection is about 10% with the initial insertion of the shunt but the rate increases with subsequent shunt reinsertions required after prior shunt infection. With modifications in the perioperative technique and meticulous attention to sterility in the operating room, Choux *et al.* (1992) in France

found that postoperative shunt infections could be reduced to less than 1%. There have been many published trials with the use of perioperative prophylactic antibiotics; however, their benefit as a method to reduce the incidence of shunt infection remains controversial. Most published protocols for shunt placement do advocate the use of perioperative antibiotics at the time of placement of a cerebrospinal fluid shunt.

The majority of shunt infections occur within 2 months of shunt placement and some occur within days after operation. Approximately 70% of cerebrospinal fluid shunt infections are caused by *Staphylococcus* species with *St. epidermidis* being much more common than *St. aureus*. The high incidence of these organisms plus *Propionibacterium acnes* among cases with infected shunts indicates that most such infections stem from the skin of the patient or less often from the gloved hand of operating room attendants. Air-borne bacilli in the operating room may account for some while others, especially Gram-negative bacillary shunt infections, evolve from intestinal perforation by the distal end of the shunt. *Enterococcus faecalis* has become an additional important cause of cerebrospinal fluid shunt infection.

The clinical signs of an infected shunt are quite variable and can range from subtle to dramatic and rapidly progressive. As a generalization, signs are usually less intense when shunt infection is caused by *St. epidermidis* and more severe when caused by the more virulent *St. aureus*. Gram-negative bacillary shunt infections usually give rise to recognizable signs of central nervous system infections and definite evidence of infection on cerebrospinal fluid examination. The most common clinical findings associated with VP shunt infection include some combination of fever, irritability, lethargy, poor feeding, vomiting, and abdominal pain or tenderness. Definite meningeal signs are not usually found. Shunt failure often, but not always, will accompany shunt infection and will lead to signs of intracranial hypertension in some. In others, fever and acute onset of abdominal signs indicative of peritoneal inflammation will represent the presenting signs of an infected VP shunt. Infrequently, an obvious wound infection on the scalp or erythema along the scalp portion of the shunt tube will indicate the probability of an infected shunt.

When suspected, diagnosis of an infected shunt is on the basis of abnormal cerebrospinal fluid findings although these also can be variable. With *St. epidermidis* shunt infections the cerebrospinal fluid cellular response is usually minimal to mild and the cerebrospinal fluid Gram stain is often negative. Reduced cerebrospinal fluid glucose content and a positive culture of ventricular fluid are generally more indicative of this infection. Both *St. aureus* and Gram-negative bacillary shunt infections are likely to reveal more striking ventricular fluid abnormalities. Unlike those with *St. epidermidis* shunt infection, those caused by Gram-negative organisms will have positive cerebrospinal fluid Gram strains in the majority of cases. Thus, with few exceptions, when a child has clinical evidence of a VP shunt infection and the cerebrospinal fluid reveals few cells and a negative Gram stain, it can be assumed that the causative pathogen will be *St. epidermidis*.

While recognition of the possibility of an infected VP shunt is often a responsibility of the pediatrician, its management is the domain of the neurosurgeon. In most cases, the infected shunt must be removed. Temporary external ventricular diversion with a ventricular cannula is often resorted to as a measure to control intracranial pressure during the time period required for eradication of the infection with intravenous antibiotics. Most antibiotics used for VP shunt infections will only gain entrance into the cerebrospinal fluid in the presence of meningeal inflammation. Because ventriculitis/meningitis associated with shunt infections, especially those caused by *St. epidermidis*, is usually associated with minimal meningeal inflammation, the effect of antibiotic therapy eradicating the infection is often sluggish. Most workers recommend either nafcillin or vancomycin for *Staphylococcus* species shunt infection, depending on *in vitro* sensitivity studies, sometimes in combination with an aminoglycoside or rifampin with vancomycin. When *Staphylococcus* species shunt infection relapses or is found to be intractable with intravenous antibiotics, vancomycin is sometimes administered by intraventricular injection.

Intracranial abscesses

Intracranial abscesses occur within the brain parenchyma or in the epidural or subdural spaces. Brain abscesses have become less common in children in the recent years as a result of the more aggressive treatment of acute otitis media, the decrease in occurrence of chronic mastoiditis, and the earlier correction of congenital cyanotic heart lesions. The widespread use of neuroimaging techniques CT and MRI have enhanced earlier diagnosis of cerebritis and abscess within the brain. Brain abscess is usually a single localized cerebral lesion which not uncommonly is multiloculated. Multiple abscesses are less common but are the rule when brain abscesses complicate meningitis caused by *Citrobacter koseri* in neonates or in early infancy.

The initiating event leading to brain abscess formation is a site of localized bacterial infection in brain parenchyma called cerebritis. The affected area undergoes necrosis over 1–3 weeks in most cases with the eventual formation of a localized purulent collection which provokes a surrounding fibrotic response referred to as a capsule. Once the encapsulated abscess has developed, the area becomes surrounded by a wide zone of edema readily seen in CT or MRI and which contributes to the mass effect of the infectious process. This evolution of the development of a brain abscess is now classified into stages including that of early cerebritis, late cerebritis, early capsule formation, and late capsule for-

mation. Each stage has different MRI findings and to some extent, different modes of therapy.

There are numerous factors which predispose to brain abscesses in children, outlined in Table 10.5. In 10–20% of cases, no obvious predisposing cause can be identified. Currently, the most common predisposing causes in infants and children include bacterial sepsis, penetrating cranial injuries, chronic immunosuppression associated with disease, treatment of disease, and organ transplantation. While less common than in past years, conditions with chronic oxygen desaturation such as congenital cyanotic heart disease and pulmonary arteriovenous malformations remain as contributing factors for the development of brain abscesses.

Brain abscesses can occur anywhere in the brain, including the brain stem, but most are found in the cerebral hemispheres. Their location is largely determined by the site of the primary, causative infection. Brain abscess complicating suppurative sinusitis is usually found in the frontal lobe resulting from extension of bacteria via veins from the sinuses or cavernous sinus to the brain. Abscess secondary to otitis media or mastoiditis is commonly localized to the temporal lobe or the cerebellar hemisphere. Otogenic infection can also give rise to epidural empyema on the same side. With cyanotic heart disease, the favored location of brain abscess is at the cortical-white matter junction in the distribution of the middle cerebral artery. These conditions with chronic cyanosis and compensatory hyperviscosity give rise to areas of cerebral microinfarction and the right-to-left shunting allows entrance of bacilli to the systemic circulation bypassing the normal filtering effect of the pulmonary circulation.

The symptoms and signs of a brain abscess in infants and children are quite variable and depend upon numerous factors including the size and the location of the lesion, the degree of intracranial hypertension, and the presence or absence of bacterial sepsis. A single, small abscess in the anterior frontal or posterior parietal lobe may be associated with few clinical signs except, perhaps, fever and headache. The classically described syndrome with symptoms and signs of increased intracranial pressure, localized neurologic signs such as seizures or hemiparesis, and signs of infection including fever and leukocytosis is diagnostically important when present but is found mainly when the disorder is in an advanced state. Headache is the most common symptom in older children while hemiparesis can be expected if the abscess is located in the posterior frontal or anterior parietal region. Papilledema is found in only 25–50% of cases. Seizures are estimated to occur in 40–50% of cases with cerebral hemisphere brain abscesses. Seizures are of greatest localizing value when they are simple partial in type. Cerebellar brain abscesses tend to have a more uniform clinical presentation with ataxia, nystagmus, and features indicative of obstructive hydrocephalus with headache, vomiting, and lethargy. Children with pyogenic brain abscesses in any location generally have blood leukocytosis to some degree although fever is more variable.

Brain abscesses in neonates or in early infancy are infrequent complications of bacterial sepsis or meningitis. Most are caused by Gram-negative bacilli including *Proteus* species, *Salmonella* species, or *C. koseri*. Usual clinical features include fever or temperature instability, poor feeding, vomiting, lethargy, seizures, and rapid enlargement of the head circumference. On occasion, an infant septic in the first week of life will seemingly remain well until 2–6 weeks of age when found to have abnormal head enlargement, usually with leukocytosis. Neuroimaging will show multiple brain abscess lesions provoked by Gram-negative bacilli. *Citrobacter koseri* septic infection in the neonate has a strong predilection for invasion of the central nervous system and up to 80% of infants with neonatal meningitis caused by this organism have been found to have periventricular brain abscesses. Although meningitis in these infants is septic-borne, the parenchymal abscesses are believed to be the result of ependymal necrosis with transmission of *Citrobacter* species bacilli directly from the ventricle into the adjacent brain tissue.

In older infants, children, and adolescents, the bacterial organisms that cause brain abscesses are legion and are determined to some extent by the primary source of the infection. With abscess resulting from penetrating head injuries, *St. aureus* is the most common offender. When septic-borne or when brain abscess develops secondary to dental, sinus, or middle ear infection, they are often polymicrobial, sometimes with both aerobic and anaerobic organisms. In addition to many aerobic and anaerobic bacterial pathogens, brain abscess can be caused by a variety of other infectious agents. Tuberculous brain abscess and abscesses caused by *Toxoplasma gondii* have become lesions seen in patients with AIDS. Multiple cerebral microabscesses sometimes complicate systemic *Candida* species infections in sick premature infants. Fungal brain abscess, including those induced by *Histoplasma capsulatum* and *Blastomyces dermatitidis*, are seen primarily in immunosuppressed patients. Chronically ill and immunosuppressed persons are also susceptible to brain abscesses caused by *Nocardia* species, a Gram-positive bacterium susceptible to sulfa antibiotics. *Aspergillus* species brain lesions in immunocompromised persons are more often in the form of hemorrhagic granulomas rather than abscess.

When brain abscess is suspected in any age group, lumbar puncture for cerebrospinal fluid examination is assumed to be contraindicated because of the danger of provoking internal herniation. Neuroimaging with CT, MRI, or both and performed both without and with contrast enhancement is highly accurate for the identification and localization of intracranial abscesses. MRI is superior for brainstem and cerebellar lesions and generally provides more information regardless of the location of the lesion. The findings on MRI

vary depending on whether the process is in the early cerebritis stage or in the more advanced encapsulated stage. In the stage of cerebritis, T_1 weighted MRI usually shows an area of hypointensity which, with contrast enhancement, reveals a bright signal either heterogeneously or diffusely. When the abscess is encapsulated, the T_1 MRI with enhancement demonstrates a hypointense central area surrounded by a hyperintense capsule which has a smooth contour and which is more thin on the medial, ventricular margin than elsewhere. The area of surrounding edema remains hypointense on the enhanced T_1 image.

Treatment of a brain abscess in most cases consists of a combination of intravenous antibiotics, methods to control intracranial hypertension, and surgical drainage of the abscess. Certain select cases can be managed with antibiotic therapy when the lesion is believed to be in the cerebritis stage or if the abscess is relatively small and without a significant degree of mass effect upon the ventricular system. Conservative treatment is also sometimes chosen in a child with uncorrectable coagulation abnormalities. The value of dexamethasone as a method to control intracranial hypertension with a brain abscess is controversial. If clinical evidence plus neuroimage findings indicate that intracranial hypertension is marginal, corticosteroids should be avoided. If pressure signs are marked, the benefits of dexamethasone in dosage of 0.6 mg/kg/day (up to 40 kg body weight) probably far outweighs the disadvantages. Intravenous mannitol in periodic doses of 0.5 g/kg given over 15–20 minutes can also be considered if there are signs of impending herniation.

Various antibiotic regimens have been recommended before the causative organism is recovered. One regimen often selected pending surgery is a combination of vancomycin, ceftriaxone, and metronidazole. Once the causative organism is found, the antibiotic regimen is altered accordingly. The goal of surgical therapy is to remove the purulent exudate to the extent possible and to prevent the major, life-threatening complications of a brain abscess such as internal herniation and spontaneous perforation of the abscess into the adjacent lateral ventricle which can precipitate fulminating meningitis (Table 10.6).

Osteoplastic craniotomy under general anesthesia for total excision of a brain abscess has become less popular in recent years. CT-guided aspiration via a burr hole has become the more common surgical approach and is believed to be equally effective when compared to total excision. When multiple abscesses of variable size are found, some will elect to aspirate the larger lesions providing decompression and also yielding a specimen for culture. The remaining smaller lesions hopefully will respond to antibiotic therapy.

Epidural and subdural abscesses are managed in a similar fashion. These lesions also have multiple possible causes in children including sinusitis, middle ear and mastoid infections, postmeningitic and postsurgical complications. Subdural empyema usually presents with impressive symptoms including those of infection and those of cortical irritation. Headache, lethargy, fever, seizures, and focal neurologic deficits are commonly described in persons with subdural empyema. Intracranial epidural abscess is usually less dramatic in regard to clinical findings although this is variable depending on its size and the virulence of the causative pathogen. Nontraumatic subdural abscess has a close association with suppurative sinusitis and most occur in the frontal region in adolescents or young adults. MRI is the preferred diagnostic image to identify these lesions.

TABLE 10.6

Dangers of Brain Abscess

Internal herniation
Spontaneous perforation into ventricle
Complication of sepsis, when present
Complication of prolonged antibiotic therapy

Viral infections of the central nervous system

Herpes virus infections

Neonatal herpes simplex virus infection

While intrauterine transmission of herpes simplex virus (HSV) can occur, 85–90% of neonatal HSV disease occurs following viral transmission during labor and delivery. Postnatal transmission from infectious contacts during the first 3–4 weeks of life can also result in severe infant disease and appears to account for the remainder of perinatal cases. HSV-2 is the cause of approximately 75% of disease during the first month of life. The risk of maternal–infant transmission of HSV is 40% for infants of mothers with primary genital infection at the time of delivery. Transmission rates are only about 4% for the infants of immune mothers with recurrent symptomatic virus shedding at delivery and less than 3% for recurrent viral shedding in the absence of lesions. Approximately 50% of mothers of infants with HSV disease have not experienced recognizable genital HSV disease. Premature birth (<37 weeks gestation) is over-represented among children with neonatal HSV infection, occurring in about 35% of cases.

There are three syndromes of neonatal HSV infection: (1) skin–eye–mouth involvement only (SEM), (2) central nervous system disease without disseminated infection, and (3) disseminated infection with or without central nervous system disease. In multicenter clinical trials the three syndromes are approximately equally represented. Most infants with neonatally acquired HSV infection develop clinical illness between 3 and 21 days of age. Children with isolated central nervous system disease have a mean age of onset approximately 4 days later than children with disseminated

infection or SEM infection. The age of onset of postneonatal HSV encephalitis overlaps temporally with central nervous system disease acquired at or near the time of delivery. Thus, infants with postneonatal HSV encephalitis can have disease onset between 4 and 8 weeks of age. The neonatal HSV disseminated multiorgan system syndrome rarely occurs beyond 3 weeks of age. Central nervous system infection occurs in about 50% of neonatal HSV cases. Of children who initially appear to have disease limited to SEM, between 15 and 20% will develop central nervous system involvement. Between 50 and 70% of children with the disseminated HSV disease have central nervous system infection. Central nervous system invasion may occur by viremic spread in children with multiorgan system infection or by neural spread in infants with isolated central nervous system disease. Central nervous system disease may be manifest clinically as lethargy, progressive obtundation, seizures, or focal neurological deficits including hemiparesis or quadriparesis. Alternatively, infants with destructive disease detected by central nervous system imaging may occasionally demonstrate only minor clinical signs of central nervous system dysfunction.

Rapid clinical recognition of neonatal HSV has remained elusive. In clinical trials, the diagnosis of HSV infection has been delayed beyond 5 days of the onset of clinical disease in about 40% of patients. All skin vesicles and mucosal ulcers observed during the first month of life should be studied for HSV. Fever or temperature instability occurs in most infants with disseminated or central nervous system disease, although fever is present as a first manifestation in just over 50% of cases. Regardless, when fever occurs during the first month of life, HSV disease must be entertained. Pneumonia, hepatitis, and DIC are prominent components of the disseminated disease syndrome. Any ill infant with seizures, obtundation, or focal neurological findings should prompt evaluation for HSV infection. Diagnosis is established using virological and molecular (polymerase chain reaction [PCR]) techniques. Viral cultures should be obtained of any skin vesicles or mucosal ulcers. In addition, cultures of the oropharynx, conjunctivae, stool, and cerebrospinal fluid (approximately 20% positive with central nervous system disease) should be performed. PCR on cerebrospinal fluid is approximately 95% sensitive for detecting central nervous system infection. PCR is also applicable to vesicle or throat swab specimens and to plasma in disseminated disease. Intravenous acyclovir (60 mg/kg/day) divided q8h is the treatment of choice. The potential for benefit is maximum when therapy is initiated as early in the course of clinical disease as possible. For children with central nervous system infection, treatment should be given for 21 days and the HSV PCR test on cerebrospinal fluid should have been shown to have converted to negative by repeat testing during the third week of treatment. In recent clinical trials, death has continued to occur in close to 50% of acyclovir-treated infants with disseminated disease. In treated children with central nervous system disease only mortality is 15% or less with antiviral therapy; however, moderate to severe neurodevelopmental impairment occurs in about 45% of these children. Concern continues regarding recrudescent central nervous system disease following neonatal antiviral treatment. Recurrences of skin lesions are characteristic of many infants surviving neonatal HSV. Whether central nervous system reactivation may be occurring together with or apart from skin exacerbations has not been defined. Oral acyclovir effectively suppresses skin recurrences in most infants. Its role in controlling hypothesized subclinical central nervous system reactivation is the subject of ongoing study.

Herpes simplex virus encephalitis and meningitis in children and adults

Herpes simplex virus is the single most common cause of sporadic, endemic encephalitis in adults and children. HSV is implicated in about 10% of the 20 000 cases of encephalitis that occur annually in the United States and represents 25% of cases for which an etiology can be defined. HSV-1 accounts for >90% of cases of herpes simplex virus encephalitis (HSE) beyond the first month of life. In adults, HSE is predominantly the result of reactivation of latent infection in cranial sensory ganglia. In children HSE can occur during primary HSV infection or as a consequence of viral reactivation. At younger ages, the likelihood that HSE is occurring in association with primary HSV infection is increased. Primary HSV infection with associated encephalitis, may or may not include other evidence of overt HSV disease (skin vesicles, conjunctivitis, pharyngitis, gingivostomatitis). Primary genital HSV-2 infection can be associated with HSV aseptic meningitis, and this syndrome may recur. HSV-2 is probably the predominant cause of recurrent benign aseptic, "Mollaret," meningitis. Patients with encephalitis (including brainstem encephalitis) associated with HSV-2 have been described, but are uncommon. In typical adult HSE, disease onset is usually subacute with signs and symptoms of central nervous system dysfunction emerging and progressing over a 2- to 4-day period. However, rapid progression to coma can occur. Dysphasia is a common early manifestation before progressive obtundation has become predominant. Most patients are febrile. Seizures often occur during the first 4 days of disease. Focal motor abnormalities are also observed early in the illness. Characteristic CT abnormalities of inflammation and hemorrhagic necrosis predominantly localized to the infero-medial fronto-temporal region are observable about 4 days into the illness. MRI is usually informative earlier. EEG abnormalities are highly prevalent in HSE and generally provide evidence of localization of pathology to the fronto-temporal distribution. The EEG pattern of periodic lateralizing epileptiform discharges (PLEDs) is characteristically associated with HSE. However, other conditions also cause the abnormality and PLEDs occur

in only about 60% of HSE cases. Diagnosis of HSE is usually established using cerebrospinal fluid PCR. The sensitivity of a single test is near 95%. Occasionally, first cerebrospinal fluid specimens may be PCR negative in HSE. In these circumstances inflammatory cell counts and protein concentrations are usually normal or near normal. Repeat PCR in 3–4 days has usually provided informative results in true HSE cases; and cerebrospinal fluid indices are usually abnormal by the second cerebrospinal fluid examination. The specificity of the test is 99%. Children and adults of all ages with acute onset of encephalopathy should be investigated for infectious and inflammatory causes unless an alternative diagnosis is rapidly established. After central nervous system imaging, samples of cerebrospinal fluid should be obtained for bacterial, viral, mycobacterial and fungal culture. Cerebrospinal fluid should be submitted for HSV and enteroviral PCR and cerebrospinal fluid should be stored frozen for subsequent microbiological, molecular, serological, or biochemical testing. Treatment for possible HSV encephalitis should be instituted with acyclovir, 45 mg/kg/day divided q8h. The standard duration of therapy is 2 weeks in adults as opposed to 3 weeks in neonates, as stated above. Demonstration of negative cerebrospinal fluid PCR results before terminating antiviral therapy is recommended.

Cytomegalovirus

Before the advent of HIV-associated immunodeficiency, cytomegalovirus encephalitis was essentially restricted to infants with congenital cytomegalovirus (CMV) infection. Approximately 1% of infants are infected with CMV *in utero*, as demonstrated by culturing urine on the first day of life. Most infants with *in utero* CMV infection are the offspring of seropositive mothers who experienced either reactivation of latent CMV during pregnancy or occasionally acquisition of infections with new CMV strains during pregnancy. Regardless, most of these infants are clinically well at birth. The most important clinical and neurological manifestation of these infections is sensorineural hearing loss, which can be established at birth or which may develop progressively during the first year of life. Infants of nonimmune mothers who acquire primary CMV infection during pregnancy are at risk for developing overt congenital cytomegalovirus inclusion disease (CID), *in utero*. These infants manifest disease at birth. The principal components of the CID syndrome include intrauterine growth failure, central nervous system disease (microcephaly, periventricular leukomalacia, periventricular calcifications, cerebral cysts, sensorineural deafness), chorioretinitis, hepatitis, leukopenia and thrombocytopenia. The neurodevelopmental prognosis for children with CMV-associated microcephaly is typically bleak. Sensorineural hearing loss, while frequently established at birth, can progress during the first year of life. A recent clinical trial of ganciclovir therapy of infants with symptomatic CID with central nervous system involvement demonstrated a beneficial effect of antiviral treatment on hearing loss progression. The congenital CID syndrome is usually readily recognized clinically. Substantiation of the virological etiology can be obtained by viral culture of urine. PCR for CMV DNA is positive in blood and cerebrospinal fluid in children with overt central nervous system disease. Blood spots utilized for neonatal screening for metabolic disorders provide a source for PCR testing for congenital CMV infection. This strategy has been applied to retrospective diagnosis of sensorineural hearing loss and destructive central nervous system malformations. The CMV IgM antibody test has a sensitivity of only 60% and should not be relied upon solely for diagnosis of disease. Risk factors for primary CMV infection during pregnancy include young maternal age and exposure to day care-attending children excreting CMV. Postneonatal CMV encephalitis occurs only in patients with marked immunodeficiency, most often related to HIV infection. CMV can be a cofactor in HIV encephalopathy.

Human herpes virus 6

Human herpes virus 6 (HHV6) is the predominant cause of roseola infantum, an acute febrile exanthematous disease of infants and toddlers. The roseola rash occurs in no more than 20% of children with primary HHV6 infection; the remainder of infections are usually discovered among children with acute febrile illnesses. Typically the fever is high grade and abrupt in onset. Given the occurrence of this highly febrile infection in infants and toddlers, it is not surprising that HHV6 infection is associated with febrile seizures which occur in approximately 20% of infected, febrile children. When PCR for HHV6 has been performed on cerebrospinal fluid specimens of children with HHV6 infection, fever, and seizures the cerebrospinal fluid PCR for HHV6 has been positive in about 40% of cases. It remains unclear whether direct viral invasion of the central nervous system contributes to the pathogenesis of seizures during HHV6 infection. Evidence for more extensive central nervous system disease during HHV6 infection is rare in immunocompetent children or adults. In contrast, HHV6 meningoencephalitis has been repeatedly observed in bone marrow transplant recipients, and occasionally in solid organ transplant patients and persons with HIV immunodeficiency (including children). Congenital HHV6 infection has also been identified in neonates with seizures.

Arbovirus encephalitis

Three Flaviviruses (West Nile virus, Saint Louis encephalitis virus, and Powassan virus), three Togaviruses (alpha virus group: Eastern equine, Western equine, Venezuelan equine), and three Bunyaviruses (LaCrosse, Jamestown Canyon, and

Snowshoe Hare) cause encephalitis in residents of North America. For travelers, European and Asian tick-borne encephalitis and Japanese encephalitis (Flaviviruses) are potential concerns. Until the arrival of West Nile virus in North America in 1999, Saint Louis encephalitis and LaCrosse virus accounted for most cases of vector-borne encephalitis in the United States. West Nile virus has spread rapidly and progressively across the United States since 1999. Globally, Japanese encephalitis virus far surpasses all other agents as causes of infection and disease.

LaCrosse virus

LaCrosse virus, a member of the California virus serogroup, has been recognized as an endemic cause of childhood encephalitis in the United States since its identification in 1965. The CDC recorded 2776 laboratory-confirmed cases between 1966 and 2000, an average of 75 cases per year. Ninety per cent of cases were identified in seven states: Ohio, Wisconsin, West Virginia, Minnesota, Illinois, Indiana, and Iowa. Smaller numbers of cases were documented along the Appalachian mountain range from New York to Georgia. Illness occurs predominantly between June and October with a broad peak in incidence during July through September. The virus is sustained in the treehole mosquito *(Aedes triseriatus)* population by transovarial transmission. Children 3–15 years of age are affected predominantly with an excess of illness among males. Illness severity ranges from headache and nausea (with classification as aseptic meningitis) to disorientation, seizures (40–60%), focal neurological deficits (15–25%) obtundation, and cerebral edema (15%). Approximately 50% of patients will need to be placed in an intensive care unit for an average of 3–4 days, but the death to case ratio is <5%. After initial recovery from the more severe phase of illness, approximately 15% of children have demonstrable neurological deficits. Among children more severely affected during acute illness, long-lasting neurodevelopmental dysfunction may occur in up to 30%. The cerebrospinal fluid white cell count ranges from normal to 500 cells with a median of approximately 75 cells/mm^3 and 60% mononuclear. Cerebrospinal fluid protein is rarely elevated substantially and glucose is normal. The peripheral white count can be slightly elevated to between 15 000 and 20 000 cells/mm^3 with a PMN fraction of 65–85%. Periodic lateralizing epileptiform discharges (PLEDs) have been observed in up to 15% of patients. CT scanning is rarely revealing except in patients with diffuse brain edema. MRI findings have not been reported from a large case series, but cortical lesions, including fronto-temporal abnormalities similar to those characteristic of herpes simplex encephalitis (Table 10.7) have been described in several case reports. Culture of cerebrospinal fluid for LaCrosse virus is rarely positive, although brain biopsy tissue can yield the etiological agent. Serological testing provides confirmation of the specific diagnosis. Serum LaCrosse virus specific IgM is diagnostic during acute illness. Cerebrospinal fluid IgM can also be of diagnostic value. If an initial sample is IgM negative, IgM seroconversion can be demonstrated within 1 week. Testing of paired sera (acute illness with convalescent serum 3–4 weeks later) for changes in concentrations of IgG antibody identifies the remainder of proven cases with negative IgM responses.

TABLE 10.7 Herpes Simplex Encephalitis

Perinatal herpes simplex virus (HSV) infection:
Most children become symptomatic between 3 and 28 days of age.
CNS involvement in approximately 60% of cases overall • Skin, eye, mouth: 20% • Disseminated: 70% • Isolated CNS: 100%
Identification of HSV infection by culture or polymerase chain reaction (PCR) testing of specimens from eye, respiratory tract, skin lesions, rectum, urine, blood
Diagnosis of central nervous system involvement by HSV PCR on cerebrospinal fluid and central nervous system imaging
Treatment: acyclovir: 60 mg/kg/day divided every 8 hours for 3 weeks
Herpes simplex virus encephalitis beyond the perinatal period:
Accounts for approximately 25% of sporadic viral encephalitis
HSV PCR testing on cerebrospinal fluid is approximately 90% sensitive for diagnosis
Fronto-temporal involvement (unilateral or bilateral) by central nervous system imaging
Treatment: acyclovir 45–60 mg/kg/day divided every 8 hours for 2–3 weeks

Eastern equine encephalitis

Eastern equine encephalitis (EEE) is endemic in the coastal states from the Gulf coast to New England. Mosquitoes prevalent in swamplands harbor the virus which is maintained in a mosquito to bird to mosquito cycle. The infected vectors attack man infrequently; thus, human cases are uncommon. Approximately five to 15 sporadic cases are confirmed annually with occasional small outbreaks. Persons of all ages are susceptible to the encephalitic manifestation. EEE is typically a severe illness with a death to case ratio that averages 35%. Moderate to severe residual neurological impairment occurs in about 35% of survivors. The illness begins as a flu-like syndrome with fever and malaise. Central nervous system involvement is usually manifest between the second and fifth days of illness with headache, stiff neck, confusion, somnolence, focal neurological findings, or seizures. There is rapid progression to coma in most patients (90%), typically within 2–3 days of the appearance of central

nervous system disease. Seizures occur in 50% of cases, focal weakness in 40%, and cranial nerve palsies in 25%. Deaths usually occur during the second or third week of coma. Among survivors with mild to moderate sequelae, the median duration of coma is 5 days. Cerebrospinal fluid examination reveals a median leukocytosis of 370 cells/mm^3 with 70% neutrophils at first examination. Median cerebrospinal fluid protein is 97 mg/dL and glucose is normal. EEGs show diffuse slowing with disorganization of background activity. MRI reveals multifocal brain injury most apparent on T_2 weighted images and usually present within 3 days of the onset of neurological findings. Lesions are concentrated in the basal ganglia and thalami, but abnormalities can also be observed in the brain stem, cortex, and periventricular regions. Diagnosis is serological with the IgM capture antibody test useful for diagnosis during the acute illness and paired acute/convalescent serologies demonstrating changes in concentrations of virus-specific IgG antibody.

West Nile virus

West Nile virus, a flavivirus, is a member of Japanese encephalitis serogroup which includes Japanese, Saint Louis, Murray Valley, and Kunjin encephalitis viruses. The virus is maintained in nature in a cycle involving *Culex* sp. mosquitoes and birds and is transmitted to man by mosquitoes. Since there is an early viremic phase of infection, disease has also been transmitted by blood transfusion, organ donation, and from mother to fetus *in utero*. West Nile virus was first introduced into the northeastern United States in 1999, when symptomatic human infections were recognized simultaneously with unusually high rates of death among crows. Seroepidemiological research has consistently demonstrated that meningoencephalitis is manifest in approximately 1 in 100–150 infected persons and that approximately one in five infected persons develops a febrile flu-like (fever, malaise, achiness) illness without central nervous system disease. Since its introduction, the virus has spread progressively across the country with increasing numbers of cases annually. In 2003, over 8900 symptomatic West Nile virus infections were documented and registered with 45 different state health departments and the CDC. Meningoencephalitis accounted for 30% of laboratory-confirmed infections, while West Nile fever was diagnosed in most of the remainder. Two hundred and five deaths occurred, presumably concentrated among those with encephalitis yielding an encephalitis death to case ratio near 10% (range 5–15%, increasing with age). In 2003, the largest numbers of infections were identified in the plains states and states on the eastern slope of the Rocky Mountains. However, disease continued to occur with substantial frequency in the upper Midwest into the mid-Atlantic states. A broad incidence peak occurs between mid-July through late September; however, illness has been encountered as late as December. The incubation period ranges from 4 to 16 days. West Nile fever is a summer flu-like syndrome with headache, malaise, myalgia, arthralgia and occasionally macular rash lasting 3–6 days. Central nervous system disease usually emerges between days two and five of fever. The aseptic meningitis/encephalitis ratio is approximately 1:2 among those with central nervous system involvement. Being over 50 years old is the major risk factor for development of encephalitis. Persons 50–60 years old are 10 times more likely to experience central nervous system disease than younger persons, while those over 80 years of age are 40 times more likely to manifest encephalitis. While West Nile infections are equally common in children and adults, children under 16 years old probably account for no more than 5% of encephalitis cases. While disordered cerebration is common, coma develops in only 15% of cases. Seizures are also relatively uncommon. Development of localized, marked, polio-like muscle weakness occurs in approximately 50% of West Nile encephalitis cases. Weakness or paralysis usually involves the extremities rather than cranial nerves. Pathological findings occur in the brain, brainstem, and spinal cord. MR imaging demonstrates abnormalities in patients with the most severe clinical illness, possibly up to one-third of encephalitis patients. Involvement of the basal ganglia, thalami, and substantia nigra has been prominent in reported cases. The findings are similar to those observed in Japanese encephalitis virus disease. PCR on blood or spinal fluid has a sensitivity between 30 and 50%. Therefore, diagnosis is usually established with IgM capture antibody testing on spinal fluid or serum. The IgM test is positive within the first 4 days of illness in approximately 75% of cases and in >90% of cases by the eighth day of disease. The IgM and IgG ELISA tests cross-react among the flaviviruses. The plaque-reduction neutralization test is virus specific.

Saint Louis encephalitis

Prior to the advent of West Nile virus infection, St Louis encephalitis virus had caused the largest outbreaks of arboviral disease in the United States. Over 4000 cases were recorded between 1966 and 2000, but close to 2000 of these cases occurred in 1975. Fewer than 20 cases were documented annually between 1991 and 2000. Disease has been concentrated in the Ohio River valley, south central states, Florida, Texas and California. SLE is maintained in nature in *Culex* mosquitoes and small birds, particularly sparrows. The clinical expression of St Louis encephalitis (SLE) has many similarities to West Nile virus infection. In SLE, encephalitis occurs in approximately one in 300 infected persons, and the risk of encephalitis increases progressively with age. However, among persons with proven symptomatic infection encephalitis is manifested by over 50% in all age groups. Marked muscle weakness is not nearly as common in SLE cases as in West Nile disease. Pathological changes are concentrated in the brainstem, midbrain and thalamus, as in WNV and Japanese encephalitis. Cerebrospinal fluid findings characteristic

of viral meningoencephalitis with leukocyte counts ranging from 10 to 200 cells/mm^3 with progressive predominance as disease progresses. Cerebrospinal fluid protein is rarely over 200 mg/dL and glucose is routinely normal. The death to case ratio ranges from 8 to 20% and is strongly and directly age related. Diagnosis is by IgM capture ELISA using cerebrospinal fluid or serum, and specific species confirmation with virus specific neutralization tests.

Paramyxoviruses

The paramyxoviruses include agents with substantial neurotropism. These include rubeola (measles), mumps, and a recently identified zoonotic infection of Southeast Asia caused by the Nipah virus.

Measles

Control of measles by immunization with live-attenuated measles virus vaccine has almost eliminated wild-type measles and measles virus central nervous system disease from the United States. When wild-type virus was endemic, viral and postviral meningoencephalitis occurred in 1:1000 measles cases with a death to case ratio of 10–30% and long-lasting neuro-developmental sequelae in approximately 30% of survivors. Prior to effective immunization, measles was the most important cause of acquired mental retardation in the United States. Since virus cultures of cerebrospinal fluid in measles encephalitis were rarely positive, there has been debate regarding the importance of viral invasion of the central nervous system in disease pathogenesis. However, molecular techniques (PCR) that might have more readily demonstrated direct viral central nervous system invasion were not available when disease was prevalent. The capacity of measles virus to invade the central nervous system is proven in subacute sclerosing pan-encephalitis (SSPE). It is also possible the measles is tropic for endothelium of central nervous system vessels and that this is of importance in disease expression. Regardless of the extent of direct viral invasion of the central nervous system during acute measles, immunological mechanisms almost certainly have a prominent role in the pathogenesis of measles encephalomyelitis. The measles encephalitis syndrome usually emerges during the period of exanthem and within 8 days of illness onset. Seizures occur in over 50% of cases and coma in close to one-third. Long-lasting sequelae include recurrent seizures, paresis, and cognitive impairment. Measles is diagnosed by isolation of the virus from respiratory secretions or by antibody testing.

SSPE is a persistent measles virus infection of the central nervous system caused by a defective, mutated measles virus which lacks M protein believed to be necessary to bring about release of the virus from its intracellular location giving rise to progressive degenerative neuronal pathology. The disease occurs in approximately 1 in 100 000 measles cases and the incubation period is approximately 5–7 years. Measles during infancy carries a higher risk for SSPE. The clinical expression of SSPE includes insidious onset progressive mental deterioration with behavioral changes, motor incoordination, myoclonic jerks, and speech impairment. The illness progresses relentlessly over 6–9 months to dementia, stupor and decorticate rigidity. Measles specific antibody titers are extremely high in serum and cerebrospinal fluid.

Mumps

Mumps was the single most common cause of viral meningoencephalitis in children in the United States until the development of effective immunization. Aseptic meningitis and mild meningoencephalitis are the most frequent complications of mumps in healthy children occurring approximately 5 days into the mumps syndrome. Fever, headache, vomiting, lethargy, and nuchal rigidity are the most common manifestations of central nervous system involvement in mumps. Seizures occur in approximately 15% of cases and disease progresses to delirium in no more than 5–8%. Death during the acute encephalitic phase is rare, but can occur. Recovery is usually complete. It is possible that acquired aqueductal stenosis may follow mumps virus infection. The cerebrospinal fluid shows typical findings of aseptic meningitis with mononuclear pleocytosis of approximately 250 cells/mm^3, with mild elevation protein and normal glucose. Specific diagnosis is by isolation of mumps virus from respiratory secretions; the virus is also isolated from cerebrospinal fluid inpatients with meningoencephalitis. Testing of acute and convalescent sera for mumps antibody provides serological confirmation of illness etiology.

JC virus

Progressive multifocal leukoencephalopathy is a chronic central nervous system papovavirus infection that occurs exclusively among persons with severely impaired immune function including genetically determined immunodeficiencies, organ transplantation, lymphoproliferative malignancies, and HIV infection. Exposure to JC virus is common. By young adulthood, close to 90% of healthy persons have serological evidence of prior infection. PML is probably the result of reactivation of latent JC virus infection in central nervous system microglial cells in the setting of profound immune compromise. Plaques of demyelination show infected microglia at their peripheral advancing edge. The clinical syndrome is one of the insidious onset of weakness, cognitive impairment and speech dysfunction in most individuals. Patients may also present with ataxia or symptoms suggestive of mass lesions. Central nervous system JC virus infection does not cause fever. The cerebrospinal fluid exam may show slightly increased protein concentration but otherwise is unremarkable. CT and MRI studies demonstrate nonenhancing lesions. The disease progresses relentlessly

to coma over 6–9 months in many instances. However, the course of illness may extend over a substantially longer period in persons with less severe immunodeficiency. Diagnosis is by cerebrospinal fluid PCR, with a sensitivity close to 90%. PML can co-exist with other brain diseases in severely immunosuppressed patients. Thus, there remains a role for brain biopsy in defining the causes of brain lesions in such patients. Successful control of HIV infection with antiviral drugs can halt PML progression. Reducing immunosuppression in organ transplant recipients may halt PML progression but does not reverse established disease.

Enteroviral infections

The enteroviruses include the polioviruses, Coxsackie and echoviruses, and more recently identified serotypes numbered sequentially including enteroviruses 68 through 72. All enteroviruses exhibit neurotropism to variable degrees. Enterovirus central nervous system disease encompasses the range from aseptic meningitis to encephalitis to flaccid paralysis.

Polioviruses

The polioviruses include three serotypes, all with neurotropic potential. Paralytic poliomyelitis occurs in approximately 1–2% of persons with primary wild-type poliovirus infection, while aseptic meningitis without paralytic involvement occurs in a similar percentage. Over 90% of infected persons are asymptomatic. Central nervous system disease can occur at any age, but the risk of central nervous system manifestations increases with age. The hallmark of poliovirus pathogenesis is tropism for anterior horn cells of the spinal cord and brainstem with consequent flaccid paralysis of innervated muscle groups. When infection was highly endemic, most adults were immune and paralytic disease occurred most frequently in infants and young children. With improved sanitation and reduced transmission of infection during childhood, an increasing fraction of older children and adults were nonimmune and susceptible to infection and paralytic disease. Tonsillectomy during asymptomatic infection increases the risk of bulbar disease. Pregnant women are at increased risk of severe infection. Intramuscular injections of DTP vaccine increase the risk of paralysis in the injected extremity. Infection can be transmitted to the infant *in utero* throughout pregnancy. When maternal disease occurs during the several days before delivery, the infant typically develops poliomyelitis between days three and ten of life. In postneonatal polio, symptoms of central nervous system disease that may or may not progress to paralysis include signs of aseptic meningitis together with diffuse muscle spasm that may be emphasized in the paraspinous muscles and hamstrings. Changes in superficial and deep tendon reflexes (loss of cutaneous reflexes followed by accentuation then loss of deep tendon reflexes) herald the emergence of paralysis. Marked paralysis may develop over a very short time interval or be spread over several days. Typically, motor involvement is asymmetrical. With involvement of the intercostal muscles, diaphragm, and pharyngeal musculature, respiratory insufficiency is common. Prevention is with inactivated trivalent polio vaccine.

Severe neonatal enterovirus infection

Life-threatening perinatal enterovirus infections due to Coxsackie and echoviruses may develop during the first 2 weeks of life. In most instances, infection is acquired by viremic spread from the mother who has developed infection during the last days before delivery. Infection can also be transmitted to the infant as a result of contact with infectious maternal body fluids at the time of delivery. Nursery outbreaks with infant–infant and infant–staff–infant transmission have occurred on multiple occasions. Severe neonatal disease is not restricted to maternal–infant viremic transmission cases. A multisystem infection occurs in the neonate with meningoencephalitis, myocarditis, hepatitis, and a multiorgan failure sepsis-like syndrome. The Coxsackie B viruses are most often implicated in the meningoencephalitis/myocarditis presentation. Fulminant hepatic necrosis dominates the clinical expression of the most severe cases of neonatal echovirus 11 infection. Overall, aseptic meningitis or meningoencephalitis occurs in about 50% of perinatal enterovirus infections. Survival usually depends on the severity of myocarditis, hepatitis, or the associated sepsis-like syndrome.

Enterovirus 71

Enterovirus 71 was first isolated from a child with aseptic meningitis in 1969. The virus appears to circulate endemically in many populations as the prevalence of seropositivity among adults can be as high as 60%. Small clusters of severe central nervous system disease were recognized sporadically after the virus was first isolated. Major outbreaks of infection with high rates of severe central nervous system disease, frequently accompanied by fatal pulmonary edema, have occurred in central Europe in the 1970s and in Australia and Southeast Asia in the 1990s. The virus causes the hand-foot-mouth disease (HFMD) syndrome in approximately 25% of infected persons and the occurrence of this syndrome permits recognition of major outbreaks. In the 1998 outbreak in Taiwan over 125 000 cases of HFMD were documented over a 9-month period of time. Although many enteroviruses can cause HFMD, EV 71 was responsible for approximately 60% of cases during the 1998 Taiwan outbreak. Within the outbreak, over 400 cases of severe disease were encountered; EV 71 was implicated in 80%. Severe disease occurred most often in children less than 5 years who accounted for 90% of mortality. The highest death to case ratio occurred in children 6–12 months of age. Encephalitis

occurred in 75% of severe EV 71 cases and was associated with pulmonary edema (considered probably neurogenic) in close to one-half of encephalitis patients. Pulmonary edema also occurred in absence of clinical encephalitis. Aseptic meningitis occurred in 5/78 patients and acute flaccid paralysis in only one instance.

Fungal infections of the central nervous system

Fungi that cause human disease occur as yeast forms such as *Candida* species and *Cryptococcus neoformans*, and filamentous or mycelial forms as is true of *Aspergillus* species and the *Phycomycetes*. Dimorphic fungi exist in the mycelial phase in nature but revert to yeasts or spherules in tissue. Among the dimorphic fungi are *Histoplasma capsulatum*, *Blastomyces dermatitides*, and *Coccidioides immitis*. With the exception of *Candida* species infections which are a common problem in sick low birth weight neonates, serious invasive fungal infections are not common among otherwise normal children. Those predisposed to invasive fungal infections usually are immunosuppressed, especially children following bone marrow transplantation and with hematologic malignancy. Chronic granulomatous disease predisposes to infection with catalase positive bacteria and fungi. Patients with AIDS are at risk of developing *Cryptococcus neoformans* meningitis, an opportunistic infection much more often seen in adults than in children. Regardless of the underlying immunocompromising condition, neutropenia, use of corticosteroids, and persistent antibiotic therapy increases the risk of invasive fungal infections.

Candida species and *Aspergillus* species account for the majority of serious fungal infections in children. Other fungal species are less common and include those caused by members of the genus *Phycomycetes* which cause the disease known as mucormycosis.

The type of tissue pathology in the central nervous system will vary with different fungal organisms. *Aspergillus* species and the *Phycomycetes* have a strong predisposition to invade vascular structures leading either to hemorrhagic granulomas or ischemic infarctions. *Candida* species classically cause cerebral micro abscesses while *Cryptococcus* and *Coccidioides immitis* result in chronic granulomatous meningoencephalitis when central nervous system invasion occurs.

Aspergillus species rank second only to *Candida* as causes of fungal disease in immunosuppressed patients. The primary infection is acquired by respiratory inhalation from where dissemination can occur to various organs including the brain. Neurologic infection with *Aspergillus* is mainly in the form of multiple granulomas with surrounding edema. The lesions are frequently hemorrhagic and can be solitary or multiple. Central nervous system aspergillus is difficult to eradicate with amphotericin B with or without intraconazole and has a high mortality rate.

Histoplasmosis has its highest incidence in the Mississippi and Ohio valley regions and is usually manifested by an asymptomatic or flu-like respiratory infection with eventual spontaneous resolution but often leaving multiple punctate calcific lesions in the lungs. While benign fungal dissemination is common in normal infected persons, symptomatic disseminated histoplasmosis is seen largely in persons with AIDS or other immunocompromising disease. Neurologic histoplasmosis is usually with a chronic granulomatous meningitis.

Blastomyces dermatitides is widespread in nature with primary infection occurring in the lungs. It is now known that symptomatic blastomycotic pneumonia can either progress to chronic pulmonary disease or can resolve spontaneously. When dissemination occurs from the lungs, spread is usually to skin or to skeletal structures. Neurologic infection can result from direct epidural extension from adjacent skull or vertebral osteomyelitis. Blood-borne spread can also bring about a chronic granulomatous basilar meningitis.

Coccidioidomycosis is endemic in the southwestern part of this country and has its highest incidence in the San Joaquin Valley in California. *Coccidioides immitis* is a normal inhabitant in dry soil and is acquired by transmission in dust. Respiratory inhalation of the fungus is associated with asymptomatic infection in 60%. Most of the remainder are in the form of a transient respiratory illness and less often as chronic pulmonary disease. In less than 1% of pulmonary infections, the disease is disseminated to skin, bone, ocular structures, or to the meninges where it produces a chronic, indulent granulomatous meningoencephalitis. The cerebrospinal fluid with meningeal infection shows a mixed cellular pleocytosis, reduced glucose content, marked elevation of cerebrospinal fluid protein and specific IgG antibodies determined by complement-fixation testing. Tissue examination reveals coccidioidal spherules containing endosporins with Grocott–Gomori staining. Coccidioidal meningitis in children is infrequent in endemic areas but is an intractable, debilitating disease poorly responsive to treatment. Hydrocephalus often complicates the illness and the morbidity and mortality are high. Amphotericin B is the mainstay of therapy and usually requires intrathecal administration. Recent studies suggest an improved outlook with use of the triazoles including fluconazole and, more recently, voroconazole.

Cryptococcus neoformans is the most common fungal cause of granulomatous meningitis in otherwise healthy adults but is unusual in children. The infection is acquired by inhalation of yeast-phase fungus from the environment. The primary respiratory illness is often asymptomatic or not recognized as a potentially serious illness. When dissemination occurs it is usually to the meninges where it causes an infection with first symptoms usually being headache and mental status changes without fever or meningeal signs. These signs can progress gradually but sometimes will persist for

weeks before advancing. Vomiting, lethargy, ataxia, localized neurologic signs and papilledema eventually emerge. Diagnosis is established by cerebrospinal fluid examination which usually shows a limited cellular response and a positive test for cryptococcal polysaccharide antigen. India ink preparation is usually positive in AIDS patients with the illness but much less so in previously normal persons. Cerebrospinal fluid culture will be positive in most. The organism is seen with proper stains as a round or oval encapsulated yeast. Cryptococcal meningitis now is a widely recognized complication in persons with AIDS and can be seen in HIV-positive persons without significant immunosuppression. Intensive antifungal therapy will eradicate the infection in over 80% of cases although relapses can occur and are frequent in AIDS patients. Amphotericin B with or without flucytosine is customary therapy, and often followed by oral therapy with fluconazole.

Mucormycosis is an invasive fungal infection resulting from members of the class Zygomycetes (Phycomycetes). The name of the disease stems from the fact that most cases are caused by members of the order Mucorales, and specifically by the genus *Rhizopus*. The illness occurs almost entirely among persons who are immunosuppressed or have conditions with persisting or chronic acidosis such as chronic renal failure or diabetes mellitus. It is far more frequent in adults than in children. Primary pneumonia or disseminated disease is seen mainly among persons with leukemia or lymphoma. The most widely recognized form is known as rhinocerebral mucormycosis, a distinctive fungal disease which follows hyphal invasion of the nasal and paranasal sinus mucosa. Fungal invasion of the vascular endothelium in these areas leads to ischemic tissue injury resulting in black necrotic lesions in the nose and sinuses. The orbit may be invaded resulting in proptosis and rapid visual loss. Spread of infection to the cavernous sinus compounds the illness when intracavernous invasion of the carotid artery causes carotid thrombosis and ischemic cerebral infarction. The child then develops hemiparesis with other neurologic signs. The resulting brain injury is mainly ischemic but fungal hyphae without surrounding inflammation can be found in the area, especially within and adjacent to cerebral arterioles. Mucorales hyphae are identified on H & E and Grocott–Gomori methanamine silver stains as broad, nonseptate structures with right angle branching and which accept stains in irregular fashion along the hyphal structure. Rhinocerebral mucormycosis, like the disseminated form, was once considered to be uniformly fatal although with intensive antifungal therapy and hyperbaric oxygen treatments, the rhinocerebral form of illness can occasionally be overcome. The logic of hyperbaric oxygen therapy stems from the prominent role of ischemia due to fungal vascular invasion causing tissue injury. It is believed that this form of treatment increases oxygen delivery to damaged tissues.

Candida species central nervous system infections

Candida species are the most common members of the fungi that cause invasive disease and central nervous system disease in infants and children. In the pediatric age group, such infections are seen almost entirely in very low birth weight neonates, in children with immunocompromising conditions, and, less often, as a complication of surgical procedures associated with compromise of mucosal barriers. The factors that predispose to *Candida* infections are outlined in Table 10.8. Most infections are caused by *Candida albicans* although in recent years there has been a relative increase in serious infections by other species including *Candida tropicalis*, *Candida krusei*, and *Candida parapsilosis*. *Candida glabrata*, previously termed *Torulopsis glabrata*, has in some series become the second most common invading offender among the *Candida* species.

Infants less than 1500 g account for most cases of disseminated candidiasis in the neonate with the organism acquired either by vertical transmission from the maternal anogenital tract or by horizontal transmission from the environment. Disseminated neonatal candidiasis gives rise to a septic-like condition and closely resembles bacterial sepsis. Tissue dissemination can be to multiple organs resulting in hepatosplenic infection, septic arthritis or osteomyelitis, endophthalmitis, meningitis, and infrequently, to the heart with endocarditis or an intracardiac fungal mass.

The most common presenting signs among premature neonates with generalized candidiasis are shown in Table 10.9 Bacterial sepsis in the neonate more characteristically is associated with hypothermia while fever is more often found with *Candida* sepsis. In a large series of neonates with disseminated *Candida* species infections, Fernandez *et al*. (2000) found that 25% were associated with *Candida* meningitis. The clinical signs in those with meningitis are mainly those of septic and disseminated infection with evidence of meningitis found by cerebrospinal fluid examination. Cerebrospinal fluid abnormalities in infants with *Candida* meningitis resemble those with bacterial meningitis with reduced glucose levels and elevated pro-

TABLE 10.8

Predisposing Factors for Invasive *Candida* Species Infections

Immunosuppressive conditions
Low birth weight neonate
Damaged mucosal surfaces
Neutropenia
Antibiotic therapy
Corticosteroid therapy
Indwelling vascular catheters
Hyperalimentation and lipid infusions
Mechanical ventilation

TABLE 10.9

Common Presenting Signs of Disseminated Candidiasis in the Very Low Birth Weight Neonate

Respiratory compromise
Abdominal distention
Poor peripheral perfusion
Metabolic acidosis
Hyperthermia

tein content, although the cellular reaction is usually much less intense and mixed pleocytosis or lymphocytic cellular responses are more common with *Candida* meningitis. In the low birth weight neonate, *Candida* species central nervous system infection is usually meningitic in type, with or without parenchymal brain lesions and, as a result, the cerebrospinal fluid is usually abnormal. Yeasts are rarely seen in cerebrospinal fluid by staining methods although cerebrospinal fluid and blood cultures are generally positive. Growth of the fungus is slow and may not become evidence for 3–4 days. In older children with central nervous system *Candida* species infections, the pathology is more often that of multiple cerebral microabscesses which are readily seen on enhanced MRI examination. Unless some of the lesions are surface located, the cerebrospinal fluid can be unrevealing.

Vascular invasion with *Candida* species in the neonate will sometimes result in a hepatosplenic syndrome in which the liver rapidly enlarges and becomes tender or with joint involvement with acute arthritis which resembles acute bacterial septic arthritis. Aspiration of joint fluid or tissue samples from any infected tissue will reveal *Candida* yeasts as pseudohypae; elongated structures consisting of stacks of single yeast cells and stained with H & E or Grocott–Gomori methanamine silver stain.

While there is a definite case fatality rate in neonates with disseminated *Candida* species infections, it is difficult to assign mortality specifically to the fungal infection in most because the illness occurs in a sick infant usually with indwelling vascular catheters and multiple other medical problems. The infection can usually be eliminated with amphotericin B which is used as the sole, initial method of therapy by most. In older patients, amphotericin B is often given in combination with 5-flucytosine; however, the latter is an oral preparation and this route may be precluded in the low birth weight neonate. Infection with hepatosplenic candidiasis is usually treated with liposomal-bound amphotericin because this antifungal agent is selectively concentrated in reticuloendothelial tissue, the site of yeast cells in liver and spleen. *Candida* species are also sensitive to fluconazole which has been successfully used in infants or children intolerant of amphotericin B.

Parasitic diseases of the central nervous system

Parasitic infections seen in the United States that affect the central nervous system are mainly toxoplasmosis, cysticercosis, and primary amoeba meningoencephalitis. Very unusual cases of *Toxocara canis* encephalitis complicating visceral larval migrans have been described and recently, malaria has been observed with increasing frequency. There are many parasitic conditions (Table 10.10) that affect the nervous system in tropical and developing nations, most of which can now be seen in this country, either among returning travelers or in immigrants from regions endemic for a particular disease. Rapid transportation by air and frequent foreign travel have made it important that these illnesses generally considered to be exotic and rare be known to caregivers in this country.

An illness called eosinophilic meningitis is endemic in Hawaii and other Pacific regions as well as Southeast Asia.

TABLE 10.10

Classification of Some of the Parasites that Can Cause Central Nervous System Disease

Protozoa
Entamoeba histolytica
Sporozoa
Plasmodium species
Leishmania species
Trypanosoma species
Amoebae
Naegleria fowleri
Acanthamoeba species
Balamuthia mandrillaris
Coccidia
Toxoplasma gondii
Nematodes (roundworms)
Trichinella spiralis
Angiostrongylus cantonensis
Gnathostoma spinigerum
Toxocara canis
Cestodes (tapeworms)
Taenia solium
Echinococcus granulosa
Taenia multiceps (formerly *Multiceps multiceps*)
Spirometra mansonoides
Trematodes (flukes)
Paragonimus westermanni
Schistosoma species

Modified from Garcia 1999.

It also occurs in the Caribbean and Jamaica, thus, close to US borders. Eosinophilic meningitis is caused by a nematode, *Angiostrongylus cantonensis*, with an incubation period of 2–3 weeks. Human infection follows consumption of raw snails which harbor the larvae. Following penetration of intestinal vascular structures, larvae are transported to cerebrospinal fluid and, on dying, provoke an eosinophilic reaction which results in headaches, believed to be symptomatic of intracranial hypertension. Fever occurs in some with the illness but most remain afebrile. Cerebrospinal fluid is clear to hazy, contains 100–1000 WBCs per milliliter of which 20–70% are eosinophils. Detection of specific antibodies by ELISA or Western blot is sometimes used for specific diagnosis. Much less often, this illness will present with more dramatic encephalitic signs. There is no specific treatment and spontaneous resolution is expected in 3–4 weeks. Corticosteroids have been found to provide symptomatic relief in some but do not shorten the duration of the illness.

Paragonimiasis is endemic in the Far East and Southeast Asia. Rare examples have been acquired in this country but many more have been identified in immigrants. This trematode disease is caused by the lung fluke *Paragonimus westermani* which is acquired by human consumption of uncooked crabs or crayfish. In the majority, paragonimiasis is a pleuropulmonary illness with blood eosinophilia. Clinically, it is a chronic afebrile disorder with cough, chest pain, dyspnea if extensive in the lungs, and hemoptysis, thus resembling advanced pulmonary tuberculosis which sometimes co-exists. *Paragonimus* ova can usually be found in the stools and in bronchial washings. Specific antibody can be identified by Western blot. When the infection is disseminated, the brain is a predisposed site in which large calcified granulomas or necrotic abscess-like lesions which result in a "soap bubble" appearance on skull x-rays and lesions with a mass effect on CT. Children are believed to be more susceptible to cerebral dissemination with larvae of this parasite which then matures into adult worms in brain tissue. Treatment of paragonimiasis is with praziquantel which is highly effective for the pulmonary and visceral infection. Brain involvement generally has a less favorable outcome and most require neurosurgical treatment.

Sparganosis is an illness provoked by the larval stage of the tapeworm *Spirometra mansonoides* and is found in China, Japan and elsewhere in Southeast Asia. The parasite also exists in the United States where numerous cases have been identified. Dogs and cats serve as the definitive hosts for the adult worms from which ova shed into water will hatch and are ingested by fish, frogs, small animals, and rodents. Human consumption of raw infected flesh leads to infection most often manifested by subcutaneous and muscular nodular lesions. Cerebral invasion by larvae results in an encapsulated granulomatous mass lesion usually initially considered to be a cerebral neoplasm preceding craniotomy and histologic examination. Sparganosis is most often a disorder of young adults but does occur in children. Unlike many other parasitic infections, it is not usually associated with blood eosinophilia. The parasite is sensitive to praziquantel.

Coenurosis is a rare parasitic disease mainly reported from Africa but with unusual cases having been acquired in North America as well. *Coenurosis cerebralis* is the larval stage of the tapeworm *Taenia multiceps*, an intestinal parasite of dogs. Human coenurosis usually is a central nervous system infectious disorder with either meningeal or parenchymal inflammatory and granulomatous lesions. Hydrocephalus can be a complication of posterior fossa leptomeningeal inflammation, which is more common than cerebral parenchymal lesions. Praziquantel has been recommended for treatment of coenurosis but its effectiveness is undetermined.

West African trypanosomiasis or African sleeping sickness is a chronic encephalopathic disorder transmitted by the tsetse fly infected with the parasite *Trypanosoma brucei gambiense*. The initial illness, often appearing long after the acquisition of the parasite, is characterized by recurrent fever, malaise, pruritis, thrombocytopenia, and posterior cervical adenopathy, the latter known in Africa to be a sign indicative of the disease and referred to as Winterbottom's sign. Encephalitic symptoms emerge weeks, months, or up to 3 years later and follow a progressive course with headaches, ataxia, dementia, tremor, myoclonus, and somnolence. Cerebrospinal fluid at this stage contains a mononuclear pleocytosis and increased protein content. Brain pathology includes generalized swelling and small vessel perivascular infiltration with plasma cells and lymphocytes. Trypanosomes cluster in Virchow–Robin spaces and surround penetrating vessels to the basal ganglia accounting for the common occurrence of extrapyramidal signs. Cortical and hypothalamic vascular compromise explains the customary sleep/wake disturbance, probably also influenced by brainstem reticular formation involvement. Trypanosomes can be found in cerebrospinal fluid with Giemsa and other stains. A markedly elevated serum IgM level is a clue to the diagnosis. Treatment in past years was with organic arsenicals but an experimental drug, eflurnithine, is now used if available from the WHO and is more effective and less toxic than arsenicals.

The Western hemisphere form of trypanosomiasis is Chagas disease, found in Mexico, Central and South America. The reduviid bug infected with *Trypanosoma cruzi* is the vector and the resulting acute illness is often asymptomatic. Children may develop an erythematous nodule at the bite site followed by malaise and generalized adenopathy. Most recover spontaneously within a few weeks. In approximately 20% of infected persons, a chronic phase of illness with dilated cardiomyopathy will develop, sometimes years later. Chronic Chagas disease is claimed to be the most common cause of chronic cardiomyopathy in South America. The

chronic phase is manifested by intestinal pseudo-obstruction in about 1% of infected persons. Chagas disease in otherwise normal children is not usually a cause of neurologic disease although rarely, encephalitis has been described in the acute phase. Immunosuppressive disease, especially AIDS, has recently been found to bring about reactivation of Chagas disease, sometimes with systemic involvement but with meningoencephalitis being the most common feature. Symptomatic Chagas disease is treated with benznidazole.

Schistosomiasis

Schistosomiasis is a disease caused by various species of blood flukes and is estimated to affect between 200 million and 300 million children and adults worldwide. It is found mainly in sub-Saharan Africa, the Middle East, Asia, the Caribbean, and in limited regions of South America. The habitat of the parasite is in blood venules, especially affecting portal, mesenteric, and bladder venules, as seen in Tables 10.11 and 10.12. Eggs produced within venules provoke an intense inflammatory reaction damaging local tissues in the chronic stage of the disease. Schistosomiasis is acquired by exposure to fresh water containing cercariae released from snails, the intermediate host. Cercarial penetration of the skin is associated with the development of a pruretic, maculopapular rash called swimmer's itch, the initial clinical expression of the illness. Once invasion of venules occurs and ova production begins, the next stage of the illness evolves and is termed Katayama fever. This is an immune-mediated reaction to multiple antigens within ova released from the parasite. Symptoms include chills, fever, headache, myalgia, hepatosplenomegaly and blood eosinophilia of variable degree.

Neurologic complications are unusual with schistosomiasis. Among adult patients in Southeast Asia who are admitted to hospital for schistosomiasis, about 4% have been found to have brain or spinal cord involvement. Any of the various species can cause central nervous system disease. Spinal cord schistosomiasis is usually the result of a granulomatous myelopathy although spinal cord injury can also be secondary to intraspinal vascular obstruction with ischemic myelopathy. Cerebral schistosomiasis is manifested in most by recurrent simple partial or generalized seizures, with or without focal neurologic deficits or signs of generalized brain dysfunction. Praziquantel is highly effective against this parasite and a favorable outcome is expected unless advanced tissue injury has already occurred.

TABLE 10.11

Organ Predilection with Various *Schistosema* Species

Urinary schistosomiasis
Schistosoma haematobium
Hepatosplenic – Mesenteric schistosomiasis
Schistosoma mansoni
Schistosoma japonicum
Schistosoma mekongi

TABLE 10.12

Clinical Stages of Schistosomiasis

Swimmer's itch – dermatitis due to cercarial penetration of the skin

Katayama fever – acute stage which coincides with larval maturation and egg deposition in venules. Positive serologic test

Chronic schistosomiasis
- Hepatic
- Intestinal
- Urinary tract
- Neurologic (rare)

Congenital toxoplasmosis

Toxoplasma gondii is a parasite with worldwide distribution and infects a wide variety of warm-blooded small and large animals. Cats are the definitive host. The parasite exists in three forms including the oocyst excreted in feces of infected animals, the trophozoite which is the proliferative form in tissue, and toxoplasma cysts, the chronic latent stage found in tissues. Humans become infected with the parasite by consumption of undercooked or raw meat or from oocysts found in cat litter, especially from farm-residing cats that have greater access to infected small rodents than urban domestic cats.

Most primary infections with toxoplasmosis in children or adults are asymptomatic or with mild flu-like illnesses and, thus, are not identified. When the illness is symptomatic, it causes an EBV-negative mononucleosis syndrome with fever, erythematous rash and diffuse lymphadenopathy but without pharyngitis, typical of EBV-induced infectious mononucleosis.

Fetal infection resulting in congenital toxoplasmosis represents the most common parasitic infection with central nervous system implications in this country and occurs when a mother acquires her primary infection with the organism during pregnancy. According to Wong and Remington (1994), untreated primary infection late in the first trimester is transmitted to the fetus in approximately 10%, in the second trimester fetal infection occurs in 30%, and in the third trimester fetal infection occurs in 60%. Among neonates with congenital toxoplasmosis, approximately 80% are asymptomatic at birth. Of the 20% of neonates who are symptomatic, 10% will exhibit severe multiorgan involvement and 10% will have milder expressions of disease (Table 10.13).

TABLE 10.13

Summary of Congenital Toxoplasmosis

Incidence is 1 in 1000 live births
80% of infected neonates are asymptomatic at birth
85% of asymptomatic infants later develop neurologic or ophthalmologic sequelae
10% of infected neonates have severe illness
Spiramycin given to mothers with primary infection during pregnancy will reduce fetal transmission by 60%

Severe neonatal toxoplasmosis can be manifested by jaundice, hepatosplenomegaly, maculopapular rash, thrombocytopenia, chorioretinitis, and toxoplasmic encephalitis, more often with hydrocephalus than with microcephaly, and frequently with intracranial calcifications seen on CT. Cerebral calcific densities are usually diffuse and punctate but can be found in a periventricular location, more characteristic of congenital CMV encephalitis. Hydrocephalus is usually secondary to intraventricular obstruction and in most is associated with a markedly elevated cerebrospinal fluid protein, often of sufficient degree to render the cerebrospinal fluid a xanthochromic appearance. Most severe neonatal infections with multiorgan involvement result from primary maternal infections early in pregnancy. When maternal toxoplasmosis occurs in the last trimester, almost all infected neonates are asymptomatic.

Of the 80% of congenitally infected but asymptomatic and untreated neonates, about 85% will subsequently develop signs of the disease later in infancy or in childhood. Macular chorioretinitis with visual loss is the most common and sometimes the only sign of inflammation. Other features that commonly emerge are sensorineural deafness, global developmental delay, specific neurologic deficits, and recurrent seizures. Abnormal progressive head enlargement can be delayed for weeks or months after birth.

Serologic diagnosis of congenital toxoplasmosis is complex, in part because specific maternal IgG antibodies will be transplacentally transferred to the fetus and can persist for 6–12 months before becoming undetectable. In addition, most infected neonates do not generate specific IgM antibodies. The lack of sensitivity of the IgM assay is why most authors recommend an assay for specific IgA antibodies as well. Specific IgG antibodies are usually measured by the indirect immunofluorescent method. PCR amplification for detection of toxoplasma DNA has recently been developed but the study is not always available.

Spiramycin is a macrolide antibiotic which remains an investigational drug in this country but can be made available upon request (see *Red Book*, American Academy of Pediatrics, 2003). Studies in France have shown that spiramycin given soon after primary infection in pregnancy will reduce transmission of *T. gondii* from mother to fetus by 60%. Studies by McAuley *et al*. (1994) have demonstrated the decided benefits of treatment of the congenitally infected neonate with pyrimethamine and sulfadiazine. Prolonged treatment is necessary and the regimen should be directed and monitored by one familiar with the use and complications of these drugs.

In addition to the congenital infection, toxoplasmosis is well known to be an opportunistic infection with cell-mediated immune deficiency states, especially AIDS. As such, the illness does occur in children but is far more common in adults. In AIDS patients, cerebral toxoplasmosis is said to occur in about 15% and is the most common opportunistic infection with this condition. It is also the most common cause of multiple ring-enhancing mass lesions in AIDS, being far more common than primary cerebral lymphoma.

Meningoencephalitis caused by free-living amoeba

Clinicians are generally familiar with brain abscess possibly occurring with infection with *Entamoeba histolytica* but less so with the central nervous system infections caused by the so-called free-living amoeba (Table 10.14). These parasites cause two distinctive types of neurologic infection, each with different clinical patterns and epidemiologic features, as reviewed by Ma *et al*. (1990) and Schumacher *et al*. (1995). The free-living amoeba have a worldwide distribution and are found in water, soil, and elsewhere in the environment. Central nervous system infection in either form is poorly responsive to therapy and most cases have been fatal.

Primary amoebic meningitis is caused by *Naegleria fowleri* and usually affects adolescents and young adults. It is a rare disorder with most cases in the USA having occurred in Virginia, the Carolinas, and Florida. The organism is acquired

TABLE 10.14

Central Nervous System Infections Caused by Free-Living Amoeba

Naegleria fowleri

Primary amoebic meningoencephalitis
Acute purulent meningitis
A water-borne infection

***Acanthamoeba* species**

Subacute or chronic granulomatous encephalitis
Most in immunosuppressed patients
Usually with focal neurologic signs
Cerebrospinal fluid lymphocytic pleocytosis

Balamuthia mandrillaris

Subacute or chronic granulomatous encephalitis
Previously normal or immunosuppressed patients
No known effective therapy

from warm water of lakes, ponds, and poorly kept private swimming pools. Portal of entry is across the nasal mucosa to the olfactory nerves and to the olfactory bulbs embedded in cerebrospinal fluid. Infection within the olfactory structures rapidly leads to hemorrhagic necrosis and explains the occasional early complaint of disturbance of smell and taste sensations. Once in cerebrospinal fluid, the parasite provokes a fulminating purulent meningitis which is usually initially assumed to be bacterial meningitis. Symptoms begin 3–6 days after exposure to contaminated water with headache, vomiting, and fever being the first complaints followed by rapid decline in consciousness. Meningeal signs appear early in the illness. Generalized brain swelling is visualized on neuroimaging with collapsed ventricles and effacement of the perimesencephalic and quadrigeminal cisterns. Cerebrospinal fluid is purulent, is under markedly elevated pressure, and contains a neutrophilic pleocytosis with reduced glucose content and a striking increase in the protein content. Diagnosis of infection with *N. fowleri* is suspected when acute, rapidly progressive meningitis occurs within a week after swimming in warm water and with purulent but aseptic meningitis. The illness progresses so rapidly that serologic tests are of no help diagnostically. A fresh cerebrospinal fluid specimen may reveal motile amoebic trophozoites with Giemsa or Wright stains. If not, meningeal biopsy will demonstrate trophozoite structures about the size of macrophages and clustered in a perivascular distribution. Recommended treatment includes intravenous and sometimes intrathecal amphotericin B, usually in combination with rifampin. It is usually a fatal illness although there are reports of recovery with early initiation of therapy.

Subacute or chronic granulomatous amoebic meningoencephalitis is caused by *Acanthamoeba* species and has been described more often in immunosuppressed or debilitated adults than in children. The organism enters the respiratory tract from environmental sources and central nervous system infection follows hematogenous spread from the lungs. The clinical illness evolves slowly over weeks, usually with low-grade fever and signs of focal or multifocal neurologic dysfunction. Parenchymal brain lesions are necrotizing and granulomatous containing multinucleated giant cells and with evidence of vascular invasion by the parasite. The site of the mass lesions and whether solitary or multiple determines the neurologic signs. Cerebrospinal fluid abnormalities consist of a lymphocytic pleocytosis and diagnosis in life is determined by brain biopsy. The infection has not been found to be responsive to any therapeutic regimen. A similar illness has recently been recognized with *Balamuthia mandrillaris*, a similar soil parasite previously assumed to be nonpathogenic. Unlike infection with *Acanthamoeba* species, that with *Balamuthia mandrillaris* can occur in previously normal persons as well as in the immunosuppressed patient. It also is unresponsive to currently available therapeutic agents.

Cerebral cysticercosis

Infection with *Taenia solium*, the pork tapeworm, either in the form of asymptomatic carriage of the intestinal tapeworm or as cysticercosis, is widespread in the world especially in Mexico, Central and South America, Africa, Southeast Asia, and many central European nations. Cysticercosis is not rare in the United States and is primarily seen in immigrants from endemic zones. The intestinal tapeworm is acquired by humans by ingestion of undercooked pork infected with *T. solium* cysticerci. Once ingested, the scolex, encysted in meat, becomes attached to the intestinal epithelium and, with maturation, ova are produced and are excreted in the stools providing one possible source of infection of other household members.

Human cysticercosis is acquired by ingestion of *T. solium* ova, excreted in feces by pigs and less often by humans. Human contamination with ova usually occurs by consumption of ova-containing foods or soil. Ova hatch in the intestine resulting in the larval stage, which penetrate the intestinal wall to be transported to various tissues including muscle, subcutaneous tissues, eye, and the brain. When the brain is affected, the larval stage becomes encapsulated within a cystic lesion which will contain the scolex of the parasite. The live, encysted parasite provokes little inflammatory reaction and remains clinically dormant until death of the organism occurs which then elicits a brisk inflammatory response with local cerebral edema and irritation of adjacent structures. During this stage with degenerating and dying organisms, the adjacent edema can be extensive and associated with headaches and seizures. Less often, intracranial localization of the encysted parasite will be within the ventricular ependyma and, if in the aqueduct or fourth ventricle, it will lead to obstruction and hydrocephalus. In others, the degenerative process of the encysted parasite remains asymptomatic and months or years later, the lesions will shrink in size and become densely calcified. This stage may also remain asymptomatic but is usually recognized when the occurrence of seizures is followed by neuroimaging. Calcific lesions are most prominent at the cortical-white matter junction and in the chronic stage are not surrounded by edema. Lesions may be few in number or dozens can be observed.

Diagnosis of cerebral cysticercosis can be made in most cases on the basis of history, exposure in an endemic area, and from findings on neuroimage examination. In the stage when dying parasites leads to cerebral edema, T_2 weighted MRI will reveal the degree of edema and will show an encysted area containing the scolex in most cases. In the chronic stage, multiple cerebral punctate calcific lesions are best seen with CT. Regardless of the stage of illness, blood eosinophilia is not usually present although eosinophils can be found in cerebrospinal fluid infrequently.

During the inflammatory phase of the illness with localized cerebral swelling, the EITB serologic test on serum (enzyme-linked immunoelectron transfer blot) will be positive and is highly sensitive. Treatment in the acute, inflammatory stage of cysticercosis is with albendazole in a childhood dose of 15 mg/kg/day for 7–10 days. The dose for patients over 40 kg is 400 mg/day. Many experts will also administer corticosteroids during the treatment regimen because drug-induced death of remaining parasites can be expected to add to the cerebral swelling. When the disease is identified in the chronic stage by finding multiple punctuate calcific lesions mainly at the cortical–white matter junction and without adjacent edema, antiparasitic therapy is not indicated.

Spirochaetal diseases of the central nervous system

The best-known spirochaetal infections that can be associated with neurologic involvement include Lyme disease, leptospirosis, and congenital syphilis. Lyme disease is the most common tick-borne infection in the USA and a wide variety of nervous system manifestations have been described with this condition. Leptospirosis is not common in the United States, but because most infections are mild and symptoms nonspecific, the majority resolve without diagnostic identification. It is one of the less common causes of acute infectious aseptic meningitis in children or adults but should be kept in mind because of possible treatment implications. Congenital syphilis is largely a preventable disease by treatment of infected women during pregnancy who are in the primary or secondary stage of the illness. Neonates with congenital syphilis are usually asymptomatic at birth but within days to weeks develop the characteristic rash, nasal discharge, adenopathy, hepotosplenomegaly, and skeletal lesions, all representative of the transplacentally transmitted secondary stage of the illness. Central nervous system infection in an infected young infant is identified by cerebrospinal fluid examination including the venereal disease reference laboratory (VDRL) test or the rapid plasma reagin (RPR) test. Tertiary neurosyphilis in older children with general paresis or tabes dorsalis as late complications of untreated congenital syphilis is now mainly a matter of historical interest.

Lyme disease

Lyme disease in the United States is caused by *Borrelia burgdorferi* and is widely distributed although most infections are acquired in northeastern states, in the upper Midwest, and in northern California. Studies by Steere (2001) indicate that about 15 000 cases of Lyme disease are reported each year resulting in the disease being the most common vector-borne illness in the United States. Lyme disease is usually transmitted by the nymph stage of the tick vector whose natural host is the white-tailed deer and with reservoir in mice. In the northeastern United States, *Ixedes scapularis* is the tick vector for Lyme disease, as well as for babesiosis and granulocytic ehrlichiosis.

Symptoms and signs of Lyme disease can be variable, largely depending on whether it is adequately treated in the early stage. Lyme disease affects mainly the skin, central and peripheral nervous systems, the heart, and the joints. The clinical illness is divided into stages although with considerable overlap. Stage 1 is characterized by a skin lesion called erythema migrans which appears at the site of the tick bite. The initial lesion usually develops between 4 and 30 days after exposure and may be followed by one or more secondary surface lesions. Over 80% of persons who acquire Lyme disease will develop erythema migrans which is usually associated with transient flu-like symptoms with fever, malaise, and myalgia. Stage 2 can emerge within weeks to months after the illness is acquired and is associated with neurologic signs in 15–20% of cases or with cardiac involvement in 5–10%, usually with atrioventricular (AV) conduction defects or mild myocarditis. Stage 3 reflects an inflammatory reaction of the joint synovia with large joint arthritis occurring months after the infection is acquired. Among untreated patients, it is believed that most will eventually develop Lyme arthritis, whether neurologic or cardiac features have occurred or not.

Diagnosis of Lyme disease rests on a compatible clinical pattern along with serologic tests performed in a laboratory experienced with the methodology and interpretation of the results. Standard serologic tests include the enzyme-linked immunosorbent assay (ELISA) and Western blot to measure IgM and IgG specific antibody levels. Serologic responses are customarily delayed in the initial stage of the illness but after 4–6 weeks IgG antibody titers are expected to rise. Steere (2001) has pointed out that, in some, IgM antibodies may persist for months or years, decreasing its value as an indicator of recent infection. PCR has been useful for testing synovial fluid for *Borrelia* DNA in the early phases of arthritis but has not been consistently reliable on cerebrospinal fluid specimens in persons suspected to have Lyme neuroborreliosis, except in those with acute aseptic meningitis.

Antibiotic treatment of Lyme disease is complex and will be determined by the age of the patient and the organs affected. Erythema migrans and early dissemination in non-pregnant patients and those over 8 years of age are treated with doxycycline given orally for 14–21 days. For children younger than 8 years and during pregnancy, amoxicillin is recommended. Lyme disease complicated by neurologic or cardiac involvement is generally treated with intravenous ceftriaxone for 2–4 weeks. Lyme arthritis can usually be managed with doxycycline although when intractable, IV ceftriaxone may be required.

Neurologic manifestations in Lyme disease have been estimated to occur in 15–20% of cases (Table 10.15). A commonly

TABLE 10.15 Neurologic Manifestations of Lyme Disease

Acute or subacute aseptic meningitis
Facial paralysis
Acute optic neuritis and other cranial neuropathies
Meningoencephalitis
Acute transverse myelitis
Acute cerebellar ataxia
Peripheral neuropathies
Increased intracranial pressure syndrome
Lyme encephalopathy

encountered pattern of neurologic disease is its occurrence with multilevel involvement or its development coincident to myocardial inflammation with AV conduction abnormalities. Multilevel neurologic disease is suspected in a child with simultaneous occurrence of facial nerve paralysis and aseptic meningitis or peripheral neuropathy with acute myelitis, encephalitis, or acute optic neuritis. Lymphocytic aseptic meningitis and acute facial paralysis are the most common neurologic complications in children. Aseptic meningitis can be relapsing with this infection and is associated with headache, mild neck stiffness, and cerebrospinal fluid pleocytosis. Lyme disease can cause optic disc abnormalities with acute optic neuritis associated with unilateral or bilateral visual loss. Papilledema reflecting increased intracranial pressure can be provoked by encephalitis, encephalopathy, or an ill-defined but postulated disturbance of cerebrospinal fluid outflow at the level of the arachnoid granulations. A late onset form of Lyme neuroborreliosis is referred to as Lyme encephalopathy in which chronic cognitive and behavioral abnormalities predominate. The cerebrospinal fluid does not show an inflammatory response in this condition although intrathecal production of antibodies has been found. The pathogenesis of this unusual complication in children with Lyme disease remains unclear.

Leptospirosis

Leptospirosis is an acute febrile infection which can present in a variety of fashions and with wide variations in severity. Some remain asymptomatic while the majority of infected patients have mild, anicteric febrile illnesses which are assumed to be viral infections and are never diagnosed. Leptospirosis is caused by one of the multiple serotypes of the spirochaete, *Leptospira interrogans*. Most cases occur between June and October and most occur in adolescents or young adults. Males are more often infected than females. Leptospires are acquired by humans by water exposure with the organism entering the blood stream across abraded areas of skin or via mucosal surfaces. Leptospirosis is a zoonosis with water contamination from urine of infected animal species. Certain animals have a predisposition to harbor specific serotypes of *Leptospira interrogans*. *L. canicola* is carried and excreted in the urine by dogs, *L. pomona* by pigs and cattle, *L. icterohemorrhagica* by rats, mice, and other small rodents, and *L. grippotyphosa* by cattle and raccoons.

Following an incubation period which varies from 7 to 21 days, the most common presentation of leptospirosis is a self-limited febrile illness with malaise, myalgia, headache, diarrhea, conjunctivitis, and a maculopapular rash in some. Mild hepatomegaly is common but usually without significant elevation in liver enzymes. The most widely known but one of the least common clinical forms of leptospirosis is an acute, fulminating febrile hepatorenal syndrome with capillary vasculitis known as Weil's disease. This disorder is characterized by high fever with intense hepatic and renal involvement with rapidly progressive renal failure. Findings include hepatomegaly, jaundice, hypoalbuminemia, and deficiency of vitamin K-dependent clotting factors which can contribute to clinical bleeding. Death is not usually caused by hepatorenal dysfunction but can result from pulmonary or gastrointestinal hemorrhage or consumption coagulopathy with shock secondary to the systemic inflammatory vasculitis. Weil's disease, although well known, accounts for less than 10% of all symptomatic cases of leptospirosis.

During the first week of leptospirosis, leptospires commonly enter cerebrospinal fluid but do not provoke an inflammatory reaction therein although leptospires can sometimes be isolated. After 1–3 weeks of illness, a small percentage of patients will develop clinical signs of acute aseptic meningitis which represents a meningeal immune response to the previously present leptospires in cerebrospinal fluid. At this stage, leptospires will not be found in cerebrospinal fluid, which does show a mononuclear pleocytosis with an elevated protein content in most.

Serologic diagnosis of leptospirosis requires the demonstration of a four-fold rise in serum antibodies over time by use of the leptospira agglutination test. Leptospires can sometimes be isolated from blood during the first week of illness or from urine thereafter although this is technically difficult and sensitivity of isolation of the organism as a diagnostic method is low. PCR has been developed for use with this organism but is not generally available. Treatment of leptospirosis when the illness is mild is usually with oral doxycline. With more severe illness requiring hospitalization, intravenous penicillin is recommended although it is often complicated by the Jarish-Herxheimer reaction which is manifested by a brief exaggeration of the clinical symptoms and signs of the infection.

Rickettsial infections

Rocky Mountain spotted fever

Rickettsia rickettsiae causes a tick-borne bacterial infection that is endemic in certain parts of the United States. The

highest numbers of cases occur in the central Atlantic states (North Carolina, South Carolina, Virginia) and Oklahoma. Lower rates of infection occur from New England through the Gulf coast states and into the Midwest. The organism is maintained in nature by transovarial transmission in ticks. In the eastern United States *Dermacentor variabilis* (dog tick) is the principle vector but *Ambylomma americanum* (Lone Star tick) has an important role, as well. In the western United States *Dermacentor andersonii* (wood tick) is the vector. Infection is transmitted to man by adult ticks which must remain attached for approximately 6 hours. Most infections occur between mid-April and October with a peak in May and June. However, infections have occurred as late as December in warmer climates. The organism is an obligate intracellular pathogen that is tropic for vascular endothelial cells. Thus, the illness is a consequence of a multiorgan bacterial vasculitis. Disease onset occurs 2–8 days after the tick bite with the appearance of fever, headache, general malaise, and myalgia. Rash, which eventually occurs in 90% of cases, usually appears between the second and fifth days of illness. A maculopapular rash begins on the wrists and ankles and spreads centrally and distally. Individual lesions of the rash progress to petechiae as they mature. Purpuric lesions develop in those with delayed treatment or the most severe infections. The death to case ratio without treatment is 25%; fatalities usually occur between days eight and twelve of illness. Headache occurs in most infected persons early in the course of illness and as disease progresses symptomatic central nervous system infection emerges beginning after 4–5 days of clinical illness. Central nervous system manifestations progress from lethargy to confusion, obtundation and coma. Focal paresis may occur. CT or MRI findings include infarction, brain edema, and meningeal enhancement, all consequences of central nervous system vasculitis. Death rates are high when central nervous system disease is severe enough to result in neuroimaging changes. Central nervous system disease usually occurs in the setting of readily recognizable disease (rash, thrombocytopenia, multiorgan system involvement, history of tick exposure); however, RMSF should be considered within the differential diagnosis of all encephalitic illnesses occurring in endemic areas. As indicated above, cases can occur outside the season of highest risk. The disease is effectively treated with doxycycline which is the drug of choice. Chloramphenicol is also effective but is rarely used. Diagnosis is usually made serologically. Elevated concentrations of antibody are not observed during the first 6 days of illness when decisions about antibiotic therapy must be made to insure a satisfactory clinical outcome. Clinicians should not consider early antibody data to have any meaningful negative predictive value. Seroconversion can be demonstrated as early as day 9–11 of illness, but more routinely during the second through fourth weeks after illness onset.

Ehrlichiosis

Human monocytic (*Ehrlichia chafeensis*) and granulocytic (*Anaplasma phagocytophila*) ehrlichioses both occur in the United States. Monocytic ehrlichiosis is most prevalent in the south Atlantic and south Central states into the plains states. Granulocytic ehrlichiosis occurs predominantly in the upper Midwest into the northeast and upper Atlantic regions. These agents are also obligate intracellular bacteria with tropism for either monocytes or neutrophils. Monocytic ehrlichiosis is transmitted predominantly by *Amblyomma americanum* while granulocytic disease is spread by *Ixodes scapularis*, the vector of *Borrelia burgdorferi* (Lyme disease). After an incubation period of 4–10 days, illness begins with fever, malaise, headache and myalgia. Illness severity is sustained and progresses gradually over 2–6 days until medical advice is sought. By 4–6 days of clinical illness typical laboratory findings of leukopenia (1500–3000), thrombocytopenia (30 000–20 000) and elevated AST/ALT (150–400) are usually demonstrable. Mild maculopapular rash occurs in approximately one-third of patients but has no distinguishing characteristics. Without antibiotic treatment, severe disease will develop between days 4 and 12 of illness in approximately 15–20% of patients. In these patients, central nervous system involvement with typical manifestations of lethargy, impaired cognition, obtundation are common. Spinal fluid shows a mild mononuclear pleocytosis in up to 15% of patients. Death occurs in about 5% of untreated, symptomatic patients with monocytic ehrlichiosis and 10% with granulocytic disease. Tetracyclines are the treatment of choice and the only proven effective therapy. Diagnosis is usually established serologically.

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CHAPTER 11

Vascular Disease

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OUTLINE

Prenatal and perinatal ischemic disease
Intraventricular and parenchymal hemorrhage
Infant, child, and adolescent ischemic disease
Metabolic strokes
Cerebral veins and sinuses
Intracranial hemorrhage in infancy and childhood
Vascular malformations
Vein of Galen malformation
Other intracranial hemorrhages in childhood
Spinal cord vascular disease

Cerebrovascular events in adults are common and are generally well explained by established risk factors, which include hypertension, diabetes mellitus, and atherosclerosis. Similar events in children have traditionally received less clinical and investigative attention because of their perceived rarity. The WHO defines stroke as "A clinical syndrome of rapidly developed clinical signs of focal or global disturbance of cerebral dysfunction lasting greater than 24 hours or leading to death with no obvious cause other than of vascular origin." Recently, there has been increased recognition of childhood stroke and other forms of cerebrovascular disease in infancy and childhood. Retrospective epidemiologic studies have reported an incidence of 2.3 pediatric strokes per 100 000 children per year in California (Fullerton *et al.* 2003) and 2.6 in Cincinnati where intracerebral hemorrhage accounted for a surprising 58% of cases (Broderick *et al.* 1993). The ready availability of magnetic resonance (MR) and computed tomographic (CT) neuroimaging techniques has allowed easier confirmation of the diagnosis and etiology. A prospective high ascertainment study using these imaging modalities in Dijon, France reported a much higher incidence of 13 strokes per 100 000/year in children less than 16 years of age excluding the neonatal period (Giroud *et al.* 1995). The incidence and etiology of neonatal cerebrovascular events varies depending on gestational age but accounts for significant morbidity and mortality particularly in premature infants. An incidence of neonatal arterial ischemic stroke of 93 per 100 000 was reported from the Canadian Registry (Andrew *et al.* 2001). In the same study cerebral sinovenous thrombosis occurred in 41 per 100 000 newborns per year. The majority of pediatric stroke patients survive the acute insult, with survival increasing by 58% in the United States between 1979 and 1998 (Fullerton *et al.* 2002), yet many are left with residual disability (Gordon *et al.* 2002). Thus the importance of this condition is related more to its high prevalence, in contrast to adult cerebrovascular disease, which has a higher incidence but generally a shorter survival time.

In this chapter prenatal and perinatal periods are grouped together and considered separately from later childhood lesions. For each group, ischemic and hemorrhagic lesions are discussed separately.

Prenatal and perinatal ischemic disease

Ischemic disease in the premature infant

The premature brain is anatomically different to that of term infants. One of the most striking differences is the presence of the germinal matrix in the region of the basal ganglia with its network of fragile vessels which are prone to hemorrhage. Secondly the lack of autoregulation in the cerebral vasculature in the premature contributes to hemorrhage. A third important developmental factor is the extreme vulnerability to anoxic and free-radical injury of immature oligodendroglia in the white matter leading to a predisposition to periventricular leukomalacia (PVL) which occurs but is infrequent at term (Volpe 2001a).

Ischemic disease in the term infant

Hypotension and anoxia are the major causes of ischemic disease in the term infant. Labor and delivery is a high-risk period for CNS insults but immaturity of cerebral vasculature and autoregulation along with white matter vulnerability also contribute to vascular disease in term infants. The germinal matrix has largely disappeared by 36 weeks gestation and so hemorrhage from this site is unusual; however, intracranial and subarachnoid hemorrhage and ischemic infarction can occur as a consequence of birth trauma and brain contusion. In the following section common eti-

ologies of ischemic disease in preterm and term infants are discussed together.

It has long been recognized by pathologists that some congenital brain injuries are the result of cerebrovascular events that occur during gestation. Anencephaly, hydranencephaly, and some porencephalic cysts have either a distribution or pathologic features suggestive of a vascular pathogenesis. The arterial border zone location of some lesions suggests that infarcts were related to circulatory failure. All of these cases are recognized as prenatal in origin. The clinical importance of focal and multifocal ischemic infarcts has acquired new emphasis in recent years as a result of improved survival of neonates and the availability of newer imaging methods.

Although there are many similarities in histopathology between cerebral infarcts that occur in the immature brain and those that occur later in life, there are a number of differences. Both groups show ischemic and hemorrhagic infarcts of venous and arterial origin. Criteria for dating early life lesions are tenuous. Acute clinical presentation occurring postnatally, enhancement of the infarct on the computed tomography (CT) scan, and the temporal relationship of these findings to the histopathology suggest that the dating of such events is similar to that for older individuals (Lenn 1987). Diffusion and perfusion-weighted MR imaging of acute lesions can assist in timing of the insult (Wardlaw & Farrall 2004). Infarcts in neonates have greatly accelerated clearing of necrotic tissue and early calcification compared with later-onset lesions. Differences in distribution relate to immature features of vascular anatomy. Pathologic studies have provided some of the most reliable data but are biased for acutely ill babies. Cerebral infarcts, excluding venous infarcts and PVL occur in at least 5.4% of autopsied neonates (Barmada *et al*. 1979). Both clinical and pathologic series usually show more left than right cerebral infarcts and a high incidence of multiple infarcts. Arterial occlusions are more common than venous occlusions in neonates.

Focal infarcts can be seen in a variety of systemic disturbances, including apnea, bradycardia, hypotension, acidosis, hypoglycemia, disseminated intravascular coagulopathy (DIC), polycythemia, respiratory distress syndrome, sepsis, surgery, congenital heart disease, germinal matrix hemorrhage, and autonomic instability. A prothrombotic state (either genetic or acquired) was found in 59% of neonatal arterial stroke, with factor V Leiden mutation found in 15% and protein C deficiency in 4% (Kurnik *et al.* 2003). Newborn infants with stroke had a significantly higher plasma homocysteine level, collected within 4 hours of birth than controls and it is known that the maternal homocysteine levels affect early neonatal levels (Hogeveen *et al.* 2002). Maternal anticardiolipin antibodies and lupus anticoagulant are both neonatal stroke risk factors (Andrew *et al*. 2001). However, a specific etiology is not demonstrable in most prenatal and in many perinatal cases of vascular occlusion. Perinatal infarcts occasionally are due to amniotic fluid embolization. Maternal abuse of cocaine has been associated with both ischemic and hemorrhagic infarction (Chasnoff *et al.* 1986). In a study of 74 term neonates exposed antenatally to cocaine, methamphetamine, or cocaine and a narcotic, 35% had intraventricular hemorrhage (IM or necrotic or cavitary lesions on ultrasonography (Dixon & Bejar 1989).

A number of factors may contribute to prenatal and perinatal infarction. Maternal or fetal thrombophilia resulting in hypercoagulability cause abnormality of the placental vasculature, placental infarctions and vessel thrombosis which can result in perinatal stroke (Chabrier & Buchmuller 2003). In a large Canadian study fetal prothrombotic states contributed to 32% of neonates with sinovenous thrombosis (deVeber & Andrew 2001). Chorioamnionitis and extracorporeal membrane oxygenation were common associations of neonatal sinovenous thrombosis in one recent study (Wu *et al.* 2002). DIC and intracardiac thrombosis may produce increased factor VIII and free fatty acids, which increase platelet aggregation (McDonald *et al.* 1984). DIC or meningitis with arteritis has been observed when sepsis is associated with cerebral infarction. Up to 30% of autopsies in neonates with meningitis show infarcts, many of which are hemorrhagic (Friede 1973).

PVL presents a somewhat different picture. These lesions are usually symmetric and are located adjacent to the lateral ventricles and represent necrosis of cerebral white matter. The lesions vary in degree and size. This region is vulnerable owing to its location in the border zone areas between major cerebral arteries, They occur predominantly in premature infants who have survived several days or more and have had severe systemic illness, such as cardiorespiratory dysfunction or sepsis. PVL is now the main cause of brain injury in the premature infant. The three major etiologic factors are incomplete development of the vascular supply to the white matter, a maturation dependent impairment of cerebral blood flow regulation and a window of extreme

KEY CLINICAL QUESTIONS

- Unexplained encephalopathy with one or more of the following signs; hypotonia, apnea, bradycardia, lethargy.
- Focal or generalized seizures.
- CT or MRI findings of ischemia.

CONSIDER CONSULTATION WHEN...

- A cerebral infarction is diagnosed or suspected.
- Neonatal seizures occur.

vulnerability of immature oligodendroglia to free-radical injury (Volpe 2001a).

Signs and symptoms

Clinical presentation of an acute ischemic event in the perinatal period may include hypotonia, apnea, bradycardia, and lethargy without focal neurological deficits. Focal seizures often appear shortly thereafter and may be apparent only on electroencephalogram (EEG). Focal deficits may not become apparent for several months. The neurological examination in the neonatal period, reflecting primarily brainstem function, is usually of no localizing help even in extensive cortical strokes. Sinovenous thrombosis is largely a perinatal disease with multiple risk factors contributing (Wu *et al*. 2002) and a mortality rate of 8% with neurological deficits in a further 38% (deVeber & Andrew 2001). Seizures, apnea and lethargy are common presentations (Table 11.1).

The baby with a prenatal lesion most often presents with developmental abnormalities at 6–12 months of age. The mother or physician notes either asymmetry of motor function (asymmetric persistent grasp reflex, asymmetric parachute reflex, or early hand preference) or developmental delay. Even when an infant has a known cerebral infarct, his or her development and examination may be normal for several months. The reasons for such delay of symptoms and signs, and for their failure to occur in some cases, are not well understood. Infants with damage confined to the basal ganglia may not present with dystonia or choreoathetoid symptoms until the second year of life or later. With prenatal vascular lesions, hemiparesis almost always spares the face. Cognitive development may be impaired, especially with left hemisphere lesions, but this may not be noted until language development or school performance is affected. It is also important to realize that 50% of children showing motor dysfunction at 1 year of age may be normal by 7 years, especially if the earlier involvement was not severe (Nelson & Ellenberg 1982). Language and cognitive development are usually good following unilateral focal pre or perinatal lesions; however, special neglect may persist (Trauner *et al*. 2001; Trauner 2003). The most common clinical correlate to PVL is spastic diplegia as the fibers from the motor cortex to the leg course closest to the lateral ventricle. Middle cerebral artery infarction produces contralateral hemiparesis with relative sparing of the leg.

Seizures are the other major symptom of prenatal and perinatal cerebral infarcts (Ment *et al*. 1984; Clancy *et al*. 1985). A large proportion of cases diagnosed in the perinatal period come to attention because of focal seizures. In neonates with sinovenous thrombosis seizures occur in 71% (deVeber & Andrew 2001) and were the presenting feature in 57% (Wu *et al*. 2002). Persistent focal seizures in the newborn, in the absence of infectious or metabolic etiologies, suggest that a stroke has occurred.

PEARLS & PERILS

Prenatal and Perinatal Ischemic Disease

- Persistent focal seizures in the neonate suggest infarction.
- Electrographic status epilepticus may be due to perinatal infarction.
- Seizures are a common feature of sinovenous thrombosis.
- The neurological examination is usually nonfocal in neonatal stroke.
- Facial sparing in an infant with hemiparesis suggests a prenatal onset.
- The development of early hand preference (younger than 1 year of age) suggests dysfunction of the contralateral cerebral hemisphere.
- Noncerebral conditions that might mimic a prenatal or perinatal stroke include spinal cord injury, brachial plexus injury, and hypoplasia of the depressor angularis oris muscle.

FEATURES

Table 11.1 Prenatal and Perinatal Ischemic Disease

Discriminating feature

1. Focal infarction on CT or MRI

Consistent feature

1. Hemiparesis or persistent motor asymmetries by the first year of life

Variable features

1. Focal seizures in the neonatal period
2. Focal EEG abnormalities
3. Cognitive and language delays after the first year of life

Diagnostic studies

Ultrasound and, often, contrast-enhanced CT or magnetic resonance imaging (MRI) scans of the head are needed to recognize a recent infarct or other focal lesion (Fig. 11.1). Diffusion and/or perfusion-weighted MR imaging allows detection of acute areas of ischemia (Wardlaw & Farrall 2004) and MR angiography can assist in the identification of arteriovenous malformations and sinovenous thrombosis. There is limited information about the safety or the yield of transfemoral angiographic studies; they are rarely performed and should be performed only at experienced pediatric medical centers.

If the injury is old, neuroimaging may reveal either a unilateral enlarged ventricle or an area of porencephaly, usually in the distribution of the middle cerebral artery.

In both groups – those with focal seizures and those with focal neurological dysfunction – one should seek the etio-

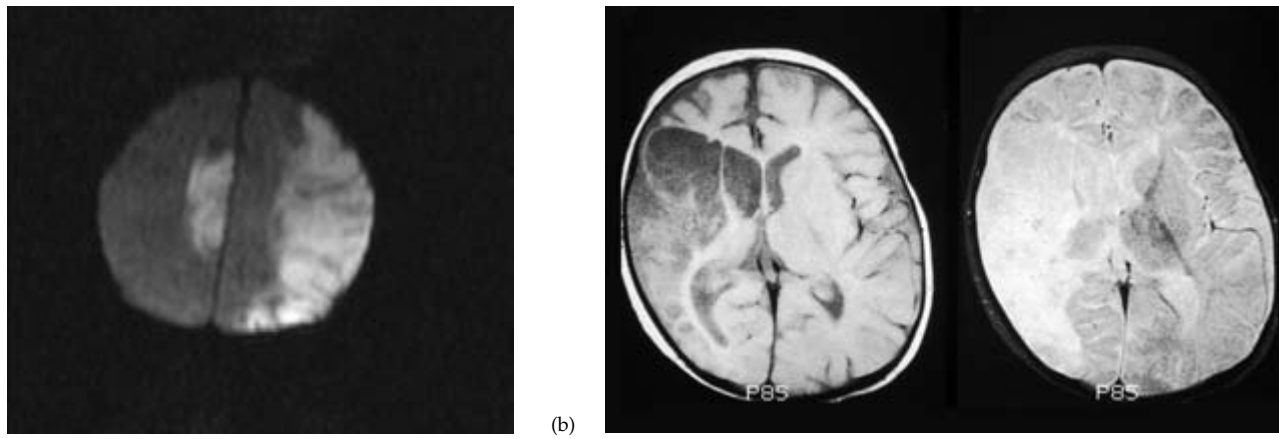


Fig. 11.1 (a) Acute neonatal stroke in a term infant with an unremarkable labor and delivery presenting with a generalized seizure at 3 hours of age. The placenta showed an umbilical vein varix with an organized thrombus supporting the likely embolic origin of these ischemic strokes through a patent foramen ovale. This child later a developed a hemiparesis and infantile spasms. The diffusion-weighted axial MRI at 8 hours of age shows restricted diffusion in the left middle cerebral artery distribution and in the right parasagittal area supplied by the right anterior cerebral artery. Time-of-flight MR angiogram shows lack of flow in the left middle cerebral artery (not shown). (b) A child who presented at 5 months of age with infantile spasms that responded to ACTH. At 15 years of age she has a left hemiparesis predominantly involving the upper extremity with mild learning disability and rare generalized tonic–clonic seizures. The brain axial MRI shows cystic encephalomalacia in the right middle cerebral distribution appearing as decreased signal on T1 and bright signal on T2 weighting indicating an old infarct.

logic factors described in the discussion of pathophysiology. In many cases the cause will not be identified; in many others more than one etiologic factor is present, producing a combination of interacting causes. If no cerebral lesion is found on CT or MRI, careful examination and localization to exclude a spinal cord process may require a spinal MRI. Peripheral nerve damage (that is, a brachial plexus injury) should be considered but is usually differentiated clinically from central lesions.

If a motor deficit of cerebral origin or seizures are recognized later in the first year or two of life, and there is no indication of acute onset or acquired etiology, careful clinical follow-up to detect progressive diseases is essential. The workup includes MRI scan for structural lesions, EEG for functional lesions, and consideration of metabolic studies if no clear etiology is identified.

PVL has a characteristic CT appearance in late infancy and childhood. Because the white matter is deficient, the lateral wall of the lateral ventricle has a scalloped contour and the gray matter at the depth of the sylvian fissure nearly touches the ventricular wall (Flodmark *et al.* 1987). MR with diffusion weighting is the preferred imaging modality for the detection, definition of severity and extent of PVL acutely (Bozzao *et al.* 2003) with fluid attenuated inversion recovery (FLAIR) also effective in the neonatal period (Iwata *et al.* 2004).

Treatment

There is no specific treatment for arterial infarcts. Recurrent infarcts are not expected in neonates. However recurrent episodes of infarction are reported later in childhood in children with genetic thrombophilias, in particular familial protein C deficiency (Strater *et al.* 2002). Most neonates have low levels of coagulation factors and so treatment with warfarin is generally avoided. Thrombolytic agents such as tissue plasminogen activator (TPA) also carry an increased risk of hemorrhage and are rarely used. Definite embolic ischemic disease without hemorrhage is one indication (Andrew *et al*. 2001). Recurrent seizures should be treated with anticonvulsants, at least over the short term. The child should have close follow-up and early institution of physical, occupational, and language therapy if deficits emerge.

Intraventricular and parenchymal hemorrhage

Intraventricular hemorrhage (IVH) is the major type of intracranial hemorrhage in the premature newborn. It originates from rupture of fragile blood vessels within the subependymal germinal matrix (Fig. 11.2).

The magnitude of this problem relates to direct correlation of IVH with the degree of prematurity, the improved survival rates for increasingly premature infants, and the persistent high rate of prematurity in our society. Probably no subject has produced more intense effort and study in modern child neurology than this frequent and devastating group of conditions (Volpe 2001b). Clarification of the pathogenesis of IVH continues, and new approaches to reducing occurrence and improving outcome have resulted (Goddard-Finegold & Mizrahi 1987). Birth-related hy-

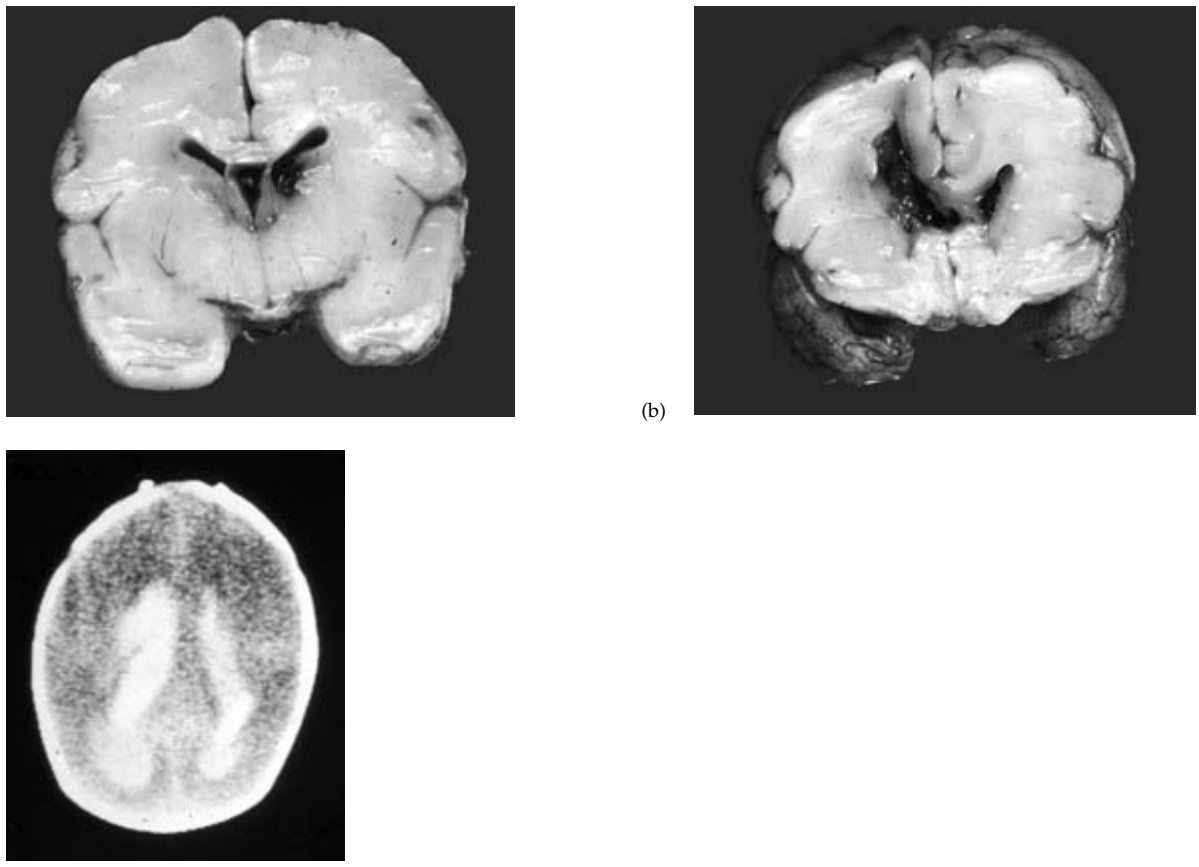


Fig. 11.2 Pathological specimen of unilateral grade IV intraventricular hemorrhage in a preterm infant: (a) left-sided germinal matrix hemorrhage; (b) bilateral intraventricular hemorrhage with parenchymal hemorrhage on the right; (c) axial noncontrast head CT scan showing bilateral grade IV intraventricular hemorrhage in a different case.

poxic-ischemic insult, impaired autoregulation of cerebral blood flow, and many secondary effects of these factors contribute. Prenatal treatment with glucocorticoids is the main factor decreasing the incidence both of respiratory distress syndrome and IVH. Careful labor management, aggressive resuscitation at birth to avoid hypoxemia, muscle paralysis with supportive ventilation, administration of surfactant, avoidance of large fluid shifts and correction of coagulopathies are all thought to be helpful in protecting the cerebral blood flow preventing IVH. Severe intraventricular hemorrhage (grade III/IV) has declined with improvements in preterm infant care with an incidence in under 1500 g infants of 18% in 1987–88 and 11% since 1993 but still accounts for significant morbidity and mortality (Fanaroff *et al*. 2003). The most recent reports do not demonstrate further improvement in IVH incidence in the last decade although exact comparison between studies is difficult because study groups are of different gestational ages and birth weight and use different grading scales. In the Danish nation-wide study for 1994–1995 the incidence of grade 3–4 IVH in survivors less than 28 weeks gestation or birth weight less than 1000 g was 10% (Kamper *et al.* 2004). The EPIPAGE study of nine regions in France in 1997 reported that for gestational ages of 22–32 weeks white matter damage was present in 22% and intraventricular hemorrhage, diagnosed by ultrasound, in 9% without ventricular dilatation and 3% with ventricular dilatation (Larroque *et al.* 2003). A recent New Zealand national study reported an incidence in 1998–1999 of grade 2–3 IVH in <1000 g infants of 9% and grade 4 of 3% (Darlow *et al*. 2003).

The weight-specific rates of IVH, like neonatal morbidity rates, changed with increasing knowledge and technology upto the early 1990s. Through the 1980s, IVH occurred in 62% of infants weighing less than 700 g (Perlman & Volpe 1986), 40% of infants weighing less than 1500 g, and 13% of those weighing between 1501 g and 2000 g at birth (McGuinness & Smith 1984). An excellent recent review of IVH etiology, management and outcome is available (Roland & Hill 2003).

IVH lesions are usually graded on radiologic criteria as follows (Papile *et al.* 1978a):

Grade I	Subependymal only
Grade II	Intraventricular blood
Grade III	Intraventricular blood with ventricular dilatation
Grade IV	Intraventricular blood with ventricular dilatation plus parenchymal hemorrhage.

In an ultrasound and pathological study of 22 very low birth-weight infants, who survived at least 6 days, 17 infants had intraventricular hemorrhage, but extension of ventricular blood into white matter unaffected by infarction was not found. Ependyma was found around the parenchymal blood showing that ventricular extension into infarcted tissue had occurred. Periventricular echogenicity was found in all cases of white matter necrosis (Paneth *et al.* 1990). The majority of neuropathological studies support the view that most cases of parenchymal hemorrhage in grade IV IVH are due to ischemic hemorrhagic infarction presumably as a result of impairment of venous drainage. The hemorrhages follow the medullary veins in the periventricular white matter and are most marked at the confluence of the veins adjacent to the ventricular angle (Gould *et al.* 1987;Volpe 2001b). These findings are supported by Doppler flow studies, MR spectroscopy and MR imaging (Dean & Taylor 1995;Toft *et al.* 1997; Counsell *et al.* 1999). There is an excellent review of MR findings in preterm brain injury (Counsell *et al.* 2003).

The forebrain germinal matrix is the source of cortical neurons in the first two trimesters and of supporting glial cells in the final trimester. Late in gestation, major changes occur. At this time, the germinal matrix is most prominent at the thalamostriate groove at the head of caudate nuclei and is the most common site for hemorrhage. The matrix gradually decreases in size until it is nearly completely involuted by term.

The risk of IVH increases with low Apgar scores, vaginal delivery, prolonged labor, blood pressure fluctuations, intrapartum hemorrhage, sepsis, coagulopathies, and rapid infusion of colloid. Defective or pressure-passive regulation of cerebral blood flow is a major risk factor (Lou & Friis-Hansen 1979); therefore, prevention of fluctuations in cerebral blood flow velocity is important.

Histopathologically, germinal matrix hemorrhage is associated with primary or secondary infarcts, edema, parenchymal extension beyond the germinal matrix, rupture of overlying ependyma, and intraventricular blood clots. As a consequence, the germinal matrix is destroyed and approximately 15% of neonates with IVH develop unilateral hemorrhagic infarction in the periventricular white matter. Studies indicate that such hemorrhage represents venous infarction rather than extension of the IVH (Volpe 2001b). Later evolution of the lesions produces porencephaly in up to two-thirds of long-term survivors of grades III and IV hemorrhages. These multicystic or confluent areas result from associated leukomalacia and infarction. A major complication of IVH is post hemorrhagic hydrocephalus which occurs in 35% of patients. This may be either obstructive at the IVth ventricle or aqueduct, or communicating due to occlusion of the arachnoid granulations responsible for CSF absorption over the surface of the brain.

The pathogenesis of IVH is multifactorial and involves intravascular, vascular, and extravascular factors (Volpe 1995). Intravascular factors are those that regulate blood pressure, volume, and flow. Vascular factors involve the vulnerable microvascular complex that comprises the germinal matrix. Extravascular factors are those referable to the space surrounding the germinal matrix capillaries, specifically the fragile and gelatinous supporting structures. The reader is referred to Volpe's *Neurology of the Newborn* (2001) for further details regarding the importance and interaction of these variables.

The incidence of minor intracranial hemorrhage in 1000 normal asymptomatic newborns accessed by ultrasound was 3.5% (Heibel *et al.* 1993). IVH may be seen infrequently in full-term infants. The majority of such hemorrhages arise from the choroid plexus. Many cases are complicated by traumatic or hypoxic events at birth; however, in 25–50% of affected infants, there is no identifiable predisposing cause. Both groups are at high risk for posthemorrhagic hydrocephalus, 35% of which will require shunting. *In utero* exposure to cocaine and amphetamines may lead to both hemorrhagic (IVH and parenchymal) and ischemic lesions (Dixon & Bejar 1989).

IVH occurs in the first 3 days of life in 90% of cases. It is present by the end of the first postnatal day in 35–50% (Rumack *et al.* 1985). There are three clinical profiles, depending in part on the gestational age and on the general condition of the infant. The least common but most dramatic is a catastrophic presentation. An abrupt deterioration characterized

PEARLS & PERILS

Intraventricular Hemorrhage

- IVH may occur in the absence of signs or symptoms, justifying the use of routine ultrasound of the head for detection of IVH in all premature infants weighing less than 2000 g or less than 34 weeks gestational age.
- Serial ultrasound studies of the head, daily head measurements, and palpation of the anterior fontanel and cranial sutures should be made in all cases of IVH. Head growth greater than 1.5–2 cm per week is indicative of progressive ventricular dilation.
- Subtle seizures may occur and require EEG confirmation.
- Serial ultrasonography and head measurements are useful in identifying abnormalities such as cerebral atrophy secondary to encephalomalacia or hydrocephalus.
- The combined use of acetazolamide with furosemide is not indicated for treatment of hydrocephalus.

by coma, posturing, seizures, fixed pupils, and apnea occurs in a previously stable neonate. Concurrent with this may be a falling hematocrit, metabolic acidosis, bradycardia, hypotension, and a bulging anterior fontanel. More common is a saltatory presentation, in which clinical deterioration occurs subacutely over several hours. Most common is a clinically silent presentation, in which despite careful clinical assessment, no changes are noted. There can also be considerable overlap between the clinical profiles of premature infants with and without IVH. A valuable sign is an unexplained fall in hematocrit or failure to rise after transfusion. Although clinical signs, such as decreased tracking, abnormal popliteal angle, and decreases in tone or motility, are correlated with IVH in infants under 36 weeks gestation (Dubowitz *et al.* 1981), these symptoms are nonspecific. Less than 50% of IVH in premature neonates can be identified on the basis of clinical findings alone.

Diagnostic studies

Because of its bedside accessibility ultrasound is the mainstay of diagnosis and follow-up for both IVH and its consequences. All high-risk babies should be routinely scanned at 3–4 days of age and at any time suggestive symptoms occur. Once IVH has been diagnosed, subsequent scans provide information on the evolution of the hemorrhage, the development of hydrocephalus, the effect of treatment, and the development of encephalomalacia or porencephaly. Ultrasound has the advantages of having no ionizing radiation, being relatively cost-effective, and being easily portable (Table 11.2).

CT is preferred if subdural hematoma or acute hemorrhage in a cortical or superficial location is suspected. It can identify skull fractures and the outer table fracture of a cephalohematoma. As discussed above MRI with diffusion weighting and FLAIR imaging is the best imaging method for infarction. Emergency MRI scans are not readily available in most centers and the complexities of transport, monitoring and ventilation of sick neonates limit its usefulness. High resolution CT carries a significant radiation dosage (Huda *et al.* 2004) but its ready availability to the sick neonate, speed (resulting in a short time out of the neonatal unit), utility in the imaging of acute hemorrhage and increasingly higher definition result in its continued usage. EEG is helpful in detecting subclinical and subtle seizures and also has prognostic importance. Spinal fluid examination is poorly discriminating for IVH but is often important to evaluate the possibility of bacterial meningitis. The characteristic cerebrospinal fluid (CSF) profile in IVH is many red blood cells and elevated protein, followed by xanthochromia and a depressed glucose. In full-term infants with unexplained intracranial hemorrhages, laboratory evaluation should include platelet count, prothrombin time and partial thromboplastin time, and screening for illicit drugs in mother and baby.

FEATURES

Table 11.2 Intraventricular Hemorrhage

Discriminating feature

1. Demonstration of the hemorrhage with head ultrasound or CT scan

Consistent features

1. Prematurity (in germinal matrix hemorrhage)
2. Associated with hypoxia and ischemia or major cerebrovascular disturbance
3. Blood in brain parenchyma and/or ventricles on CT scan

Variable feature

1. Associated parenchymal damage from periventricular leukomalacia, hemorrhagic infarction, or hematoma

Treatment

Clearly the best method of treatment is prevention. Prenatal intervention includes identifying women at high risk for premature delivery and providing appropriate care and education. When premature delivery appears inevitable, transporting the mother to a high-risk perinatal center and administering tocolytic agents and glucocorticoids are useful measures. Postnatal administration of phenobarbital, vitamin E, indomethacin, and fresh-frozen plasma have also been advocated to reduce the risk of IVH but remain investigational. No single interventional strategy has been sufficiently proven to decrease the incidence and severity of IVH, hence none warrants routine clinical use. Details of postnatal care are of great importance. Use of neuromuscular paralytics in ventilator-dependent infants has been shown to minimize erratic fluctuation in cerebral blood flow, hence minimizing incidence and severity of IVH. The goals of avoiding hypoxia, hypertension, rapid volume expansion, seizures, and excessive use of heparin in intravascular catheters are now often obtainable and remain important even after IVH has occurred. Studies vary on the effect of surfactant on IVH. Most studies have shown the incidence and severity of IVH to be either reduced or unchanged.

The management of posthemorrhagic hydrocephalus is complex because of clinical variables, limitations of the data available for individual patients, and limited knowledge of the risks and benefits of various approaches. Ventricular dilation spontaneously resolves in 65% of neonates. In the remaining 35%, dilation occurs rapidly (5%) or slowly (30%). Serial lumbar puncture is a temporizing measure in those with progressive dilatation and may be sufficient to arrest the process. Communication between the lateral ventricles and lumbar subarachnoid space is essential for this approach to be successful. Removal of 10–15 mL/kg is often

CONSIDER CONSULTATION WHEN…

- An infant is found to have intraventricular hemorrhage. Neurological and neurosurgical evaluation and follow-up are needed.

necessary. If CSF protein content is too high for CSF shunt placement (100–200 mg/dL), serial lumbar punctures are often sufficient to avoid external ventricular drainage, with its higher risk of infection. Serial lumbar puncture does not prevent the development of hydrocephalus and should be reserved for the treatment of hydrocephalus only (Anwar *et al.* 1985). When the CSF protein level falls, a ventriculoperitoneal shunt may be placed if hydrocephalus is still present. Many infants with less severe hydrocephalus, if managed with serial lumbar punctures and monitored with ultrasound examinations, have resolution of the problem without need for a shunt. Similar efficacy has been reported in a limited number of patients treated with acetazolamide (maximal dose: 100 mg/kg/day) and furosemide (1 mg/kg/day) (Shinnar *et al.* 1985). An international study subsequently found no benefit to the combination treatment and 24% of the combination treated infants developed nephrocalcinosis (1998). It is unknown if acetazolamide alone is beneficial. With serial lumbar punctures or acetazolamide treatment, close surveillance for the development of progressive hydrocephalus is essential.

Neurological outcome

The long-term neurological prognosis is clearly linked to the grade of IVH, presence of hydrocephalus, and degree of parenchymal involvement; however, multiple other factors also play a role. Short-term mortality is about 20% and occurs largely with grades III and IV lesions (McGuinness & Smith 1984). Progressive ventricular dilatation occurs in approximately half of the babies with IVH (usually 1–3 weeks following the hemorrhage), more often with grades III and IV hemorrhage, and in only 10% of grade I cases.

The long-term outcome for infants with IVH is one of markedly increased incidence of all major neurological handicaps. With grades III and IV hemorrhages, 30–40% have major sequelae (Catto-Smith *et al.* 1985; Papile *et al.* 1983). Morbidity depends the most on the degree of associated parenchymal injury. In cases complicated by periventricular hemorrhagic infarction or PVL, the evidence of severe neurological sequelae approaches 90%. On the other hand, in infants with grade II IVH, 75% of infants have normal intellectual and motor development. Survivors of grades I and II IVH do not clearly have a worse outcome than similar-weight babies without IVH (Ment *et al.* 1985).

Infant, child, and adolescent ischemic disease

Our approach to arterial and venous ischemic disease in this section is etiologic and anatomic. Localizing information can often be obtained from the history and examination as well as from neuroimaging. The ready availability of CT and of MRI technologies allows a diagnosis of even small ischemic and hemorrhagic strokes in adults and children. Many of these would have remained unsuspected clinically. Incidence and prevalence figures produced in the past originate largely from clinical data and may underestimate the true incidence of childhood stroke.

Thrombotic occlusions of the carotid artery or branches of the middle cerebral artery are the most frequently documented causes of stroke in children. Over the 20-year period 1979–1998 analysis of the National Center for Health Statistics database revealed 244 deaths per year in the United States in children less than 20 years of age (Fullerton *et al.* 2002). Boys had an increased risk of death from subarachnoid and intracranial hemorrhage but not from ischemic stroke. Ischemic strokes accounted for 26% of deaths with hemorrhagic strokes and subarachnoid hemorrhage accounting for 74%. Between 1979 and 1998 the death rate from stroke in children declined from 5.5 per million to 2.3 per million. The mortality from childhood stroke is fortunately low, and therefore the prevalence of this condition is far higher than the mortality figures suggest. Incidence of stroke in childhood determined in recent US retrospective studies is 2.3 per 100 000/year (Fullerton *et al.* 2003). The Canadian Registry found an incidence of ischemic stroke alone of 7 per 100 000/year (deVeber 2003) and a prospective high ascertainment study from France reported a total stroke incidence of 13 per 100 000/year with 8% ischemic and 5% hemorrhagic (Giroud *et al.* 1995). Earlier retrospective studies found hemorrhagic stroke (subarachnoid hemorrhage and parenchymal hemorrhage) to account for 22–56% of pediatric stroke cases (Broderick *et al.* 1993; Earley *et al.* 1998; Lanthier *et al.* 2000). Taking all of the current epidemiological data together it seems likely that the French incidence figures are likely close to the US and Canadian true incidence.

The two basic pathophysiologic mechanisms involved in an ischemic stroke regardless of age are thrombosis and embolization. In adults, hypertension, diabetes mellitus, atherosclerosis, cardiac arrhythmias, and valvular abnormalities are the common underlying risk factors for stroke. However, in childhood the potential etiologies are more variable and numerous. The pathophysiological mechanisms are not always well understood. The diagnostic challenge in such patients is formidable even for an experienced child neurologist. The various potential risk factors are reviewed in a systemic fashion, although an extensive discussion of each is not possible within the confines of this text.

Cardiac disorders

In most early series of pediatric stroke patients, congenital cyanotic heart disease is frequently identified as a predisposing factor. Tetralogy of Fallot and transposition of the great vessels account for most of the defects. The incidence of stroke in this population is 4%, and 75% occur within the first 2 years of life. Potential mechanisms of stroke include hyperviscosity due to polycythemia, diminished oxygenation, paradoxic emboli from right-to-left cardiac shunting, and emboli from vegetations secondary to valvular disease. Other abnormal structural defects predisposing to emboli include atrial myxoma, cardiac rhabdomyoma, cardiomyopathies, bacterial endocarditis, rheumatic heart disease, and prosthetic valves. Cardiac arrhythmias, particularly atrial fibrillation, also predispose to embolic phenomena. In a recent retrospective study of 212 children presenting with a first ischemic stroke 22% had cardiac abnormalities but intracardiac thrombus was only identified in two cases (Ganesan *et al.* 2003).

Infectious disorders

A variety of infectious processes can lead directly to stroke. Meningitis in particular can produce intense basilar inflammation, locally damaging vessels in the circle of Willis and the anterior and posterior circulations. Pharyngitis, cervical adenitis, tonsillitis, sinusitis, and retropharyngeal abscess and tonsillectomy are all reported precursors of internal carotid artery thrombosis. The mechanism is thought to be local inflammation of the wall of the artery. Less commonly, cat-scratch fever, ophthalmic herpes zoster, viral encephalitis (herpes simplex, Coxsackie virus A9, rubella), and mycoplasma infections have been associated with cerebrovascular disease. The mechanism is again believed to be related to vasculitis with subsequent thrombosis. Acquired immunodeficiency syndrome (AIDS) is now responsible for an increasing number of exotic systemic and central nervous system (CNS) infections, which may produce embolic occlusion. Chickenpox is a major risk factor for childhood stroke. A recent British retrospective review of 212 patients admitted to a tertiary care pediatric hospital found a history of varicella zoster infection in the previous year in 18% (Ganesan *et al*. 2003). A prospective cohort study of 70 consecutive children with arterial ischemic stroke found a three-fold increase in preceding varicella infection in the previous 12 months suggesting that varicella zoster infection accounts for one-third of childhood acute ischemic stroke (Askalan *et al.* 2001). These children also have a twofold increase in recurrent ischemic stroke and transient ischemic attacks. Varicella angiitis tends to unilaterally involve the proximal middle cerebral and anterior cerebral arteries (Lanthier *et al.* 2001).

Hematologic disorders

A variety of hematologic causes lead to arterial ischemic disease in children, although venous occlusion and hemorrhagic events may also occur in the same disease processes. Hyperviscosity syndromes (polycythemia vera, hyperleukocytosis [acute leukemia], and thrombocytosis [rarely]) can lead to arterial occlusion. Hemoglobinopathies, the prototype of which is sickle cell disease, are often complicated by stroke. The frequency of stroke in sickle cell disease is between 5% and 10%, with the median age of first stroke at 7 years of age. Recurrence occurs in up to 90%, most within 3 years. The Baltimore-Washington Cooperative Young Stroke Study reported an incidence of stroke in sickle cell disease in children ages 1–14 years as 285 per 100 000/year (Earley *et al*. 1998). Autopsy studies have revealed multifocal infarcts of various ages involving both large and small vessels. More recently MRI studies have shown a high incidence of vasculopathy and stroke in even asymptomatic sickle cell patients. Silent infarction (asymptomatic MR finding) was found in 35% of 185 patients with sickle cell disease studied at St Jude's Hospital (Steen *et al.* 2003). This raises the question of the need for transfusion therapy in the asymptomatic patient. Use of ultrasound Doppler has been shown by the Stroke prevention Trial in Sickle Cell Anemia (STOP) to be a useful screening tool for children with sickle cell disease at risk for stroke (Adams *et al.* 2004). Transfusion therapy is the mainstay for treatment of CNS symptomatic sickle cell disease; however, iron overload and transfusion reactions can limit its utility. Chelation with desferrioxamine is eventually needed to limit iron toxicity which results in endocrine damage, cirrhosis and cardiomyopathy. Treatment with hydroxyurea, which stabilizes sickle hemoglobin, and arginine, which is the substrate for nitric oxide production, have been advocated as treatments for the systemic complications. It is unknown whether these treatments are helpful in preventing CNS disease. Bone marrow transplantation offers a potential cure. An excellent recent review discusses the management of sickle cell disease (Claster & Vichinsky 2003). Patients with hemoglobin SC disease and hemoglobin S-thalassemia are also at increased risk but tend to have milder courses. Patients with sickle cell trait are not at risk, although there have been rare reports of strokes occurring in this population (Greenberg & Massey 1985).

There has been a recent recognition of hypercoagulable states; some are genetically determined, some associated with autoimmune disorders, and some found to be independent of an underlying disease. Antithrombin III, protein C, and protein S are naturally occurring anticoagulants that have deficiencies that are inherited as autosomal recessive traits (Camerlingo *et al.* 1991). Homozygosity causes severe systemic disease often with stroke. Affected patients are prone to both venous and arterial thrombosis. Heterozygosity is a

predisposing factor to stroke. Acquired deficiencies of these proteins occur in various systemic diseases, particularly in liver disease and malignancies. The presence of antiphospholipid antibodies, which include the lupus anticoagulant and the anticardiolipin antibody, also predisposes the patient toward thrombotic events (Olson *et al.* 1994). These are found in 50% of children with systemic lupus erythematosus but also in children with other autoimmune disorders and in some individuals without any apparent systemic disease. The presence of recurrent thrombosis and antiphospholipid antibodies in patients without features of lupus is called "the primary antiphospholipid syndrome." Thrombocytopenia and recurrent spontaneous abortions are important features of this syndrome. Recurrent thromboembolism occurred on follow-up in 3.3% of neonatal arterial stroke patients. In five of seven cases of recurrent thromboembolism prothrombotic risk factors, including the methylene tetrahydrofolate reductase (MTHFR) C677T mutation, elevated lipoprotein a, hyperhomocysteinemia or protein C deficiency, were involved in the recurrence (Kurnik *et al*. 2003).

Autoimmune disorders

Systemic vasculitic diseases may involve the central nervous system. Vasculitic damage to the arterial wall results in the development of local thrombi and the potential for occlusion and embolization. Small arterioles are generally involved in this process, but larger vessels may also be damaged. Both carotid and vertebrobasilar arterial distributions may be affected. In the case of systemic lupus erythematosus, neurological involvement is seen in over 50% of patients. Arterioles are predominantly involved in this disease, with the production of microinfarcts leading to cortical atrophy. However, steroid treatment of these disorders may cause reversible shrinkage simulating atrophy. Polyarteritis nodosa, Wegener's granulomatosis, Henoch–Schönlein purpura, ulcerative colitis, Kawasaki syndrome, and the dermatomyositis and polymyositis complex have had rare associations with childhood ischemic stroke. Takayasu's disease ("pulseless disease") causes a large vessel vasculitis, affecting the aorta and its major branches. It, too, has been linked to childhood stroke and occurs primarily in Asian teenage women. An idiopathic angiitis may involve only the CNS without systemic evidence of inflammation. Small or medium and large vessels may be affected. The patients with small vessel involvement tend to present with chronic headache with focal seizures, or defects of mood or cognition in some. MRI scans typically have gadolinium enhancing focal T2 signal hyperintensities which may simulate tumors. Patients with large vessel involvement typically present with acute stroke. Immunosuppressive therapy should be initiated rapidly in these conditions (Lanthier *et al*. 2001).

Mechanical and toxin-related disorders

Trauma to the neck predisposes an individual to carotid thrombosis and dissection. This can be a blunt injury to the neck, intraoral trauma (for example, falling with a pencil in the mouth), or trauma to the cervical spine (for example, diving and trampoline injuries). Cervical spine trauma and anomalies can lead to a vertebrobasilar occlusion. The vertebral artery is vulnerable to injury as it passes through the vertebral foramina. Arterial dissection was identified in 6.6% of 212 children presenting with arterial ischemic stroke (Ganesan *et al*. 2003) and 15% of young adults with acute ischemic stroke (Williams *et al.* 1997). Dissection should be

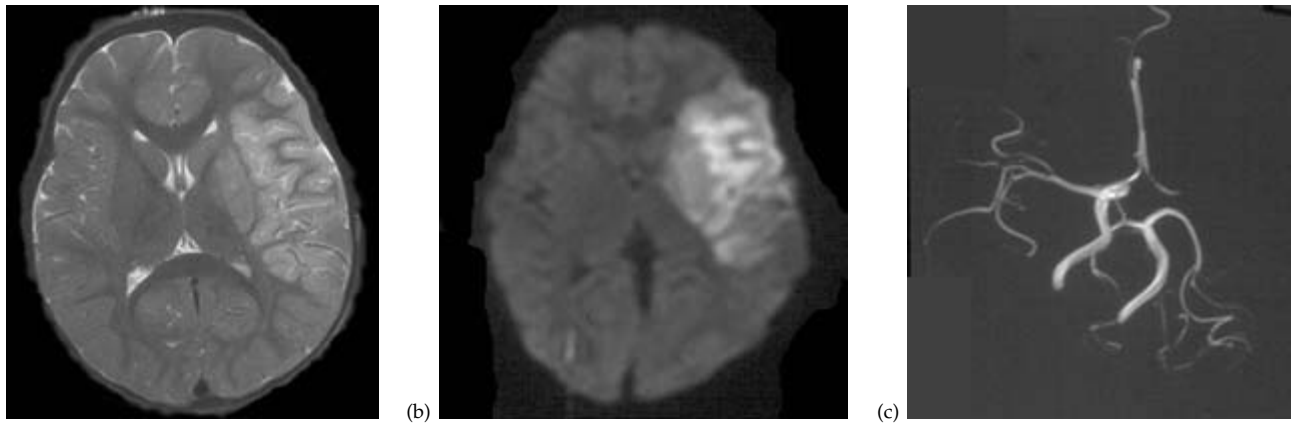


Fig. 11.3 Carotid dissection in a 3-year-old boy presenting with an acute right hemiparesis following a side impact motor vehicle accident: (a) an axial MRI T2-weighted image shows an area of high signal intensity in the left parietal lobe and left putamen and globus pallidus; (b) the diffusion-weighted image more clearly shows restricted diffusion in the same region; (c) time-of-flight MRA of the circle of Willis shows lack of flow in the left internal carotid and middle cerebral arteries. An axial T1-weighted image with fat saturation at the level of the skull base demonstrates a crescentic focal area of increased signal intensity in the wall of the left internal carotid artery due to the presence of hemorrhage within the dissected wall (not shown). (Courtesy of Dr Rosalind Dietrich.)

considered in any pediatric stroke patient, especially when vascular risk factors are absent and even minimal trauma can rarely cause dissection. Diagnosis usually requires standard transfemoral or magnetic resonance angiography (MRA).

Emboli may be introduced into the cerebrovascular system by several different mechanisms. Fat emboli occur 12–24 hours after long bone fractures. Iatrogenic causes include emboli from indwelling central venous catheters, fat emboli from parenteral nutrition, and accidental air emboli following thoracic surgery. A cardiac right-to-left shunt must be present for emboli to find their way to the cerebral circulation.

Various drugs, both illicit and legally prescribed, have been linked to ischemic and hemorrhagic strokes. Cocaine, phencyclidine, lysergic acid, and amphetamines predispose an individual to vascular injury via hypertension and vasospasm, and may induce a vasculitic picture. Phenylpropanolamine, a legal stimulant that is present in many over-the-counter cold medications, has been reported to induce a similar pathologic picture. Corticosteroids may cause endothelial hyperplasia and increase platelet adhesiveness. Birth control pills have been causally implicated in unexplained strokes in women and contribute to stroke risk in teenage girls. Current pills, with lower doses of estrogen, are thought to have a much lower risk.

Primary vascular disorders

Despite increasingly sophisticated diagnostic technology, many children with strokes have no recognizable cause. They are assumed to have a primary vascular disorder. Acute infantile hemiplegia refers to a condition in a young, previously healthy child with sudden hemiplegia, fever, coma, and seizures. Alternating hemiplegia of childhood also primarily affects young children. It is characterized by repeated attacks of abnormal eye movements and dystonic episodes followed by hemiplegic spells and autonomic disturbances, with gradual motor and mental deterioration (Mikati *et al.* 2000). Fibromuscular dysplasia is a systemic arterial disease primarily affecting middle-aged adults, which affects predominantly the renal arteries. When the internal carotid arteries are involved, aneurysms, thrombosis, and emboli may occur. Pathologically, there is fibrosis in the media with associated hyperplasia of intima or adventitia. Migraine-related stroke, although probably rare among all migraineurs, has been reported (Rossi *et al.* 1990). Conversely, migraines were causally implicated in as many as 25% of "idiopathic" strokes in young adults (Broderick & Swanson 1987).

Moyamoya disease (Suzuki & Takaku 1969) is characterized by a characteristic angiographic picture of progressive, occlusive disease involving unilateral or bilateral supraclinoid carotid arterial occlusion and the development of a fine web-like collection of abnormal anastomotic vessels at the base of the brain, particularly involving the circle of Willis (Fig. 11.4). The name comes from the Japanese for "puff of smoke" describing the angiographic appearance of the abnormal vascular network. This disorder is usually bilateral but initial motor and sensory symptoms in childhood (hemiparesis, involuntary movements, sensory impairment) are often unilateral. Headache is common and seizures may be problematic. Mental retardation is a frequent outcome in moyamoya disease.

The majority of cases are idiopathic 10% are familial indicating a genetic basis for some. Familial cases have been linked to chromosomes 6 and 17 with linkage to 3p24–26 found in Greek and Japanese families (Zafeiriou *et al.* 2003). Adults more frequently present with sudden intracranial hemorrhage. Several associated conditions have been reported: postirradiation therapy, neurofibromatosis, tuberous sclerosis, sickle cell disease, and Down syndrome (Pearson *et al.* 1985). Surgical treatment is available utilizing a variety of methods to bypass stenotic or occluded vessels. Superficial temporal artery-middle cerebral artery anastomosis is an effective procedure but technically difficult in children under the age of 2 years.

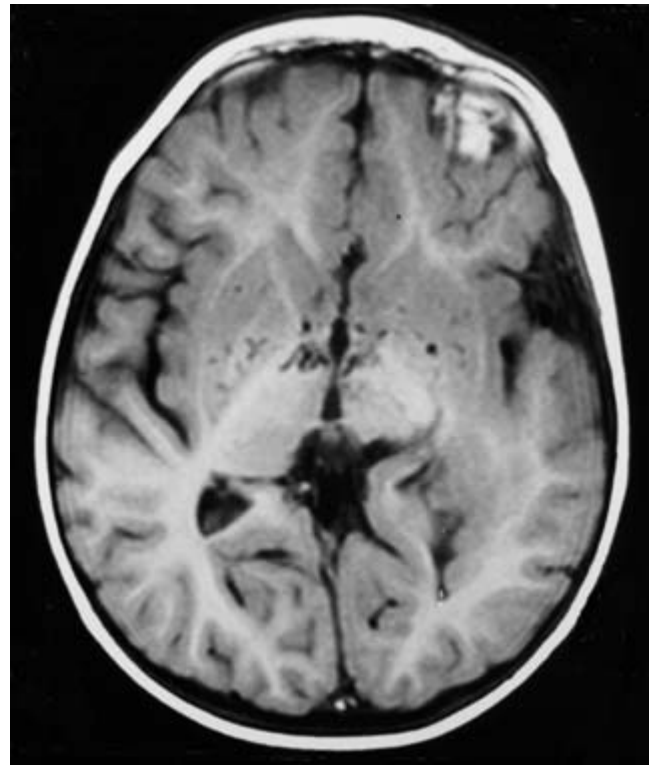


Fig. 11.4 Moyamoya in a 16-month-old boy with seizures. Axial T1-weighted MRI image at the level of the basal ganglia shows multiple low signal intensity punctate areas in the lentiform nuclei bilaterally. These represent collateral vessels from the lenticulatostriates vessels. Incidently noted is the presence of heterotopic gray matter adjacent to the posterior portion of the left lateral ventricle. (Courtesy of Dr Rosalind Dietrich.)

Hypoxic-ischemic injury

Hypoxic-ischemic injury is the most common cause of more widespread ischemic brain injury in childhood. Causal events include cardiorespiratory arrest, asphyxia, near-drowning, and hypotension. Damage tends to be widespread and bilateral, although preexisting variations in collateral blood supply may result in asymmetric lesions. Areas of the brain particularly susceptible to damage are those with a border zone or terminal end-arterial supply. Medial hemisphere infarctions occur in the border zone between the anterior and middle cerebral artery distributions, typically clinically affecting primarily the arms. Occipital infarcts producing cortical blindness are a common result of ischemia at the boundary of the middle and posterior cerebral artery distributions. Multiple rounded infarcts, which tend to be symmetric, are often found scattered throughout gray and white matter in these circumstances. The basal ganglia are largely supplied by the distal portions of small perforating arteries originating at the anterior portion of the circle of Willis, producing additional sites of enhanced susceptibility to hypoxic ischemic change.

Signs and symptoms

Patients with cerebral emboli typically present acutely with a sudden loss of neurological function. Thrombi may present in a subacute fashion, with prodromal transient ischemic attacks or possibly a stuttering course. There may be considerable overlap, and it may not be possible to distinguish an embolic event from a thrombotic event by clinical criteria alone. Signs and symptoms depend on the location and size of the occluded vessel, as well as the age of the patient. Children have anterior circulation strokes much more commonly than posterior strokes, and the left hemisphere is affected more often than the right.

Two-thirds of children present with an acute hemiplegia. Seizures, lethargy, or coma may complicate presentation. Prodromal self-limited episodes of hemiparesis are experienced in 25% of patients. Medical attention is often sought for these transient events but cerebrovascular disease is not usually considered at that time. The remainder present with a more indolent course noted over several weeks. Although a profound motor weakness (initially flaccid and later becoming spastic) is the most striking presentation, some very young children have no clinical manifestations of major arterial occlusive disease. Pathologic early hand preference is commonly the presenting complaint. In these cases the potential for recovery is so great that children may be seen without major deficit months or years after an ischemic event, despite large areas of brain infarction. Clinical signs may not be identified until brain maturation reaches a stage allowing expression of the clinical deficit.

Sensory symptoms and signs often accompany hemiplegia and may include visual field loss and loss of sensation in affected limbs. These signs are usually unilateral. Speech often becomes slurred (dysarthria), and language involvement is often seen when the language-dominant hemisphere is involved. Receptive and expressive dysphasias, as well as difficulty with reading, writing, and naming objects, may be demonstrated in older children. When arterioles or small arteries are involved in a thrombotic or embolic process, symptoms and signs are often subtle. This is particularly the case if the "silent" areas of the brain, such as the posterior parietal lobes or the frontal lobes, are involved. If only the vertebrobasilar system is involved, the child can present with any combination of brainstem, cerebellar, and occipital lobe dysfunction. Symptoms may include drowsiness, ataxia, vertigo, and visual loss. Signs may include eye movement disorders including internuclear ophthalmoplegia and are referable to cranial nerves III, IV, and VI or their central connections. Ataxia and cerebellar or bulbar dysarthria are common in brainstem ischemia. Long-tract motor signs and sensory loss may occur. Respiratory abnormalities, including apnea, apneustic breathing, hyperventilation, and gasping or ataxic breathing patterns, may be seen. Children with large brainstem infarcts are usually comatose.

Diagnostic studies

The evaluation of a child with an acute deficit due to focal cerebral ischemia has two components. The first is to distinguish an ischemic event from other processes that might mimic it. The differential diagnosis of an acute focal loss of neurological function in a child is listed in Table 11.3. Once an infarct is confirmed, the second component is to identify the underlying cause in hopes of preventing a recurrence.

As in all of medicine, nothing can replace a detailed history and physical examination including past medical, social, and family histories. Emphasis on the family history should include premature coronary and cerebrovascular disease suggestive of hyperlipidemia, unexplained thrombotic events suggestive of metabolic or hypercoagulable disorders, and migraines. Social history should include inquires regarding drug and alcohol abuse, and risk factors for human immunodeficiency virus. Other potentially important historical items that might be overlooked include recent head or neck trauma (even mild), migraine headaches, recent viral infection, and systemic signs such as rashes, arthralgias, fevers, and weight loss. A careful general examination includes the skin (in an attempt to locate rashes that might suggest an autoimmune disorder, stigmata of neurocutaneous syndromes, intravenous needle tracks, and evidence of systemic emboli) and particularly the cardiovascular system. The head and neck should be carefully auscultated for bruits. A thorough neurological examination should always be performed and documented.

TABLE 11.3

Differential Diagnosis and Discriminating Features of Acute Focal Loss of Neurological Function

Condition	Discriminating features
Focal cerebral ischemia	History, neurological examination, neuroimaging
Primary intracerebral hemorrhage	Neuroimaging
Traumatic epidural or subdural hematoma	Neuroimaging, neurological examination, history
Subarachnoid hemorrhage	History, CSF, neuroimaging
Cerebral abscess	History, fever, neuroimaging
Epilepsy: postictal Todd's paralysis or a focal inhibitory seizure	History, neuroimaging without stroke, EEG
Brain tumor (via hemorrhage, infarction, herniation, or hydrocephalus)	History, neuroimaging
Focal encephalitis	History, EEG, neuroimaging, CSF
Complicated migraine	History, family history, transient signs, normal neuroimaging
Alternating hemiplegia of infancy	History, neurological examination, unrevealing diagnostic evaluation
Multiple sclerosis	History, neurological examination, MRI
Malingering/conversion disorder	History, neurological examination, exclusion of organic disease

The MRI scan is the most sensitive method for detection of small or early ischemic lesions. Diffusion-weighted imaging is particularly useful early in the course (Soul *et al.* 2001). Posterior fossa and brainstem lesions are much more reliably seen on MRI than on CT. CT scanning, however, is more readily available and more suitable for seriously ill patients. It will detect most hemorrhagic and many ischemic lesions. However, a CT scan may not reveal ischemic changes for the first 12–24 hours following a stroke and may need to be repeated or followed up with an MRI scan.

The timing and role of cerebral angiography is controversial. It can be of value in localizing pathology, excluding arteriovenous malformations and establishing prognosis. However, because of its invasiveness, associated risks, and possible need for general anesthesia, the physician should carefully consider the risk-to-benefit ratio before proceeding. Early angiography is generally recommended in cases of unexplained subarachnoid hemorrhage or recent trauma and if a surgically remediable lesion is likely. Regardless of timing, such a procedure should always be performed in a medical center with considerable pediatric experience. MRA and CT angiography (CTA) are noninvasive methods that have been growing in acceptance. Resolution of these newer methods is constantly improving but still lags behind traditional transfemoral angiography, especially in viewing small vessels, but it serves as a screen of the intracranial vasculature and images large vessels well. MRA or CTA can delay or avoid the need for a cerebral angiogram.

Identifying the underlying etiology in a child with a stroke may be a very simple process in some cases or can be a challenging and frustrating task in others. In a child known to have a predisposing cause or systemic illness such as congenital heart disease, meningitis, or sickle cell disease, an extensive evaluation as suggested in Table 11.4 is not necessary. However, if preliminary evaluation fails to reveal a definitive cause, further testing is mandatory. Laboratory testing should be individualized in each patient. An organized, systematic approach is best. However, despite an extensive evaluation, Schoenberg and colleagues (1978) found that one-third of childhood strokes remain unex-

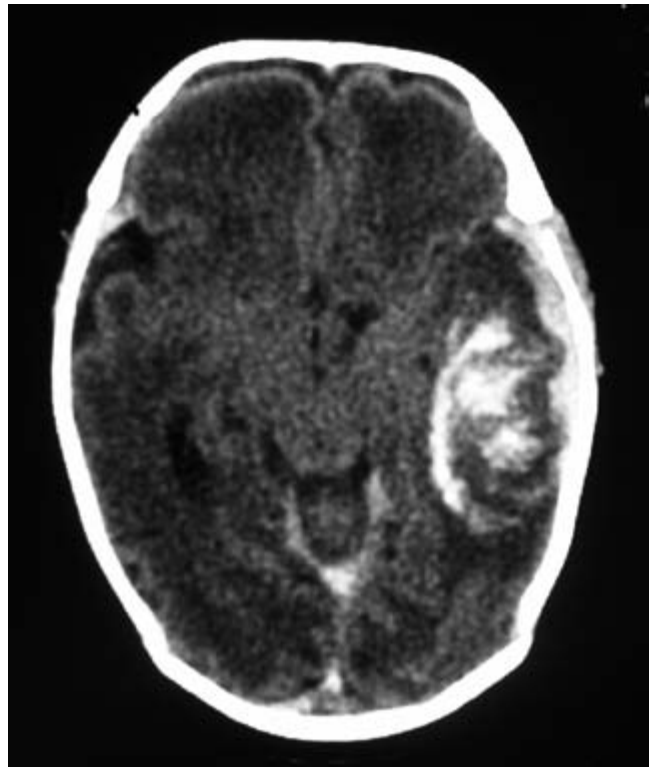


Fig. 11.5 Neonatal hemorrhagic infarct in a 35-week gestation infant with a tight nuchal cord at birth who presented with apnea on the second day of life. Noncontrast axial head CT shows patchy hemorrhage within the left parietotemporal infarcted area with associated subarachnoid blood.

plained, leaving parents and physicians confounded. With current advances in understanding of the pathophysiology, with comprehensive evaluation and newer brain imaging techniques 15% of cases have no identified stroke risk factor (Lanthier *et al*. 2000). Transesophageal and saline contrast echocardiograms have increased the cardiologist's ability to detect subtle structural defects that are overlooked on transthoracic studies. Full evaluation for thrombophilias requires a panel of diagnostic testing but hypercoagulable states may be difficult to diagnose because of the complexity of the involved pathways, often requiring hematological consultation to evaluate effectively. Recognition of the potential importance of homocysteine, lipid, and mitochondrial disorders is important (see section on metabolic strokes below).

Treatment

The acute treatment of cerebral ischemia is largely supportive and requires an intensive care unit setting. Attention to oxygenation, fluid and electrolyte status, seizures, and infections is critical. If an underlying systemic disorder is identified, it is treated to reduce the risk of recurrence. Thus an aggressive diagnostic approach to evaluation is important for prevention of future episodes.

Cerebral edema is maximal over the first 72 hours. Initially edema is cytotoxic, although a vasogenic component occurs after 2–3 days, following breakdown of the blood-brain barrier. Edema is usually effectively managed with hyperventilation and fluid restriction. In general, the use of steroids and osmotic agents is not indicated. However, in cases with progressive deterioration, mannitol (0.25–0.5 g/kg intravenously, repeated every 4–6 hours) and dexamethasone (0.5 mg/kg intravenously, repeated 0.25 mg/kg every 8 hours) may be used. However, mannitol may lead to rebound increase in intracranial pressure, and the dexamethasone has not been proved to have clinical benefit.

The use of anticoagulation in ischemic stroke is controversial and places the child at risk for hemorrhage. It may be indicated in the presence of a continuing source of emboli or evolving thrombotic stroke. It is contraindicated in hemorrhagic infarct and uncontrolled hypertension. Long-term anticoagulation with warfarin has been advocated in deficiencies of proteins C and S and antithrombin III and in the presence of antiphospholipid antibodies (Khamashta & Hughes 1995). Low-dose aspirin, as an antiplatelet drug, is a consideration for patients when recurrent stroke is a concern, although controlled studies in children have not been performed. In patients with sickle cell disease, strokes should be initially treated with an exchange transfusion and then with a hypertransfusion protocol to maintain sickle hemoglobin less than 20–30% (Wilimas *et al.* 1980). As discussed above prophylactic chelation treatment in patients at high risk of stroke is advocated. Early thrombolytic therapy with intravenous tissue plasminogen activator (TPA), is recommended routinely in the United States in adults who

TABLE 11.4

Investigative Studies for Systemic Disease in Cerebral Ischemia

Disorder	Test
Infection, leukemia, polycythemia, thrombocytosis	Complete blood count, differential, platelet count
Meningitis, encephalitis with hemorrhage	CSF analysis, MRI scan
Hemoglobinopathies	Sickle prep, hemoglobin electrophoresis
Vasculitis and autoimmune diseases	Erythrocyte sedimentation rate, antinuclear antibody, VDRL, complement profile
Renal disease (hemolytic uremic syndrome), renal causes of hypertension, systemic vasculitis, diabetes mellitus	Blood urea, creatinine, electrolytes, calcium, phosphorus, glucose, urinalysis
Coagulopathies, DIC, hypercoagulable states, thrombophilias	Prothrombin time, partial thromboplastin time, fibrin split products, platelet count
	Factor V Leiden, protein C and S (functional and immunologic assay) antithrombin III, antiphospholipid antibody (lupus anticoagulant, anticardiolipin antibody)
Cardiac source for emboli	Electrocardiogram (ECG), chest x-ray study, blood cultures, echocardiogram (transesophageal/contrast), Holter monitor
Homocystinuria, amino and organic disorders	Amino acids (serum and urine), organic acids (urine)
Mitochondrial encephalopathy, MELAS	Lactate (plasma and CSF), MRI and MR spectroscopy, mitochondrial DNA studies, muscle biopsy
Dyslipoproteinemias	Lipid profile (triglycerides, high-density lipoproteins, low-density lipoproteins), apolipoproteins A-I and B
Drug abuse	Urine toxicology

PEARLS & PERILS

Infant, Child, and Adolescent Ischemic Disease

- In infants, the symptoms and signs of cerebral ischemia may be subtle. A high index of suspicion is needed.
- Neuroimaging studies may be needed to diagnose small ischemic lesions and define the extent of larger lesions. CT scan may not reveal ischemic changes for the first 12–24 hours following a stroke and may need to be repeated or followed up with an MRI. MRI or CT should be obtained in all cases.
- A history of previous transient neurological deficit suggests the possibility of complicated migraine, seizures, hysteria, or, rarely, demyelinating disease.
- In children as in adults transient ischemic attacks be a prodrome to an ischemic stroke.
- Delay in the identification of underlying disease may allow recurrent ischemic episodes.
- Anticoagulation should be used only after very careful consideration and then only in cases with clear evidence of continued risk for continuing thrombosis or embolization.

present within the first several hours after an acute occlusive event (Lyden *et al.* 2001). Such approaches might be reasonable with children although children with stroke rarely present for urgent treatment within the 3–6 hour window recommended for thrombolytic therapy. The time to diagnosis of stroke in one recent survey averaged 36 hours (Gabis *et al*. 2002). Preliminary investigative studies are also being performed on several cytoprotective agents. These include voltage-regulated calcium channel antagonists, N-methyl-o-aspartate channel antagonists, free-radical inhibitors, gangliosides, and opiate antagonists. Until lay and medical education succeeds in increasing awareness of the symptoms of stroke in childhood there will be few opportunities for early intervention.

Rehabilitation through aggressive physical, occupational, and speech therapy appropriate to the deficits is essential for all patients. Behavioral problems and learning disabilities may become apparent on returning to school, and children may require neurocognitive testing and counseling.

The outcome following a childhood stroke is dependent on numerous variables: the type of stroke, the location of the lesion, and the underlying etiology (Table 11.5). The prognosis after a cerebral ischemic event in childhood is thought to be better than for adults. The plasticity of the developing brain is one reason for the improved outcome. Although survival is expected in almost all patients, residual deficits persist in the majority (Schoenberg *et al*. 1978). Recovery from hemiparesis follows the same pattern in children and adults; recovery of the ability to walk occurs faster and more completely, whereas recovery of the fine movements of the hand occur over a longer period of time. Despite the better outlook for recovery in pediatric stroke both patients and parents scored lower than controls in quality of life health scores following stroke (Gordon *et al*. 2002). Early studies by Solomon *et al.* (1970) noted the poor prognostic implications of presentation with seizures, occurrence during infancy, and the angiographic pattern of bilateral basal occlusive disease with telangectasia. In Lanska's group (Lanska *et al.* 1991) of children with strokes related predominantly to congenital heart disease and perinatally acquired injuries, 40% had moderate to severe deficits and seizures were found in 19%. Abram *et al.* in a study of 42 children with exclusively idiopathic ischemic stroke found a poor outcome in 43% of patients an average of 7.4 years following the stroke (Abram *et al.* 1996). Those children who did well made an earlier recovery. Risk factors for poor outcome included persistence of hemiparesis 1 month after the stroke, cortical location, and a "moyamoya" pattern on cerebral angiogram. Previously noted risk factors such as presentation with seizures or during infancy were not noted. Although there may be residual motor deficits early onset unilateral focal stroke has a good prognosis for cognitive outcome but subtle residual findings such as hemispacial neglect may persist (Trauner 2003). The prognosis for language and cognition is less good with bilateral cortical injury.

FEATURES

Table 11.5 Infant, Child, and Adolescent Ischemic Disease

Discriminating feature

1. Focal infarction on CT or MRI

Consistent feature

1. Children with cerebral ischemia lose neurological function in ischemic areas of brain. This loss may be temporary or permanent. It may not be detectable clinically or by neuroimaging. Thus there are no consistent features of cerebral ischemia

Variable features

1. Headache
2. Focal seizures
3. Predisposing disease
4. Clinical presentation of brain ischemia ranges from very subtle changes in mentation to gross motor deficit with or without coma
5. Small lesions may not be seen on neuroimaging studies. CT scanning may miss early ischemia and often cannot detect abnormality when lesions are isodense 1 week after the ischemic event. MR diffusion weighted imaging and FLAIR are best for early identification of ischemic stroke

Metabolic strokes

Many serious metabolic disorders produce cortical infarction, which is often multifocal. In lactic acidemia, the organic acidemias, and hyperammonemic states, cerebral ischemia and infarction may occur, particularly during episodes of severe metabolic decompensation. Several inborn errors of metabolism have strong associations with childhood strokes.

Basal ganglia infarction is often seen in disorders of oxidative metabolism such as Leigh's disease, methylmalonic acidemia and propionic acidemia, glutaric aciduria type II, and molybdenum cofactor deficiency or sulfite oxidase deficiency. Stroke-like episodes in a nonvascular distribution are seen in mitochondrial cytopathies and in particular in mitochondrial myopathy and encephalopathy with lactic acidemia and stroke-like episodes (MELAS) (Pavlakis *et al.* 1984). Fabry's disease and carbohydrate glycoprotein deficiency syndromes are storage disorders associated with stroke. Disorders of lipid metabolism continue to generate interest. As in adults high-density lipoproteins are considered to be protective to vascular endothelial cells, whereas low-density lipoproteins are thought to be toxic. Although hypercholesterolemia is a known risk factor for adult coronary and cerebrovascular disease, its effect is long term. Whilst lipid-induced arteriopathy begins in childhood, stroke and coronary artery disease from this cause are adult phenomena. Progeria, familial hypoalphalipoproteinemia, Tangier disease, and several other familial forms of hypercholesterolemia are conditions associated with stroke in children and young adults.

Homocysteinemia

Elevated blood homocysteine levels can result from homozygous or heterozygous mutations and are very common in the adult stroke, peripheral artery disease and coronary artery disease populations. Folate supplementation is thought to decrease the risk (Boushey *et al.* 1995). Homocystinuria, an autosomal recessive condition due to one of several enzyme deficiencies, may present as a thrombotic syndrome. In its homozygous form this error of methionine metabolism is associated with a marfanoid body habitus, lens dislocation, and mental retardation. High levels of homocysteine lead to endothelial damage and increased platelet aggregation. Homozygosity for the thermolabile tetrahydrofolate reductase gene tMTHFR was found in 18 of 119 children presenting with a first arterial ischemic stroke and 7 other children had high homocysteine levels. Thus 25% of children with ischemic arterial strokes had a risk of homocysteinemia (Ganesan *et al*. 2003). Young adults heterozygous for homocystinuria are also at increased risk (Boers *et al.* 1985; Clarke *et al.* 1991). Such patients may respond to dietary changes and supplementation with vitamin B6, vitamin B12 or folic acid. Hyperhomocysteinemia has been shown to be a risk factor for ischemic stroke in childhood (Van Beynum *et al.* 1999) and in newborn infants (Hogeveen *et al*. 2002). Methyltetrahydrofolate reductase deficiency has been reported in neonatal sinovenous thrombosis (Wu *et al*. 2002).

MELAS

The phenotype of mitochondrial myopathy encephalopathy and with lactic acidosis and stroke-like episodes (MELAS) was recognized as a distinctive syndrome in 1984 (Pavlakis *et al*. 1984). The majority of cases are due to a pathogenic mitochondrial DNA mutation in one of the leucine tRNAs, A3243G. Like most mitochondrial disorders MELAS is a multisystem disorder with short stature, cardiac, renal and GI dysfunction commonly seen with diabetes and deafness the most common manifestation. There is often basal ganglia disease with calcification often noted. Stroke-like episodes in nonvascular distributions are common, in particular in the occipital lobes producing cortical blindness. These lesions are to some extent reversible and diffusion-weighted MR imaging suggests an element of cytotoxic edema (Wang *et al.* 2003) but in addition there is a likely vasogenic component due to mitochondrial DNA mutations in the endothelium.

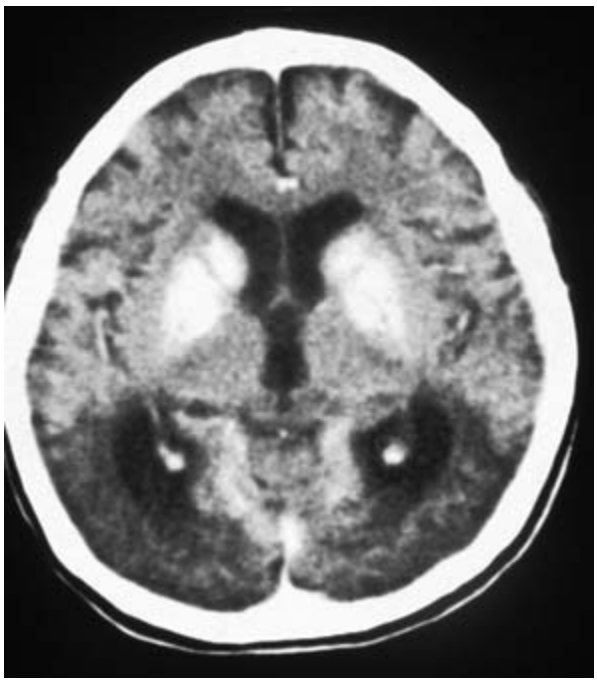
Organic acidemias and fatty acid oxidation defects

Propionic acidemia and methylmalonic acidemia are classical organic acid disorders and both are associated with "metabolic strokes" affecting the basal ganglia. The etiology of these strokes is not thought to be vascular but rather is the result of mitochondrial failure impacting a particularly vulnerable part of the CNS. In propionic acidemia these lesions may progress to hemorrhagic infarction with fatal outcome (Haas *et al.* 1995). In methylmalonic acidemia acute metabolic decompensation may be associated with acute basal ganglia metabolic strokes and diffusion-weighted MRI can discriminate acute from chronic lesions (Burlina *et al.* 2003).

Fatty acid oxidation defects may produce basal ganglia strokes as well as more widespread atrophy and white matter disease. Glutaric aciduria type 2 is due to a deficiency of electron transfer factor (ETF) or in the more severe form the ETF dehydrogenase enzyme. As in other forms of mitochondrial disease the presumed mechanism is localized mitochondrial failure coupled with the accumulation of toxic metabolites. Patients may present with an athetoid cerebral palsy picture due to these lesions.

Hypoglycemia

Profound symptomatic hypoglycemia may produce stroke. Surprisingly lesions are often unilateral despite the generalized nature of the insult. Insulin-dependent diabetics are



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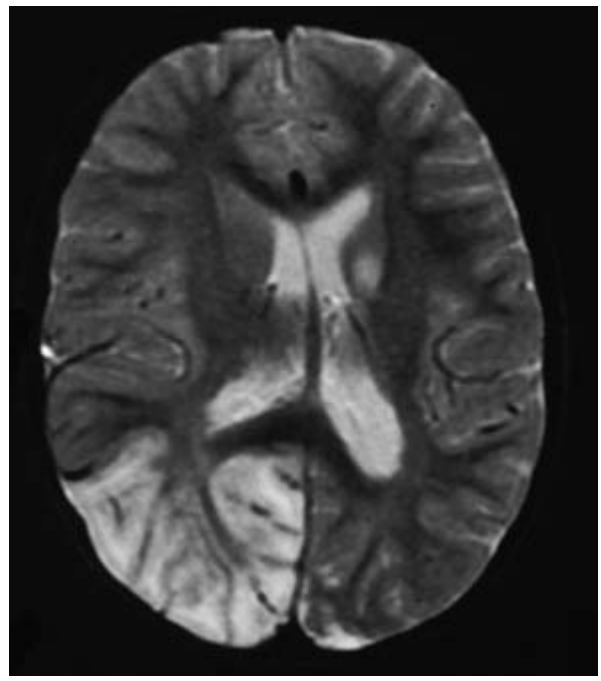


(b)

Fig. 11.6 (a) Head CT scan of a severely affected 19-year-old with MELAS syndrome with cortical blindness, dementia, ataxia, growth retardation and deafness. The axial head CT shows bilateral occipital stroke-like areas of decreased density with generalized cortical atrophy and bilateral basal ganglia calcification. (b) A 7-year-old with MELAS due to the A3243G mutation with headache, seizures, right arm and left leg weakness and acute onset visual disturbance. There is a maternal family history of diabetes and deafness. Axial brain T2-weighted MRI shows right occipital stroke-like lesion with bright signal also seen in the left basal ganglia and scattered in the left occipital lobe gray matter.

most prone to this complication but it occurs in sepsis and hepatic failure. Hypoglycemia may complicate metabolic decompensation in a number of metabolic inborn errors, in particular glycogen storage diseases and disorders of fatty acid oxidation. Patients often present with obtundation, sympathetic overactivity (tachycardia, sweating, dilated pupils) and focal or generalized seizures. Urgent diagnosis and treatment of hypoglycemia with IV 25% dextrose is necessary and prompt treatment may limit brain damage. If there is a possibility of Wernicke's encephalopathy IV thiamine 250 mg should be administered with glucose.

Fabry disease

In this X-linked lysosomal storage disease glycosphingolipid storage occurs due to deficiency of alpha-galactosidase A. Ceramide trihexoside is the storage material and it is found predominantly in vascular endothelium (intima and media) in multiple organs. This leads to stroke, painful neuropathy, coronary artery occusion and renal failure. Patients also have characteristic nonblanching clusters of small dark vascular reddish skin lesions, angiokeratomata and may develop cataracts. Affected males have a mean age of stroke of 34 years untreated with T2 hyperintense lesions seen on MRI seen in 100% of cases older than 54 years (Crutchfield *et al.* 1998). Less commonly females can be symptomatic as manifesting carriers. There may be a positive family history. Onset of symptoms of the neuropathy is in the teenage years or earlier with complaints of pain in the hands and feet. Strokes affect the posterior circulation predominantly (70%) with small perforating arteries in the anterior circulation another common site. It is important to make the diagnosis of this disease as effective treatment with enzyme replacement is now available. Patients are also treated prophylactically with antiplatelet agents.

Cerebral veins and sinuses

The cerebral veins and sinuses provide the major drainage pathway of intracranial blood and sites of CSF reabsorption. A thrombosis involving these structures leads to increased intracranial pressure by interfering with the outflow of these fluids. Specific clinical syndromes occur depending on which vessels are obstructed. Sinovenous thrombosis is most common in infancy and the neonate. In 160 consecutive children with sinovenous thrombosis enrolled in the Canadian Pediatric Ischemic Stroke Registry 43% were neonates and 54% were less than 1 year old. A prothrombotic state was present in 41%, an acute systemic disease in 54%, with bacterial systemic infection in 9%. Chronic systemic disease was present 36%, dehydration in 25% and head and neck infection in 18% (deVeber & Andrew 2001).

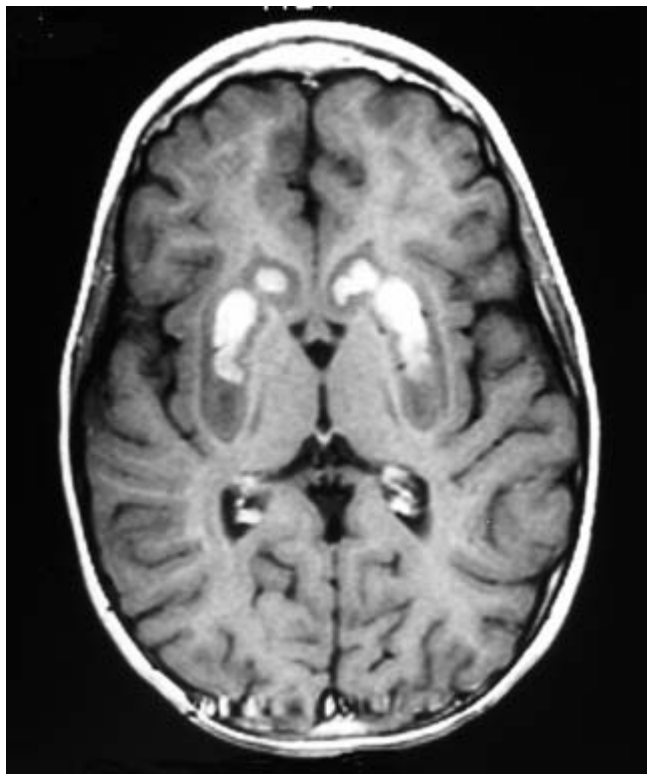


Fig. 11.7 An 8-year-old girl with propionic academia, in good metabolic control developed sudden deterioration with aphasia, hypotonia and generalized muscle weakness progressing to coma. Bilateral hemorrhagic infarction of caudate and lentiform nuclei is shown on this T1-weighted axial MR image with bilateral high signal intensity produced by methemoglobin.

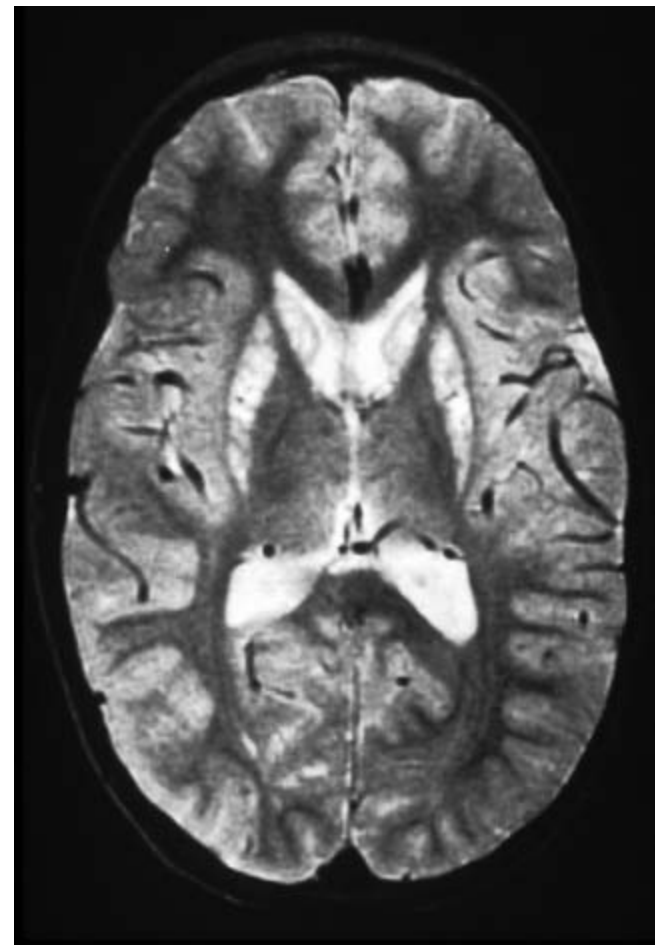


Fig. 11.8 A 5-year-old with glutaric aciduria type 2 presented with a clinical picture of athetoid cerebral palsy. T2-weighted MR images show bilateral areas of high signal intensity in the caudate and putamen attributed to gliosis resulting from a basal ganglia "metabolic stroke."

The pathophysiologic mechanisms affecting the cerebral venous system can be divided into those related to local infection of the head or neck and "primary" cerebral venous or dural sinus occlusions, which usually occur in a child with a systemic illness.

Many of the previously discussed systemic diseases that cause arterial occlusion also affect the venous system. The most common cause of dural sinus thrombosis is dehydration, especially hypernatremic dehydration. This is a problem generally occurring in infants and young children with acute gastroenteritis. Such children are often hypotensive and acidotic, compounding the ischemic insult. Hematologic causes include hemoglobinopathies (particularly sickle cell disease) and hypercoagulable states. As noted earlier, deficiency of protein C, its cofactor protein S, and antithrombin III can lead to arterial occlusion; however, venous thrombosis is more common. This tends to be seen in older children and adolescents heterozygous for these proteins. Homozygous deficiency of protein C presents in the newborn with purpura fulminans. Genetic thrombophilias were present in four out of seven neonates with sinovenous thrombosis. Three had factor V Leiden heterozygosity and one had methyltetrahydrofolate reductase homozygosity (Wu *et al*. 2002). Acquired protein S and antithrombin III deficiency are sometimes associated with L-asparginase therapy, the nephrotic syndrome, and protein-losing enteropathy. Children with cyanotic congenital heart disease are at increased risk for cerebral venous thrombosis, accounting for 5% of cases (deVeber & Andrew 2001), primarily owing to increased viscosity due to polycythemia and diminished oxygen transport. Oncologic causes of venous thrombosis include direct invasion of cerebral veins and dural sinuses with tumor cells. Both primary CNS tumors and secondary tumors, particularly neuroblastomas, can cause thrombotic complications. Venous thrombosis may complicate radiotherapy for neoplasms. Hyperleukocytosis from leukemia

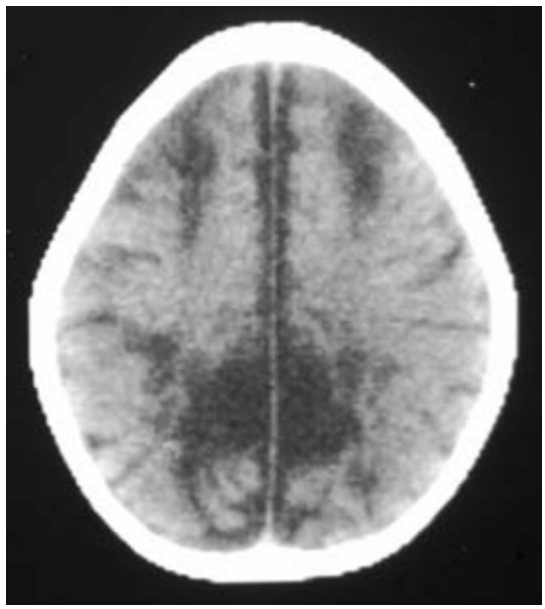


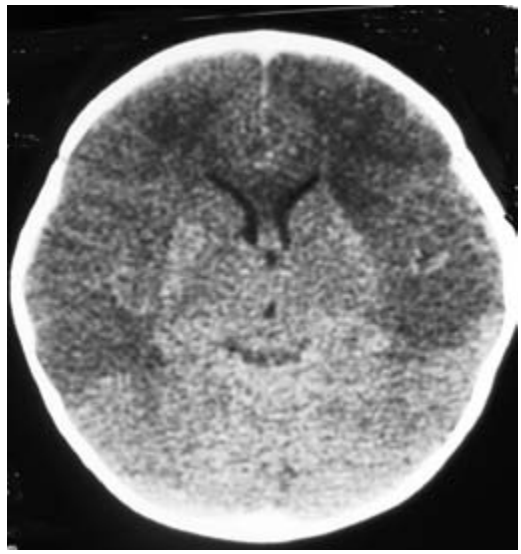
Fig. 11.9 Infarction following sinus thrombosis in infancy. Axial CT image shows bilaterally symmetric areas of infarction adjacent to the interhemispheric fissure and bifrontally.

can lead to sludging of blood in the venous system and subsequent infarcts. The primary inborn error of metabolism linked to venous thrombosis has been homocystinuria. Infections of the head or neck adjacent to veins or dural sinuses may involve the wall of the vessel and produce local inflammation and thrombosis. The most common cause of cerebral vein thrombosis is purulent meningitis. Cortical vessels running through the subarachnoid space are particularly susceptible to injury in meningitis. Stroke from venous thrombosis is a major cause of neurological sequelae in meningitis and small cortical strokes may be missed unless searched for by MRI. Meningitis can produce major ischemic injury.

Trauma may produce local venous or dural sinus damage, leading to thrombosis. Infection secondary to trauma produces an additional risk of thrombosis. Infectious causes of dural sinus thrombosis are usually close to the site of infection. Otitis media and mastoiditis may cause lateral sinus thrombosis. Facial soft tissue, periorbital, paranasal, or frontal sinus infections may produce cavernous sinus thrombosis. Infectious sagittal sinus thrombosis usually arises from retrograde spread from dural sinuses involved in a head or neck infection. Venous occlusion produces ischemia in the area of the brain drained by the affected vein or sinus, with accompanying microscopic and larger areas of hemorrhage. In these hemorrhagic infarctions, edema is often more marked than with arterial occlusive disease and thus raised intracranial pressure is a common problem. The edematous phase can last for several days and presents a major management challenge. Neuronal and glial necrosis occurs in the infarcted area, and ultimately macrophages remove necrotic material, leaving a cystic cavity. Cerebral veins and dural sinuses tend to recanalize rapidly after thrombotic occlusion, making early radiologic study important if the diagnosis is to be confirmed.

Generalized or extensive cerebral vein or dural sinus thrombosis is usually rapidly fatal. In neonates the usual presentation is nonfocal, with seizures (71%) and encephalopathy often with a decreased conscious level in 36%, how-

(a)



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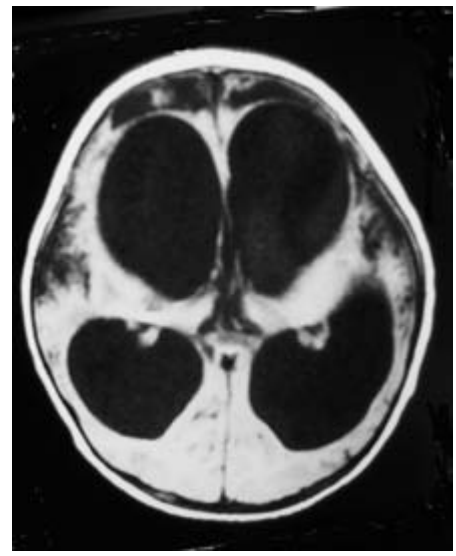

Fig. 11.10 Infarction and abscess formation following streptococcal pneumonia and meningitis in a 6-month-old girl who presented with fever, vomiting and possible seizure. (a) Axial CT image at the level of the lateral ventricles, 3 days after presentation, shows decreased density in the distribution of the anterior and middle cerebral arteries bilaterally. (b) Follow-up axial T1-weighted MR image, 2 months later, shows marked enlargement of the ventricles and multiple focal areas of encephalomalacia due to abscess formation. (Courtesy of Dr Rosalind Dietrich.)

ever 29% had focal neurological signs (deVeber & Andrew 2001). The older child presents with a rapidly evolving encephalopathic picture (90%) consisting of confusion, headache, irritability, seizures (48%)(deVeber & Andrew 2001), and increasing lethargy as the intracranial pressure rises. Localized thrombosis of cerebral veins or dural sinuses can produce more focal CNS signs. Depending on the vessels involved, various clinical syndromes can occur. The most dramatic constellation of signs arises from cavernous sinus thrombosis, which is fortunately rare. Impaired drainage of the ophthalmic veins and direct involvement of cranial nerves III, IV, V (first division), and VI lead to a chemosis, exophthalmos, unilateral fixed-dilated pupil, ptosis, decreased facial sensation, strabismus with a severe headache, and eye pain. Sagittal sinus thrombosis and the resultant impairment of parasagittal cortical venous drainage tend to produce bilateral cortical signs, seizures, and deepening coma. Lateral sinus thrombosis impairs venous drainage from the ipsilateral cerebellum and occipital lobe, producing visual field loss and ataxia along with headache. Because the right lateral sinus is often larger than the left, a right-sided thrombosis is more likely to be clinically evident. Thrombosis of the sagittal sinus or lateral sinus may lead to a generalized increase in intracranial pressure and is one cause of the syndrome of pseudotumor cerebri. When otitis media or mastoiditis leads to such a scenario the term otitic hydrocephalus has been applied.

Diagnosis of cerebral vein or dural sinus thrombosis is usually difficult. Only in the case of cavernous sinus thrombosis are there discriminant symptoms and signs. Differential diagnosis includes toxic and metabolic causes of coma, viral encephalitis, bacterial meningitis, and cerebral abscess, as well as the various causes of intracranial hemorrhage. Lumbar puncture reveals raised pressure, and CSF will often be xanthochromic or blood tinged.

PEARLS & PERILS

Cerebral Veins and Sinuses

- Severe headache with a rapid deterioration in consciousness is a common presentation of extensive cerebral venous or dural sinus thrombosis.
- An urgent CT scan helps exclude other causes and may confirm the diagnosis. Early radiologic study is important if the diagnosis is to be confirmed.
- An urgent MRI scan provides the best noninvasive test for cerebral venous or dural sinus thrombosis, but risks of transport and difficulties with patient monitoring in the scanner may be contraindications for MRI in sick and unstable patients.
- Urgent treatment of the precipitating cause and of raised intracranial pressure is essential.
- Anticoagulation therapy has risks and is generally contraindicated in patients with hemorrhage.
- Prolonged seizures, hypoxia, or hypotension increase the cerebral insult.

KEY CLINICAL QUESTIONS

- Has sinovenous thrombosis been considered in the differential for a deterioration in neurological status?
- In an infant or older child particularly if seizures are present? Such patients will deteriorate as intracranial pressure increases and should be monitored in an intensive care unit.
- Has MRI scanning included MRA in any child with a possible diagnosis of sinovenous thrombosis?
- Have plasma homocysteine and a comprehensive evaluation for thrombophilias been carried out in confirmed cases of sinovenous thrombosis?

Neuroimaging studies are warranted (Table 11.6). Because of the tendency for occluded veins and sinuses to recanalize, studies must be carried out early, preferably within 48 hours. With CT scanning, hemorrhagic infarctions are seen adjacent to the venous thrombosis and edema is usually obvious. A ring or delta sign on CT scanning occurs when intravenous contrast material surrounds the thrombosis. MRI with MRA is the study of choice. A dural sinus thrombosis is seen as an area of high signal intensity on the T-weighted image, which replaces the normally low signal sinus. Angiography with venous phases, if necessary, may or may not confirm cerebral vein occlusion or identify localized dural sinus occlusion and probably is not needed if MRA is available.

A good outcome can occur in isolated sinus thrombosis if intracranial pressure is controlled. Treatment is thus primarily supportive and directed at control of intracranial pressure, cerebral edema, seizures, and the predisposing cause

FEATURES

Table 11.6 Cerebral Veins and Sinuses

Discriminating features

1. History of gradual deterioration helps discriminate between arterial ischemia and cerebral venous or dural sinus thrombosis
2. Cerebral edema is often severe in venous infarction
3. Neuroimaging studies provide the best confirmatory test

Consistent features

1. Location and extent of both cerebral venous thrombosis and dural sinus thrombosis determine the physical findings
2. Headache is generally present
3. Raised intracranial pressure is usual

Variable features

1. Focal findings may be seen in localized cerebral vein or dural sinus thrombosis
2. Usually irritability, lethargy, and generalized symptoms of pressure are seen
3. In some patients fluctuating neurological signs are found

CONSIDER CONSULTATION WHEN...

- An infant or child with gastroenteritis develops seizures, irritability or decreased level of consciousness.
- A febrile child develops acute headache.
- Signs or symptoms of raised intracranial pressure (vomiting, bradycardia, hypertension, sixth or third nerve palsy, decreased conscious level) develop in a child with systemic illness.

of the thrombosis, whether it is local infection or a systemic disorder such as dehydration. In acute and extensive thrombosis, dexamethasone (0.25–0.5 mg/kg intravenously, then 0.25 mg/kg every 8 hours) for 3–4 days then gradually tapered may be helpful in controlling edema. A pressure bolt or ventricular catheter allows accurate intracranial pressure monitoring and may be useful. Mannitol is generally to be avoided, particularly in patients who are dehydrated, because it may lead to further thrombosis. Antibiotics are initially given empirically. In patients with the syndrome of pseudotumor cerebri, repeated lumbar puncture may save vision and should not be delayed if visual impairment is present or if there is any concern that medical therapy is not working. Use of anticoagulants has been controversial. Because hemorrhage is often present, use of anticoagulants is generally contraindicated. Yet in one study of adult patients, the majority of heparin-treated patients made a complete recovery (Rousseaux *et al.* 1985). The use of anticoagulants has not been established in childhood; however, in patients who are clinically deteriorating despite symptomatic treatment, heparin is an option (Solomon *et al*. 1970). The benefits of anticoagulation may outweigh the risks in such cases. In a prospective pediatric study of unfractionated heparin in 65 children of which 13 of the subjects were newborns there was no significant bleeding (Andrew *et al.* 1994).

Intracranial hemorrhage in infancy and childhood

Outside of the neonatal age group, the incidence of childhood intracranial hemorrhage is similar to that of ischemic infarction. In the Baltimore-Washington Cooperative Young Stroke Study 18 children with ischemic infarction and 17 with intracerebral hemorrhage were identified (Earley *et al*. 1998). Children with intraparenchymal and subarachnoid hemorrhage (SAH), similar to adults, typically present dramatically with the sudden onset of severe headache, vomiting, meningismus, and progressive neurological deterioration. Hemorrhage may occur following a primarily ischemic event due to any of the previously mentioned causes (hemorrhagic conversion) or can occur subsequent to an underlying vascular abnormality such as an aneurysm or vascular malformation. There are other less common conditions that also deserve consideration. Trauma, a common cause of intracranial hemorrhage, is discussed elsewhere in the text.

In this and the following sections, conditions associated with intracranial hemorrhage in infants and children are considered together. Unlike the situation for ischemic disease and IVH of prematurity, these causes of intracranial hemorrhages are for the most part similar across this age spectrum, and most of these events are rare in neonates.

Although 5–7% of the population develops an intracranial arterial aneurysm 2 mm or larger by the time of death, aneurysms are very rare in children. There is a slight predominance in boys (1.5:1 male-to-female ratio). Most present after 10 years of age, although they rarely may be observed in infancy.

Intracranial aneurysms

These can be divided into three types: congenital, traumatic, and infectious. These types occur in the proportions of 75%, 15%, and 10%, respectively, during childhood. Childhood aneurysms are more variable and more peripheral in location when compared with those in adults. Most (85%) are located in the anterior circulation, particularly at the bifurcation of the internal carotid artery and in the anterior cerebral artery-communicating artery complex, although the most common site varies from study to study. Cerebral arteriovenous aneurysms were reported in 35% of 17 neonates presenting with massive cardiomegaly in the first 10 days of life (Kachaner *et al*. 1977). Multiple lesions are rare and raise the possibility of bacterial aneurysms from infected emboli.

The main histopathologic features are abnormalities of the elastica and media portions of the arterial wall, with inflammatory changes in infectious cases. Unlike in adults, saccular, fusiform, or irregular aneurysms are less common. A clot is usually present in some portion of the lumen. A mural defect responsible for hemorrhage can often be found. Perivascular and extensive subarachnoid blood is the rule. Traumatic aneurysms are less common in children, occurring mainly in adolescence. Ninety per cent are located in the anterior circulation, predominately on the anterior cerebral artery and its branches. Their pathogenesis is presumed to be due to arterial wall damage following closed head injuries.

Infectious aneurysms comprise 2–5% of all intracranial aneurysms. They may be separated into true mycotic aneurysms (fungal) and the much more common bacterial aneurysms (usually staphylococcus). Infectious aneurysms have a far higher relative incidence in children than in adults. They occur in children with congenital heart disease with bacterial endocarditis and less commonly are seen as a complication of a local infection such as meningitis or sinusitis. The mortality rate is as high as 18%, but morbidity in the remainder is said to be low, probably on the basis of informal observations.

Intracerebral hemorrhage complicates aneurysmal SAH in 25–50% of cases. Although vasospasm complicates SAH in 30% or more of children, it does not seem to affect the outcome as it does in adults. Most studies indicate that the majority of aneurysms (up to 95%) are asymptomatic until they rupture. The sudden onset of a severe headache (often described by the patient as "the worst headache of my life"), associated with focal neurological deficits and frequently followed by diffuse cerebral dysfunction of mild to profound extent, represents a clinical picture as characteristic in children as in adults (Table 11.7). There is a retrospective history of headache in 20%. Because some children bleed at the time of or soon after head trauma of variable severity, aneurysm may not be considered and may be missed on head CT scan. Vasospasm, or obliteration of the aneurysm may compromise detection. Mass effect from enlarging giant aneurysms has been described as producing progressive lower cranial nerve, brainstem, and oculomotor nerve dysfunction, as well as hydrocephalus owing to aqueductal stenosis. Seizures may occur early if the bleeding occurs near the cerebral cortex but are uncommon except in infancy. Blood spilling into the subarachnoid spaces causes meningismus, fever, leukocytosis, nausea, and vomiting. Examination may show nuchal rigidity, alteration of consciousness, and focal deficits referable to cranial nerves or any portion of the cerebrum or brainstem. Bruits are rare. Retinal hemorrhages can occur. Although intracranial pressure is generally elevated and the fontanel reflects this in infants, papilledema is uncommon. If the patient is seen early, progression of these findings is frequent, may be very rapid, and is of ominous significance.

Giant aneurysms (greater than 25 mm) represent 5% of aneurysms if all ages are considered; however, in childhood they represent up to one third of aneurysms. When clustering in the first year of life, they usually present more commonly with mass effect, seizures, and hydrocephalus.

There are several medical conditions with which cerebral aneurysms have been associated. Genetically acquired disorders include the autosomal dominant adult form of polycystic kidney disease (more rarely, the childhood autosomal recessive form), Ehlers–Danlos syndrome, Marfan syndrome, pseudoxanthoma elasticum, tuberous sclerosis, and Klinefelter's syndrome. Other conditions include fibromuscular dysplasia and coarctation of the aorta. The association of aneurysms with cysts and malformations, such as agenesis of the corpus callosum, suggests a developmental basis for some aneurysms.

FEATURES

Table 11.7 Aneurysms

Discriminating features

1. Neuroradiologic demonstration of the aneurysm on CT with contrast or MRI
2. Confirmation with MRA or cerebral angiogram

Consistent feature

1. Symptoms or signs of acute SAH

Variable features

1. Antecedent headache (20% of patients)
2. Focal cerebral ischemia secondary to vasospasm

Diagnostic studies

Early recognition is important, and hemorrhage is most readily first demonstrated by CT However, a CT scan might not detect the hemorrhage if the amount of intracranial blood is small or the study is delayed till several days after the bleed. Recent studies suggest that MR with FLAIR is more sensitive than CT for detection of subarachnoid hemorrhage. Five per cent of CT scans will be normal if performed on the first day of a SAH. If the study is delayed to the third day this number increases to 25% owing to rapid reabsorption of blood. Hence, if the clinical picture strongly suggests SAH and the CT is normal, CSF analysis for xanthochromia or red blood cells should be performed. A CT scan with contrast will detect lesions larger than 15 mm, whereas the resolution of the MRI is sufficient to detect 3- to 5-mm aneurysms. CT angiography (CTA) is another noninvasive option. Currently the best diagnostic approach is to carry out an MRA or CTA and then only perform catheter angiography if an aneurysm is strongly suspected but not seen on MRA or CTA. Angiography is often needed to define the anatomy of an aneurysm such as wide or narrow-necked which can help in the decision as to whether coiling or surgery is the better option.

Confirmation of the aneurysm is by MRI or cerebral angiography in virtually all cases. MRA is a noninvasive option; however, its resolution for small vessels is still below that of the cerebral angiogram, which remains the "gold standard." The angiogram provides the diagnosis and the basis for planning surgery and is optimally performed in medical centers with expertise in pediatric neuroradiologic and neurosurgical procedures. The timing of the initial studies is based first on the need to establish a diagnosis in an acutely ill child in whom the differential diagnosis includes not only aneurysm and arteriovenous malformation but also neoplasm, meningitis, hemorrhagic encephalitis, hemorrhagic infarction, and trauma. Additionally, the timing, especially of angiography, should be related to the total management approach to the lesion, in coordination with the neurosurgical consultant. Factors to be considered are time since bleeding, condition of the patient, medical therapy modalities, and preferred time of surgery. Probably the most common current approach in cases arriving within 24 hours of the event is early angiography, with subsequent management planned thereafter. In the case of unruptured aneurysms,

PEARLS & PERILS

Aneurysms

- Consider associated medical conditions in children with aneurysms.
- Unusual severe, sudden-onset headache in children deserves evaluation.
- Prognosis for a child with an aneurysm is better than that for an adult with similar involvement.
- Consider infectious aneurysm if lesions are multiple and/or congenital heart disease is present.
- An unruptured aneurysm may produce a mass effect.
- An aneurysm or other vascular anomaly should be considered in any child with unexplained SAH or intraparenchymal hemorrhage.
- If the clinical picture suggests a SAH and the CT is normal, a lumbar puncture should be performed.

this study helps define the prognosis, because the probability of rupture increases with size. Interventional radiography treatments are available for smaller lesions; however, surgery is generally indicated if the diameter is greater than 10 mm because of the high risk of a fatal hemorrhage.

In many ways more difficult for the physician is the approach to the unfounded anxiety that parents have about the possibility of an unruptured aneurysm, particularly in children with chronic headaches. This fear is often based on the occurrence of rupture in an acquaintance or a relative and is precipitated by a severe headache in the child. The associated conditions listed earlier should be considered. Barring evidence for these, or a family history of aneurysm, CTA or MRA can be deferred. Clearly in most cases reassurance rather than MRA or angiography is appropriate. A brain MRI scan may be indicated in some cases of chronic headache, primarily to exclude tumor. Reports of familial occurrence of aneurysms are rare, with as few as six cases reported. This fact may help with reassurance.

Improved treatment of ruptured aneurysms appears to have lowered mortality, particularly in the first 24 hours. However, 40–60% of adult patients still die or survive significantly disabled. The functional survivors are predominantly from the early diagnosis group hospitalized in a neurological center. Children do better than adults when operated on early and there is a greater risk of rebleeding if not surgically treated (Wojtacha *et al.* 2001). The patient's

KEY CLINICAL QUESTIONS

- Is urgent pediatric neurosurgery available? If not stabilize and arrange transfer to a specialized pediatric neurosurgical unit.
- Is MRA and angiography urgently available?
- Is there evidence of possible infected embolism?

CONSIDER CONSULTATION WHEN...

- A child presents with sudden onset severe headache or coma.
- Meningismus is found with red cells in the CSF.
- Head CT scan shows subarachnoid blood.

level of consciousness on admission is the most important predictor of survival. Surgical mortality for clipping is less than 10%. In one series of 33 children, surgical mortality was 3%, and 80% of patients had no deficit except on psychometric testing (Heiskanen & Vilkki 1981). Given this and the high mortality from rebleeding, early surgery is surely indicated for alert patients. Authors disagree about the benefit of surgery for the moribund child. The good results in children from aneurysm clipping raise the question of the role of endovascular detachable coil treatment by interventional radiology in children. In adults the International Subarachnoid Aneurism Trial has shown that this procedure has a lower morbidity and mortality than surgery (Molyneux *et al.* 2002). In the case of an asymptomatic unruptured aneurysm, studies have also revealed a 1–2% risk of rupture per year. The cumulative rate of rupture was 35% at 15 years (Yasui *et al.* 1996). Lesions greater than 5 mm are believed to have an increased risk. In experienced centers, the rate of mortality and morbidity, resecting such lesions approximates 5%. Hence any patient with a life expectancy of greater than 3 years should benefit from intervention.

Treatment

Treatment advances include endovascular detachable coil treatment, the care of intracranial hypertension, supportive intensive care, and prevention of rebleeding by surgical means. The treatment of vasospasm continues to be controversial. There have been no controlled studies demonstrating benefit from use of antifibrinolytic agents (aminocaproic acid) and calcium-channel blockers (nimodipine) in children with SAH. Bacterial aneurysms are treated with prolonged courses of antibiotics continued for 4–6 weeks. Half will resolve and one-third will decrease in size with this approach. Intervention is indicated if the aneurysm is unchanged or larger on repeat angiogram.

Vascular malformations

There are four major types of congenital vascular malformations: arteriovenous malformations (AVMs), venous angiomas, cavernous angiomas, and capillary telangectasia. AVMs, in which there is a direct connection of arteries and veins, most frequently produce clinical symptoms, 10% manifesting in the first decade.

Pathophysiology

Vascular malformations vary greatly in location, size, number of arteries, character of the abnormal vessels, and changes over time. All consist of a mixture of normal and abnormal blood vessels. Fibrosis, inflammation, gliosis surround the lesions, and calcification within the malformation are common.The most common lesion is the AVM "proper." In this lesion one (60%) or several arteries drain directly into venous channels, without intervening capillaries. Both the arteries and the veins may be either enlarged normal or anomalous vessels. Locations are parietal in 30% of patients, frontal in 17%, occipital in 10%, temporal in 10%, and in the basal ganglia in 16%. Specimens show unsuspected old hemorrhage in 10% of cases.

Venous angiomas are the most common asymptomatic vascular malformation and are present in 2.6% of persons coming to autopsy (Sarwar & McCormick 1978), more than four times the incidence of AVMs. They are pathologically distinct and consist of a convergence of multiple venous channels into a single anomalous draining vein. Up to 20% may calcify. Cavernous angiomas are malformations in which large, venous channels form a complex mulberry-like meshwork. There is no intervening brain parenchyma. These lesions are frequently multiple, and various parts of the central nervous system as well as other organs (retina, liver, kidneys, or skin) may be affected. They occur predominantly in frontal and parietal regions and are much less frequent than AVMs. A significant familial incidence has been reported, compatible with an autosomal dominant trait (Rigamonti *et al.* 1988). Capillary telangiectasias are much smaller than any of the malformations mentioned earlier and occur in the posterior fossa (pons and medulla) and in the subependymal region in the cerebral hemispheres. A hemorrhage in these areas can be catastrophic.

Cryptic vascular malformations are sometimes found on pathologic examination. They are hypothesized when a patient presents with intracerebral hemorrhage and/or SAH, but angiogram, surgical specimen, or autopsy fail to demonstrate a specific lesion. Clinical manifestations depend largely on the type of anomaly, patient's age, and the anatomic location. Patients with AVMs may present with acute intracranial hemorrhage, ischemia, seizures, or a bruit. AVMs are occasionally discovered incidentally or during evaluation of extensive cutaneous hemangiomas.

Signs and symptoms

If a primary SAH occurs, the signs and symptoms are the same as for aneurysms, that is, severe headache with meningeal signs. If it is intraparenchymal, focal neurological signs develop often with increased intracranial pressure. For either type of hemorrhage, symptoms at presentation may be sudden and catastrophic or gradually progressive, or they may fluctuate. Seizure is the first symptom in one-third of AVMs and 50% of adult patients with AVMs have seizures preoperatively with a reduction by half after surgery (Thorpe *et al.* 2000). Other series have reported 89% of patients were seizure-free postoperatively (Piepgras *et al.* 1993). Of patients presenting with seizure, 20–70% hemorrhage before their AVM is diagnosed. Focal and secondarily generalized seizures are equally common. In children, presentation with seizures is less frequent than in adults (21%) and surgery seems more effective at seizure control when the new technique of gamma knife surgery is employed (Gerszten *et al.* 1996). Seizures are successfully treated with anticonvulsants as frequently as seizures resulting from other structural etiologies. Headache is a symptom in 70% of cases, and altered state of consciousness is present in 35%. Ischemia may result from a distal thrombotic infarction, in which case it may produce focal signs. A "steal" syndrome can produce ischemia of variable degree, with reversible dysfunction, but at times resulting in infarction of deprived areas. After bleeding, vasospasm may produce ischemia as well (Table 11.8).

Many children with intracranial AVMs have bruits heard over the head; however, bruits are common in children without vascular malformations, especially in those with heart murmurs. Authors who have systematically sought bruits report figures that are much higher than most physicians find in general practice: 60% in 4- to 5-year-old children and 10% in 10- to 15-year-old children, versus 1% in adults. Occasionally they are reported by the child. The vast majority are not due to AVMs. Bruits over the great vessels of the neck, which are particularly common, are usually modified by turning the head in various directions, and rarely indicate pathology. Conversely, bruits heard in infants less than 4 months are almost always associated with AVMs regardless of the presence of cardiac murmurs (Cohen & Levin 1978).

Cavernous angiomas typically present with seizures, headaches, and intracranial hemorrhage in adults. Venous angiomas and capillary telangiectasias are usually asymp-

FEATURES

Table 11.8 Arteriovenous Malformations

Discriminating feature

1. Radiologic demonstration, angiography

Consistent feature

1. None

Variable features

1. Occurrence of headache, seizure, bruit, signs and symptoms of hemorrhage
2. Neurological symptoms and signs depending on size and location of lesions
3. Natural history and surgical risks

PEARLS & PERILS

Arteriovenous Malformations

- Bruits over AVMs may be limited to a 1-cm diameter spot on the skull; one may have to search to find the spot.
- Most neck and cranial bruits in children are of no significance. However bruits heard in infants less than 4 months are almost always associated with AVMs.
- It is easy to confuse the clinical manifestations and CSF findings of aseptic meningoencephalitis with traumatic tap on the one hand and SAH, especially from AVM, on the other. Care to observe the color of spun CSF for the presence or absence of xanthochromia and to compare red and white blood cell counts in two tubes usually prevents this error.
- It is easy to confuse the presentation of AVM with seizures or stroke with the occurrence of other symptoms from other etiologies. This again emphasizes the need for thorough workup in cerebrovascular disease of childhood.

tomatic but may have a similar presentation to AVMs. Seldom are either of these associated with bruits.

Diagnostic studies

CT scan with contrast usually reveals the abnormality. However MRI is more sensitive and specific. Cerebral angiography not only confirms the diagnosis of AVM, but also defines major feeding and draining vessels – a step critical in deciding therapeutic options. If the hemorrhage is recent, angiography may fail to reveal the malformation, either because the lesion was obliterated by the hemorrhage, vasospasm, or clotting within the malformation.

Treatment

The mortality rate in patients with the first bleed from an AVM is 5–25%, and the morbidity rate is 50%. Rebleeding occurs in 25%–50% of patients, with a higher mortality rate of 28–41%. The risk of rupture in incidentally discovered AVM is 3–4% per year, with a 1% annual risk of death. Smaller lesions (diameter less than 3 cm) have a higher risk of rupture because of higher feeding arterial pressure (Spetzler *et al.* 1992). The decision to treat must be based on the size of the AVM, the functional importance of the adjacent cortex, and the pattern of venous drainage. There is not always full agreement regarding the best approach to treatment. Surgery gives excellent results in selected cases with a low rate of morbidity or mortality. Conservative treatment has a high long-term risk: roughly 20% mortality, 30% of patients disabled, and 11% of patients with moderate dysfunction in variable follow-up periods in reported series.

Initially treatment is supportive: maintaining oxygenation and the airway, monitoring of fluid and electrolyte balance, and administration of steroids if herniation is threatened. Surgical approaches vary from occlusion of feeding arteries to total excision, and both strategies may be implemented in stages. Interventional neuroradiology with embolization aiming to occlude feeders is an option. A flexible approach that includes combinations of methods has been advocated (Stein & Wolpert 1980a; 1980b). For small, surgically inaccessible locations, stereotactic gamma radiation is relatively safe and effective.

Unruptured venous angiomas should be considered incidental lesions that do not require surgical intervention. These malformations have a low risk of bleeding. Removal has resulted in venous infarcts because these lesions often provide the primary venous drainage for the adjacent brain. In the rare instance of associated hemorrhage, a cavernous angioma or other source of hemorrhage should be sought. In two studies, the risk of rupture in cavernous angiomas was found to be 0.25–0.7% per year (Del *et al.* 1991; Robinson *et al*. 1991). Outcome in both studies was uniformly good. Hence surgical resection is not recommended unless recurrent hemorrhages occur or there is progressive neurological deterioration or intractable seizures.

KEY CLINICAL QUESTIONS

- Seizures with encephalopathy with bleeding AVM.
- Signs of SAH or focal deficit due to parenchymal hemorrhage with bleeding AVM.
- AVMs which have not bled are usually clinically silent.
- Venous angiomas are usually benign.

CONSIDER CONSULTATION WHEN...

- Cranial bruit is found in an infant with cardiac failure.
- CT or MRI suggests the likelihood of AVM.
- CSF is xanthochromic or blood-stained without clearing from tube to tube.

Vein of Galen malformation

Vein of Galen malformations are the most common AVM presenting in the neonatal period, comprising 63% of such malformations presenting before 6 months of age. They result from a direct connection between the carotid or vertebral arteries and the vein of Galen. The vein of Galen is enlarged due to high pressure and in some cases is malformed.

Signs and symptoms

A patient with a vein of Galen malformation can present in one of three ways depending on the size of the malforma-

tion and blood flow. These features can be highly variable and correlate with both age and mode of onset. The largest lesions present in the neonate with high-output congestive heart failure due to massive shunting of blood flow. On examination, a systolic heart murmur, a wide arterial pulse pressure, a loud cranial bruit, hepatomegaly, tachycardia, and respiratory distress are noted. The shunt may produce a cerebral steal syndrome sufficient to produce cerebral ischemia.

Older infants with smaller shunts may present with hydrocephalus, dilated scalp veins, bruits, seizures, and hemorrhage. Hydrocephalus is a result of aqueductal compression by the malformation. Much less common is presentation in later life with headaches and signs typical of an intracranial bleed.

Diagnosis

Diagnosis depends on proper clinical suspicion when faced with unexplained congestive heart failure in the setting of a cranial bruit. Ultrasound of the head may reveal the malformation, which should then be confirmed by MRI or CT Angiography aids in planning therapy.

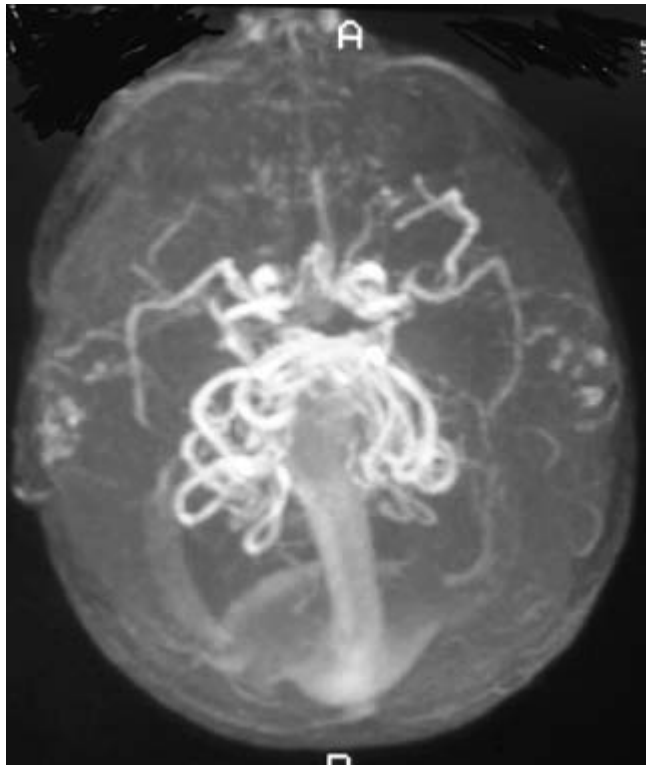

Fig. 11.11 Vein of Galen aneurysm in a 3-day-old infant with congestive heart failure. Axial time-of-flight MRA of the circle of Willis shows high signal intensity flow within the enlarged vein of Galen, straight sinus and the multiple vessels within the arteriovenous malformation. (Courtesy of Dr Rosalind Dietrich.)

Treatment

Treatment options are limited. Neonates are usually in a fragile cardiovascular status, rendering surgery difficult. Congestive heart failure is treated with digoxin and diuretics. Surgical outcome traditionally has been poor. At major pediatric centers, staged procedures involving selective embolization and microsurgical techniques have been more effective.

Other intracranial hemorrhages in childhood

The previous sections have presented intracranial hemorrhages that occur in the settings of IVH or asphyxia, as hemorrhagic infarcts, with aneurysms, and with vascular malformations. The remaining causes of intracranial hemorrhage in childhood are discussed below.

Intracerebellar hemorrhage is similar to posterior fossa subdural hematoma in newborns in regard to predisposing factors and the clinical picture; however, neurological outcome is much poorer. Clinical features indicating a significant cerebral insult may lead to discovery of this lesion. Recent reports and personal experience indicate that, even with no specific therapy, the outcome can be good (Koch *et al.* 1985) (Table 11.9).

Any bleeding disorder may cause intracranial hemorrhage, which can be subarachnoid, subdural, or intracerebral. Primary processes include sickle cell disease and those conditions that are associated with coagulopathy, primarily the hemophiliac and idiopathic thrombocytopenic purpura. In hemophilia, 25% of patients have an intracranial hemorrhage; 40% of deaths and 10% of all bleeding episodes involve intracranial bleeds. Secondary causes include hepatic dysfunction, disseminated intravascular coagulopathy (DIC), thrombocytopenia (platelet count less than

FEATURES

Table 11.9 Other Intracranial Hemorrhages in Childhood

Discriminating features

1. Results of neuroimaging studies
2. Laboratory tests for the various underlying medical conditions

Consistent feature

1. These conditions have a predisposing traumatic or medical basis

Variable features

1. Size of hematoma or amount of cerebral damage, even in apparently similar circumstances
2. Early clinical course in cases with life-threatening lesions

Other Intracranial Hemorrhages in Childhood

PEARLS & PERILS

- Always consider the possibility of child abuse. The history is usually factitious, and there may be no external sign of trauma because of impact with padded surfaces. Retinal hemorrhages, if present, are a strongly suggestive sign.
- Consider both encephalitis and various causes of intracerebral hemorrhage when multifocal dysfunction and multiple lesions on imaging are present.
- Transfer the patient with intracranial hemorrhage to a neurosurgical center.

20 000), hemorrhagic disease of the newborn (due to vitamin K deficiency), and various hypercoagulation states, including those in dehydration of infancy, diabetic ketoacidosis (Atluru 1986), collagen vascular diseases, dysproteinemias, parasitic infections, poststreptococcal glomerulonephritis, and moyamoya disease. The bleeding sites are apparently random, reflecting only the relative mass of the various parts of the brain.

Bleeding into neoplasms occurs at all ages and should always be considered in the differential diagnosis of an intraparenchymal hemorrhage, particularly in adults. Abuse of sympathomimetic drugs such as phenylpropanoloamine, cocaine, and amphetamines has also been associated with intracranial hemorrhage. Intraventricular hemorrhage has been reported in infants born to cocaine and methamphetamine abusing mothers (Dixon & Bejar 1989). Cocaine causes intracranial aneurysms in young patients which may bleed (Nanda *et al.* 2000).

Separate mention should be made of the potential confusion clinically and on imaging studies of hemorrhage in necrotizing encephalitis, particularly that due to herpes simplex virus, as opposed to bleeding from vascular lesions or other causes listed above. In addition to a careful history and physical examination, MRI, CSF analysis, and EEG are the most useful early diagnostic tests for encephalitis.

Spinal cord vascular disease

Pathophysiology

In theory the spinal cord is susceptible to the same systemic disorders that produce vasculitis and thrombosis in cerebral arteries. In practice, however, spinal cord ischemia is rare in childhood. This may in part be due to the extensive blood supply of the spinal cord. The anterior and posterior spinal arteries have a limited anastomosis and are supplied by several arterial branches at various levels of the cord. The anterior two-thirds of the spinal cord is supplied largely from branches of the anterior spinal artery. The levels of maximal susceptibility to generalized ischemia lie at arterial border zones, usually located at the lower cervical and lower thoracic levels of the spinal cord. Tumor and arteriovenous malformation are the most common lesions causing cord ischemia. Cord compression or vascular steal reduces the blood supply, resulting in ischemia. Sickle cell disease has been reported with thrombosis of the spinal cord (Rothman & Nelson 1980). Severe scoliosis can compromise flow in the anterior spinal artery, but actual cord ischemia is rare in scoliotic patients. Traumatic lesions to the spinal cord generally produce contusion without arterial or venous thrombosis, although epidural and subdural hematomas can produce cord ischemia by vascular compromise. Iatrogenic causes of spinal cord ischemia are important but fortunately rare. Umbilical artery catheterization in the newborn is associated with a significant risk of aortic, iliac, and femoral artery thrombosis. In some of these infants the arterial supply to the spinal cord is in jeopardy. Surgery for aortic coarctation is associated with symptoms of cord ischemia in some patients. Usually this ischemia is reversible, but some patients are left with irreversible cord infarction.

Signs and symptoms

The clinical signs of spinal cord ischemia depend on the level of the lesion. Initially a cord shock syndrome is seen at and below the level of the lesion. Later this evolves into upper motor neuron signs of spasticity below the level of the lesion, with flaccidity and areflexia confined to the level of the cord infarction itself. A dermatomal level of sensory loss may be present. Bladder and bowel function is often affected, with urinary retention most common. An anterior spinal artery syndrome is characteristic, with loss of anterior cord function and preservation of the dorsal column functions of vibration and joint position sense.

Diagnosis and treatment

Diagnosis of spinal cord ischemia in childhood is made when signs of partial or complete ischemic damage to the cord appear and a predisposing cause is apparent. Cord ischemia is usually a sudden event, although a more stuttering progression of symptoms and signs may be seen and

Spinal Cord Vascular Disease

PEARLS & PERILS

- In acute spinal cord syndromes, treatable causes of cord compression must be urgently excluded with MRI or myelography.
- If there is subarachnoid hemorrhage and no causes can be found on cerebral angiography, a spinal AVM should be considered.
- A segmental cutaneous angioma over the spine should raise suspicion of a spinal vascular malformation.

KEY CLINICAL QUESTIONS

- Loss of neurological function below the level of the lesion. A sensory level may be identified.
- Pain is a common manifestation of both acute and chronic lesions. This is an uncommon symptom in childhood and should trigger a high index of suspicion for spinal cord pathology.

clinical presentation may be delayed for some hours (Lenn 1977). Causes of spinal cord compression and ischemia, including AVM, tumor, abscess, or transverse myelitis, must be identified. MRI provides an excellent view of the spinal cord without bony artifact, but myelography is still necessary in selected cases.

Treatment is supportive. Early use of high-dose corticosteroids decreases spinal cord edema and may significantly improve outcome depending on the etiology. Hypotension, which may further damage the ischemic cord, must be avoided. An organized spinal cord injury protocol should be instituted at once. Urinary retention requires catheterization. Early passive and later active physical therapy is important to prevent joint contractures and improve residual function. The prognosis depends on the extent and duration of the ischemic insult.

A spinal cord syndrome due to a vascular malformation is rare in childhood. Venous angiomas are the most common vascular malformation of the spinal cord but are usually asymptomatic. In childhood the cervical region is the most common site for an AVM.

In adults, the location of the AVM is cervical in 30% of cases, and these AVMs have the slowest clinical evolution. Thoracic AVMs (20% of cases) have the worst prognosis, frequently being associated with early necrosis of the cord. The 50% of cases with thoracolumbar lesions have a variable clinical course. Half of the lesions are intramedullary, 20% are extramedullary, and 30% are mixed. Associated skin lesions have been described in 20–35% of cases, consisting of a port wine stain or the cutaneous manifestations of Osler–Weber–Rendu disease, Klippel-Trenaunay syndrome, familial hereditary cutaneous hemangioma, or Cobb's syndrome (Barek *et al*. 1982). When a spinal AVM and cutaneous hemangioma are both present (20–30%of cases), they are in the same dermatome in almost half the cases. Spontaneous spinal epidural hematomas have been attributed to cryptic vascular malformations (Posnikoff 1968).

CONSIDER CONSULTATION WHEN…

- A child presents with an acute focal neurological deficit.
- The etiology of an apparent cerebrovascular event cannot be readily identified.
- A child with a recent hemorrhage or ischemic stroke has progressive neurological deterioration.

Signs and symptoms

Spinal vascular malformations may present acutely or insidiously. Acute presentation due to SAH may occur with sudden motor impairment, which includes severe local back pain that may radiate. Pain and parasthesias follow a dermatomal pattern. However, the majority of patients present with a slowly progressive spastic paraplegia and bowel and bladder dysfunction. Pain is a common feature in this group. A bruit over a spinal AVM is rare.

Diagnosis and treatment

Spinal cord AVMs are difficult to document. CT alone is not useful. MRI and MRA are often diagnostic. If the AVM is localized to the dura, a myelogram may be the only revealing study. Myelography demonstrates some abnormality in almost all spinal AVMs but often does not discriminate the nature of the lesion. Treatment options for intraspinal vascular malformations are similar to those for intracranial malformations.

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CHAPTER 12

Inborn Errors of Metabolism I: Neurologic Degenerative Diseases

Paul Maertens, MD

OUTLINE

Polioencephalopathies
Leukoencephalopathies
Corencephalopathies
Spinocerebellopathies
Diffuse encephalopathies
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes syndrome

Neurodegenerative diseases with onset *in utero*, infancy, childhood or adolescence make up a sizable portion of the practice of pediatric neurology. Our knowledge of the incidence of such disorders is inexact and varies from one reporter to the next. This variation is explained in part by lack of consensus on what is progression, the major feature of neurodegenerative diseases. Most would agree that progression is characterized by a subacute or chronic clinical course. A normal early psychomotor development is observed in most patients. In some patients with degenerative disease beginning *in utero*, significant clinical and pathologic features are present at birth leading to the erroneous diagnosis of static dysgenetic encephalopathy (i.e. Zellweger syndrome). The early phase of normal development is usually followed by a phase of developmental slowing. In some conditions, duration of this phase is so long that diagnosis of cerebral palsy is mistakenly suspected (i.e. Pelizaeus–Merzbacher disease). After developmental slowing, most patients reach a plateau phase before entering a phase of deterioration leading to death. An exception to these rules, Rett syndrome, starts with a phase of deterioration followed by another phase of slow development or plateau. Our understanding of mechanisms responsible for these various patterns of presentation in neurodegenerative disorders is still fragmentary.

This chapter is organized as an overview of some of the more characteristic neurologic degenerative diseases encountered in pediatric neurology presented in the manner suggested by Dyken and Krawiecki in 1983. These authors used an anatomopathologic classification in which progressive neurodegenerative illnesses are organized into five subtypes according to clinical phenomena and pathologic features most characteristic for a group of illnesses. In the polioencephalopathies, the clinical and pathologic features are maximum in the cerebral cortex. In the corencephalopathies, there is more obvious involvement of the subcortical gray matter including structures of the basal ganglia, thalamus, and midbrain. In the leukoencephalopathies, there is a prominent involvement of the subcortical and/or periventricular white matter. In the spinocerebellopathies, the clinical and pathologic features are maximum in the cerebellum, spinal cord, and sometimes medulla and pons regardless of whether gray or white matter is affected. In the diffuse progressive encephalopathies, clinical and pathologic studies fail to characterize a maximum central nervous system involvement. In this chapter the discussion will be limited to the most common genetic disorders leading to various progressive encephalopathies.

Although no curative therapy is available for most neurodegenerative diseases, palliative therapy (diet, vitamins, anticonvulsant) may sometimes delay or prevent neurodegeneration. Supportive therapy (physical therapy, gastrostomy, splinting, bracing, communication devices) should be provided to individual patients and their families (or caregivers) to improve individualized care. Preventive therapy includes genetic counseling and prenatal diagnosis. The only permanent solution for all genetic neurodegenerative disease is gene therapy. To be a candidate for gene therapy, patients must be asymptomatic or only show early signs of the illness. It is, therefore, important to develop new methods to aid predicting the clinical course in a newly diagnosed patient. The continual progress in this area makes a prediction of the ultimate success of this modality of treatment possible.

Polioencephalopathies

The progressive polioencephalopathies are either primary, resulting from an intrinsic metabolic defect of the cerebral cortex neurons or secondary to infection (i.e. subacute sclerosing panencephalitis), autoimmune disease (i.e. Rasmus-

sen's encephalitis) or recurrent metabolic insults (i.e. glucose transport protein deficiency). This discussion is limited to some inherited polioencephalopathies. Common clinical features are intellectual deterioration, epilepsy, progressive spasticity, and progressive sensory impairment. Peripheral neuropathy is not a feature of polioencephalopathies except for Niemann–Pick syndrome.

Neuronal ceroid-lipofuscinoses

The neuronal ceroid-lipofuscinoses (NCLs) are autosomal recessive neurodegenerative diseases characterized by loss of vision, seizures and progressive mental deterioration. Brain and retinal atrophy are associated with selective necrosis of neurons, presence of fluorescent lipopigments (ceroid and lipofuscin), and accumulation of hydrophobic protein. This group of conditions is genetically heterogeneous. Subunit C of mitochondrial ATP synthase has a propensity for self-aggregation in various forms of NCL, except for the infantile disease (NCL 1). The infantile form is characterized by the prominent storage of saposins A and D (Palmer *et al*. 1997). Infantile NCL results from a deficient lysosomal palmitoyl-protein thioesterase 1 (PPT1) activity (Vesa *et al*. 1995), an enzyme which removes long chain fatty acids from cysteine residues in S-acylated proteins. The result is accumulation of hydrophobic proteins. The classic acute late-infantile NCL (NCL 2) results from a deficiency in lysosomal tripeptidyl peptidase 1 (TPP1), a peptidase that removes three amino acids from small protein (Wisniewski *et al*. 2001). The classic chronic juvenile NCL (NCL 3), the variant acute late-infantile Finnish forms of NCL (NCL 5) and the variant acute late-infantile/early-juvenile Lake forms of NCL (NCL 6) result from defects in proteins targeted to lysosomal membrane and named battenin, NCL 5 protein and linclin respectively. The genes for NCL 1, NCL 2, NCL 3, NCL 5, NCL 6 and NCL 8 have been mapped to human chromosome 1q32, 11p15, 16p12, 13p31–32, 15q21–23 and 8p23 respectively (Wisniewski *et al*. 2001). The genes for the chronic adult forms of NCL (NCL 4) and the variant late-infantile Turkish form of NCL (NCL 7) remain unknown. Studies are in progress to identify genetic defects in these rare forms of NCL and other patients with atypical clinical course (Wisniewski *et al*. 2001). The genes have been sequenced and several point mutations have been identified. The neuronal ceroid-lipofuscinoses are the most common neurodegenerative diseases of childhood with an estimated incidence of 1 to 7 per 100 000 (Rider & Rider 1980).

The clinical presentation of NCL is dependent on the specific syndrome represented (Dyken 1988). The most commonly encountered form of NCL has been described as chronic juvenile NCL or Batten disease (NCL 3). As the descriptive name implies, onset is usually during a period between 4 and 12 years of life and takes on a chronic course. Initial symptoms are usually visual failure, behavioral reaction, speech disturbances (frequent echolalia) or intellectual failure. These symptoms are slowly progressive, usually over a period of years. Within this framework neurologic symptoms owing to slowly pyramidal and extrapyramidal dysfunction are seen. Seizures are at first uncommon but later become much more frequent. Early clinical diagnosis can often be made by the typical retinal picture, which shows an early attenuation of retinal vessels, macular degenerative changes, patches of retinal atrophy, and a so-called waxy yellow type of optic atrophy. Later, minimal peripheral retinitis pigmentosa may be seen. Because the disease is slowly progressive, a monophasic staging process can be identified over years of follow-up. The results of the laboratory investigations – including electroencephalogram (EEG), computed tomography (CT) scan, magnetic resonance imaging (MRI), measurement of evoked potentials, and cerebrospinal fluid (CSF) analysis – are greatly dependent on the stage of the disease. The electroretinogram (ERG) is consistently abnormal once retinopathy and visual failure have begun clinically. Even early in the development of the disease, the ERG is often absent if not attenuated. Pathohistologic confirmation of the disease is by electron microscopic examination of lymphocytes, which are excessively vacuolated even on light microscopy. Within the vacuoles highly characteristic osmophilic cytosomes are identified, with the so-called fingerprint profile predominating. Other tissues also show these cytosomes, including many cells of the brain, muscle, skin, conjunctiva, and rectum. The pathologic reaction is of accumulation of autofluorescent lipopigments within cells, particularly neurons. This reaction is not as obvious within the retina, where the major brunt of the disease appears to be a primary loss of cells in the rod and cone layer. Retinal ganglion cells do show less dramatic accumulation of intracellular lipopigments. Some patients have excessive excretion of dolichols in the urine. Batten disease is inherited as an autosomal recessive trait.

The next most common type of NCL has been called the acute late-infantile type or Bielschowsky disease (NCL 2). In this variety, the onset of the disease occurs between 2 and 4 years of age. Initial symptoms are overwhelmingly of seizures of a wide variety. If a seizure is not the first complaint, progressive psychomotor regression is encountered. In rare cases, sudden onset of incoordination as frank ataxia is seen. These early symptoms often occur together. The course is dramatically downhill so that within months the patient is often nonambulatory if not bedridden. In this condition, mental and motor regression has been so severe that visual failure is often unnoticed. The retinal picture is similar to the findings in Batten disease if the disease has become well developed. In the early stages, however, the retina may be normal, only to be characterized within weeks by severe pigmentary disturbances. Laboratory findings are also variable depending on the stage of the disease. The EEG is almost always severely abnormal and of an epileptogenic type, especially early in

the course or at the onset of the disease. Evoked potential studies may show an early exaggerated response which is replaced by poor or absent responses later. The ERG may also be absent. CT scans and MRI may show atrophic changes more readily than in Batten disease even early in the course. These changes are especially located in the cerebellum and brainstem. CSF analysis may be normal. Pathohistologic study of lymphocytes is often abnormal, showing excessive vacuolation with electron microscopic cytosomal osmophilic profiles within the vacuoles. These are mostly curvilinear bodies even though fingerprint and other types of cytosomes are also seen. Other tissues also show the ultrastructural diagnostic bodies, including a variety of cells in brain, skin, muscle, conjunctiva, and rectum. Pathologic study of the nervous system and other tissues shows changes very similar to those encountered in the chronic juvenile variant of NCL, although in the acute infantile form, there are usually more atrophic changes and less prominent storage. Some patients with Bielschowsky disease show excessive dolicholuria. Urine samples consistently reveal elevated level of subunit c. Diagnosis is confirmed by demonstration of TPP 1 deficiency in lymphocytes, fibroblasts or brain samples. Rare chronic adult-onset and juvenile-onset cases with TPP 1 deficiency but less characteristic ultrastructural changes (mixed profiles) form milder variants of this disorder. Behavioral abnormalities, coordination problems and intellectual deterioration occur between 4 and 8 years of age and precede by several years the onset of seizures and myoclonia. Visual impairment occurs late in these milder variants.

All other types of NCL are less common and can be summarized by differences in their clinical course, age of onset, morphologic picture, and genetics. An acute-infantile form of the disease (NCL 1) was stressed by Finnish workers (Santavuori–Haltia syndrome) in 1975. This syndrome deviates from the other acute NCL disorders by occurring within the first 2 years of life and by a rapidly downhill course characterized by severe seizures (simple or complex partial) or myoclonia, severe mental-motor regression, and blindness. Aggressive behaviors and irritability are frequently reported. By the age of 2, funduscopic exam reveals a brownish discoloration of the macula, retinal degeneration, and optic atrophy. By 3 years of age, electrophysiologic studies demonstrate abnormal electroretinograms, abolished visual evoked responses and frequently a markedly suppressed EEG with disappearance of eye opening/closing reaction. MRI shows a severe progressive brain atrophy. The ultramorphologic picture is quite different in the Santavuori–Haltia syndrome. Granular osmophilic deposits (GROD) are the characteristic electron microscopic cytosomes and rarely are the other electron microscopic cytosomes encountered. Vacuolated lymphocytes are not found in peripheral blood smear. Pathologic reaction is characterized by a more severe atrophic picture, more signs of acute cellular destruction, and a severe, almost diagnostic, macrophagocytosis.

PEARLS & PERILS

- Diagnosis of late infantile NCL should be entertained in any infant or toddler who was previously normal, develops some seizures, and shows no etiology for seizures after extensive workup.
- Diagnosis of juvenile NCL should be entertained in any young school-age child who develops poor vision without refractive error.
- If the presentation and course are chronic and if behavioral and visual symptoms are present, it is probably Batten disease (chronic juvenile NCL).
- Look at the retina for the most important diagnostic feature in Batten disease.
- If the disease is acute with seizures, it is probably Bielschowsky disease (acute late-infantile NCL).
- The presence of early incoordination and abnormal EEG are the most important clinical features of Bielschowsky disease.
- Pathologic reports on tissues studied by electron microscopic methods may be misleading owing to lack of experience in searching for the bodies and naïveté in recognizing them.
- In some rare cases of NCL, pure autism, pure pervasive psychosis, and pure cerebellar ataxia are prominent, but NCL accounts for a minute fraction of these syndromes.

Definite diagnosis is currently based on measurement of the PPT1 activity in CSF, plasma, leukocytes or fibroblasts. Outside of Finland, the clinical presentation of NCL with PTT1 deficiency and GROD is heterogeneous, with subacute late-infantile or subacute juvenile variants in addition to the classic acute infantile onset. In the subacute late-infantile and juvenile variants with PTT 1 deficiency, behavioral changes and intellectual decline may be the presenting symptoms. However other presenting symptoms may include early visual deterioration, rapid motor dysfunction and seizures. Myoclonic jerks are less prominent in the juvenile variant.

Another rare variety of NCL is represented by the chronic adult-onset form of the disease (Kufs disease) (NCL 4). Most cases display an autosomal recessive mode of inheritance with only a few families reported to have a dominant transmission (sometimes referred to as Boehme or Parry disease). There are probably at least two clinical subtypes of this disease. Type A is characterized by progressive myoclonic seizures as early features, which are followed even years later by dementia. Type B is characterized by early dementia with or closely followed by prominent motor symptoms. The motor features are usually either a pure cerebellar syndrome or a pure basal ganglion deterioration. It is important to emphasize that NCL 4 shows no retinal disturbance. In families, the subtypes show homotypism (same characteristics) and homochronism (same onset and course). In the uncommon instances when this disorder has been studied, granular cytosomes have been identified ultrastructurally

KEY CLINICAL QUESTIONS

- Did you have your child checked by the ophthalmologist? Eyeglasses do not improve the visual defect and examination of the retina most often demonstrates specific changes suggestive of NCL.

in the lymphocytes. As the underlying molecular defects in Kufs disease remain unknown, a skin biopsy is the least invasive diagnostic approach demonstrating membrane-bound granular osmophilic deposits (GROD) and/or sporadic fingerprint profiles (FP) without membrane bound vacuole. Pathologic study of the CNS shows less striking storage. The class type of lipofuscin, which is seen in the aging process, is encountered but is the least diagnostic cytosome, while the presence of mixed (membrane-bound granular osmophilic deposits, rectilinear and curvilinear) profiles in association with fingerprint cytosomes without membrane bound vacuole is diagnostic.

The "Finnish" variant of the acute late-infantile form of NCL (NCL 5) is characterized by impaired concentration and motor clumsiness between 3 and 6 years of age. Visual failure and macular degeneration occur early between 5 and 8 years of age and usually precede onset of myoclonus and seizures. Myoclonic jerk may precipitate or follow the seizures. Usually complex partial seizures begin first followed 2 years later by generalized tonic–clonic seizures. In the early teens, independent walking is lost and dystonic posturing is noted. By that time, dysarthria appears and dementia becomes severe. Giant visual evoked potentials, somatosensory potentials and posterior spikes in the EEG during photic stimulation are characteristically found between 7 and 10 years of age. Early in the course of the illness, MRI shows a lower signal in the thalami than in the basal ganglia and a high signal periventricular rim on T_2-weighted images. Routine laboratory investigations including CSF are normal. No vacuolated lymphocytes are seen. At electron microscopy, fingerprints without membrane bound vacuole in association with atypical curvilinear and rectilinear profiles are seen in lymphocytes and biopsy samples. The diagnosis is confirmed by molecular genetic and biochemical studies. TPP1 activity is normal.

The "Lake" variant of the acute late-infantile/early-juvenile form of NCL (NCL 6) is characterized by a clinical presentation similar to NCL 1 with early ataxia, myoclonia and/or seizures with a later age of onset between 18 months and 8 years of age. Visual loss is rarely the initial clinical sign and symptom. Intellectual decline and loss of appropriate social response accompany the motor regression. The clinical course is slower than in the classic NCL 1. Visual failure occurs in most within 2 years of clinical onset. The retinal changes are frequently less prominent than in the classic NCL 1. Electrophysiologic studies demonstrate abnormal electroretinograms, grossly enlarged visual and somatosensory evoked responses and large polyphasic spikes during photic stimulation on EEG. As in NCL 1, vacuolated lymphocytes are not found in peripheral blood smear, however biopsy material analyzed by electron microscopy reveals the presence of fingerprint with occasional curvilinear and rectilinear profiles. The diagnosis is confirmed by molecular genetic and biochemical studies. TPP1 activity is normal.

The "Turkish" variant of the acute late-infantile form of NCL (NCL7) has a phenotype similar to Bielschowski disease but ultrastructural examination reveals fingerprint, rectilinear and curvilinear profiles. Vacuolated lymphocytes are found in the peripheral smear. TPP1 activity is normal.

In the chronic juvenile "Northern epilepsy" form of NCL (NCL 8), the infantile and early childhood periods are normal. The youngsters develop epilepsy (generalized tonic clonic seizures, complex partial seizures) between 5 and 10 years of age. Mental regression is most rapid when epileptic activity is most pronounced. As seizure activity decreases in adulthood, mental deterioration slows down. Behavioral problems such as inattentiveness, restlessness, disobedience, irritability and insomnia are frequently encountered. It is not until middle age, however, that gait and station disturbances become so obvious that a progressive neurological disease is first considered in the differential diagnosis. Then patients develop definite cerebellar symptoms and signs, consisting of both truncal and appendicular involvement. Ataxia, dyssynergia, dysmetria, dysdiadochokinesis, scanning speech, and nystagmus may develop. Hyperreflexia is common throughout the course of the disease, even early in the course. The retina does not show the typical picture believed to be diagnostic of NCL, although vague ocular abnormalities have been seen. These usually represent the retinal picture that can be seen in severe refractive errors and are not diagnostic of retinal NCL. Progression of neurologic symptoms is slow, covering a period of many years. The slow progression is out of proportion to the course in all the other syndromes of NCL. Neurophysiologic studies are nonspecific and depend on the stage of the illness. MRI shows in early adulthood cerebellar and brainstem atrophy. No vacuolated lymphocytes are found in the peripheral smear. Ultrastructural study of lymphocytes and skin shows accumulation of a wide variety of osmophilic cytosomal profiles with atypical curvilinear and rectilinear patterns predominating.

In none of the NCLs has there been a consistent beneficial therapy. Antioxidant treatment programs using vitamin E, vitamin C, D-L-methionine and butylated hydroxytoluene, or vitamin E and selenium in large dosages have shown some promise in arresting progression, especially in the chronic forms of the disease, but have been ineffective in the acute forms. Enzyme replacement therapy is presently under investigation for the acute infantile and late-infantile NCL. Key features of the NCLs are summarized in Tables 12.1 and 12.2.

FEATURES

Table 12.1 Neuronal Ceroid-Lipofuscinoses

Discriminating feature

1. Vacuolar or avacuolar osmophilic cytosomes in lymphocytes, conjunctiva, skin, rectum, muscle, and brain

Consistent features

1. Waxy, yellow type of optic atrophy
2. Peripheral retinitis pigmentosa
3. Abnormal ERG

Variable features

1. Progressive dementia
2. Seizures, myoclonia
3. Ataxia
4. Early blindness
5. Mental changes (disruptive behavior, psychosis, neurosis)
6. Basal ganglia symptoms
7. Rett-like symptoms (hand wringing)

Gaucher disease

Gaucher disease is a group of autosomal lysosomal storage disorders characterized by the accumulation of an extremely insoluble sphingolipid, glucocerebroside (glycosylceramide), in various tissues. In the vast majority of cases, the enzyme required for lysosomal degradation of glucocerebroside, glucocerebrosidase (glycosylceraminidase), is deficient (Beutler & Saven 1990). The gene for glucocerebrosidase is located on chromosome 1 in the region of q21 (Beutler 1992). The entire sequence of the gene is known. Some of the mutant forms of glucocerebrosidase are unstable and kinetic abnormalities of the residual enzyme include abnormalities in activation by the activator glycoprotein, saposin C, and inhibition by active site inhibitors (Reiner *et al*. 1989). Rare cases are caused by a deficiency of saposin C, a heat-stable cofactor required for normal catalytic function of glucocerebrosidase. The gene encoding for precursor protein of saposins, prosaposin, has been mapped to chromosome 10 and the full-length human "prosaposin" cDNA sequence has been established. A mutation in the saposin C gene has been reported in a patient with Gaucher-like disease (Schnabel *et al*. 1991).

Gaucher disease has been divided into three clinical subgroups, according to the presence and severity of neurologic symptoms. Type I disease (adult type), the most common subgroup, is a nonneuronopathic chronic disorder characterized by splenomegaly with hypersplenism, pulmonary involvement, and skeletal changes. Type II disease (infantile type) is an acute neuronopathic disorder characterized by hepatosplenomegaly and neurologic symptoms by 6 months of age. Brainstem abnormalities are responsible for stridor, difficulty in sucking and swallowing, and bilateral fixed strabismus or oculomotor apraxia. Retroflexion of the head is an early sign, probably due to laryngomalacia and hypotonia of pharyngeal muscles. Corticospinal signs are common. There is a profound psychomotor deterioration. Seizures are uncommon. Most patients die before 2 years of age in a vegetative state.

Type III disease (juvenile type) is a rare subacute neuronopathic disorder characterized by hepatosplenomegaly, hypersplenism, and slowly progressive neurologic deterioration beginning between early childhood and adult life. The most common neurologic manifestations are seizures and mental deterioration (Nishimura *et al*. 1980). A progressive myoclonic epilepsy may become severe and interfere with all activities. Mental deterioration may range from mild memory deficits to severe global dementia. Other neurologic abnormalities may include spasticity, ataxia, dystonia, parkinsonism and supranuclear gaze disorders (slow saccades, saccadic palsies, vertical oculo-

TABLE 12.2

Neuronal Ceroid-Lipofuscinoses

	Major clinical features	Prominent morphologic features
Acute form		
Infantile (classic) (NCL 1)	Motor dysfunction, seizures	Granular (GROD)
Late infantile (classic) (NCL 2)	Seizures	Curvilinear (CV)
Late infantile (Finnish) (NCL 5)	Motor dysfunction, seizures	FP without vacuole
Late infantile (Lake) (NCL 6)	Seizures	Mixed
Late infantile (Turkish) (NCL 7)	Seizures	CV, GROD, mixed
Chronic forms		
Juvenile (classic) (NCL 3)	Visual loss, dementia	FP
Juvenile (atypical) (NCL8)	Seizures, ataxia, no visual loss	RL, CV
Adult (dominant with seizures) (NCL 4)	Seizures, myoclonia	Mixed
Adult (recessive with dementia) (NCL 4)	Dementia (motor loss)	Mixed

FP: fingerprint profiles; RL: rectilinear profiles; GROD: granular osmophilic deposits; CV: curvilinear bodies

motor apraxia). Death may occur between the second and fourth decade.

Ancillary laboratory findings on the serum may include elevation of acid phosphatase and angiotensin converting enzyme. Cerebrospinal fluid (CSF) is usually normal. Diagnosis of Gaucher disease is established by direct assay of glucocerebrosidase activity in leukocytes, skin fibroblasts, or amniocytes. Prognostic information and genetic counseling are now possible by DNA analysis with techniques that use the polymerase chain reaction technique. Patients homozygous for the mutation at nucleotide 1448 of nuclear DNA are very likely to have neuronopathic disease, whereas the presence of even a single allele for the mutation at nucleotide 1226 appears to protect against the occurrence of neuronopathic disease (Beutler 1991).

Gaucher cells are the hallmarks of the disease (Table 12.3). The typical Gaucher cell is a large macrophage measuring 20–100 μm in diameter and containing one or multiple central or eccentric small nuclei. The cytoplasm is filled with fibrillary material, which gives an appearance of "wrinkled tissue paper." On electron microscopy, membrane-bound inclusions (Gaucher bodies) are filled with "tubules" composed of 10–12 fibrils that spiral the entire length of the tubule. The fibrils are formed by the accumulation of cerebroside molecules (Lee 1968). Gaucher cells are found in most tissues (e.g. spleen, liver, lymph nodes, bone marrow, lungs, adrenals), but not in the skin. Hepatocytes are not involved in storage of glucocerebroside. No evidence of neuronal storage is present in neurons of the gastrointestinal tract.

FEATURES

Table 12.3 Gaucher Disease

Discriminating features

1. Gaucher cells in bone marrow and other tissues, except skin
2. Glucocerebroside deficiency in leukocytes, serum, and skin

Consistent feature

1. Hepatosplenomegaly

Variable features

1. Anemia
2. Fractures
3. Cirrhosis
4. Pinguicula
5. Spasticity
6. Opisthotonos
7. Horizontal oculomotor apraxia
8. Myoclonic seizures
9. Ataxia
10. Mental retardation
11. Cranial nerve involvement

PEARLS & PERILS

Gaucher Disease

- The neurologic triad – strasbismus, trismus, and retroflexion of the head – and its association with hepatosplenomegaly are suggestive of type II Gaucher disease.
- Patients with type II or type III disease have no clinical or neurophysiologic signs of peripheral nerve involvement.
- Gaucher cells from bone marrow aspirate must be differentiated from foam cells seen in Niemann–Pick disease. Gaucher cells are commonly multinucleated and their cytoplasm has a "wrinkled tissue paper" appearance. Gaucher cells are not found in the skin.
- Cells that can be mistaken for Gaucher cells are found in patients with unusually rapid turnover in the marrow, i.e. those with leukemia, thalassemia, or multiple myeloma (who do not have Gaucher disease).
- Gaucher bodies are only occasionally seen in neurons.
- Caution is advised in recommending splenectomy.

The most characteristic CNS change is the proliferation of histiocytes in the perivascular spaces and the transformation of a few of these into Gaucher cells. The quantity of Gaucher cells increases in an anterior-posterior fashion, with the occipital lobes being the most severely affected. The storage material in the neurons consists of polar glucocerebroside and psychosin (glucosylsphingosine). In those cases with the most advanced nerve cell loss, the highest levels of psychosin are found in the brain, suggesting a possible causality between intraneuronal accumulation of psychosin and neuronal degeneration.

All three types of Gaucher disease are inherited as autosomal recessive traits. In general, if one sibling has one clinical type of Gaucher disease, another affected sibling will have the same form, although the symptoms may differ significantly. Ethnic predilection only exists for type I disease, with an incidence in Ashkenazi Jews of about 1 in 2500 births. The absence of functional complementation between phenotypes in somatic cell hybridization studies suggests that the phenotypes of these disorders are a result of allelic mutations in the structural gene for glucocerebrosidase. The glucocerebrosidase gene is encoded on chromosome 1. The nuclear DNA sequence predicts a primary polypeptide of 516 amino acids. A leader peptide is removed from the precursor and the addition of a carbohydrate (mannose-6-phosphate) occurs as part of the posttranslational processing and lysosomal targeting. A single base change in the glucocerebrosidase gene may result in the synthesis of catalytically defective glucocerebrosidases that are abnormally processed or improperly compartmentalized. Prenatal diagnosis has long been available for families at risk for additional chil-

KEY CLINICAL QUESTIONS

- Is there any Ashkenazi Jewish ancestry? In a Jewish infant presenting with early strabismus, generalized hypertonia, opisthotonic posturing, and difficulty in swallowing, Gaucher disease should be suspected. Although the incidence of Gaucher disease is high in Ashkenazi Jews, the disease is not restricted to this population. In any case, abdominal exam should be performed looking for organomegaly. In the non-Jewish population, children frequently present later in life with difficulties tracking moving objects.

dren with type II Gaucher disease. Heterozygote detection is possible, but has not come into widespread use.

Supportive therapy in Gaucher disease is difficult. Splenectomy is advisable when hypersplenism develops. However, total splenectomy is followed by a high mortality from sepsis, an increase in bone involvement with osteolytic changes within a few months of surgery, and rapid deterioration of the neurologic status in patients with type II or type III diseases. Therefore, it has been suggested that splenectomy be postponed or avoided if at all possible. Partial splenectomy has been advocated with the dual goals of avoiding postplenectomy sepsis and minimizing the deleterious effects of glucosylceramide on bones, liver, and the CNS. Specific enzyme replacement has been attempted with variable success. Delivery of exogenous enzyme by infusion of purified glucocerebrosidase has been of limited value in reversing neurologic signs. Organ grafts as a source of enzymes have largely been unsuccessful. Bone marrow transplants have been shown to normalize leukocyte glucocerebrosidase activity and improve bone marrow involvement. No evidence exists at present to demonstrate that bone marrow transplants will increase glucocebrosidase activity in the CNS, and their usefulness might be limited to nonneuronopathic cases of Gaucher disease. More recently, somatic gene therapy has been suggested. A functional nuclear DNA for the human enzyme has been introduced into a retroviral vector. It is possible that retroviral infection of bone marrow stem cells will prove to be as effective as bone marrow transplants and less risky.

GM_2 gangliosidoses

The GM_2 gangliosidoses are autosomal recessive neuronal lipidoses in which lysosomal catabolism of a glycosphingolipid, GM_2 ganglioside, in the neurons of the cerebral cortex is deficient, leading to progressive mental and motor deterioration. Two proteins are involved in the degradation of GM_2 ganglioside: the GM_2 activator protein and hexosaminidase A (Hex A). GM_2 activator (encoded on chromosome 5) is a specific, nonenzymatic glycoprotein that binds to ganglioside GM_2 and extracts GM_2 ganglioside from the membranes and solubilizes it. The resultant complex is then recognized by lysosomal Hex A, which hydrolyzes the ganglioside GM_2. Hex A consists of two polypeptide chains, α and β, in the combination $\alpha_1\beta_2$. The α chain encoded on chromosome 15 is only found in Hex A. The β chain, encoded on chromosome 5, is found in Hex A and hexosaminidase B (Hex B), a homopolymer of β subunits with the structure $\beta_2\beta_2$. Three types of GM_2 gangliosidoses are distinguished biochemically. Mutations in the α subunit lead to various forms of type I GM_2 gangliosidosis (Hex A deficiency). Mutations in the β subunit lead to various forms of type II GM_2 gangliosidosis (Hex A and B deficiency). Type III GM_2 gangliosidosis is a rare variant characterized by a GM_2 activator deficiency with partial or no hexosaminidase A deficiency.

The three types of GM_2 gangliosidosis, infantile, juvenile, and adult, differ by age of onset and clinical course. The infantile acute form (Tay–Sachs and Sandhoff diseases) is characterized by an early onset of symptoms. Infants appear normal at birth and develop normally, except for irritability and an exaggerated startle response to a relatively modest sound. By 6 months of age psychomotor retardation becomes apparent. After 6 months of age, motor weakness becomes obvious, with flaccid paralysis, hyporeflexia, and hypotonia. Visual acuity deteriorates. The patient lacks the ability to fixate and frequently shows searching eye movements. The characteristic cherry-red spot is present due to lipid around the normal macula. Blindness usually occurs before 1 year of age. After 1 year of age, the symptoms continue to progress, and the hyporeflexia and hypotonia give way to generalized spastic paralysis with hyperreflexia and opisthotonos. The child becomes progressively deaf. The occipitofrontal circumference increases at an abnormal rate because storage of ganglioside and glial proliferation enlarge the brain. Various major and minor seizures occur; some seizures may begin with inappropriate laughter (gelastic seizures). Feeding difficulties, owing to ineffective swallowing, lead to progressive weight loss and cachexia. Late in the disease, a state of decerebrate rigidity is reached. The patient usually expires from a respiratory infection before the age of 5 years. Tay–Sachs disease (infantile type I GM_2 gangliosidosis), Sandhoff disease (infantile type II GM_2 gangliosidosis), and GM_2 activator protein deficiency (infantile type III GM_2 gangliosidosis) are clinically similar (Okada *et al.* 1972). A mild splenomegaly, when present, is characteristic of Sandhoff disease. Occasional infants with Sandhoff disease have bony deformities similar to those in type I GM_1 gangliosidosis.

Juvenile subacute GM_2 gangliosidosis has an onset between 2 and 6 years of age and progresses more slowly than the infantile GM_2 gangliosidosis. Spinocerebellar ataxia, dysarthria, and loss of speech are frequently the initial symptoms. Dysphagia tends to appear later in the illness. Dementia is a universal feature but frequently is not appar-

ent during the first years of the illness. Movement disorders, such as choreoathetosis, dystonia, and oculogyric crisis, may occur early or late in the course of the disease. Often, a progressive spasticity, leading to a decerebrate rigidity, is reported. Seizures are not always present. Cherry-red spots are uncommon and not well defined when they are present. Blindness occurs late in the disease. Megalencephaly does not develop. Death occurs up to 10 years from the onset of clinical symptoms (Meek *et al.* 1984). Some juvenile patients with onset in childhood have a protracted course with long survival in adulthood.

The onset of adult chronic GM_2 gangliosidosis is variable. Presenting symptoms include dementia, psychosis, progressive muscle weakness with atrophy (with clinical course similar to that of Kugelberg–Welander disease), seizures, ataxia, dystonia, rubral tremor, and supranuclear ophthalmoplegia, either alone or in various combinations. A slow, progressive ataxia with dysarthria is not always present. Intellectual function is normal or mildly impaired. Seizures rarely occur. Funduscopic exam is frequently normal (Harding *et al.* 1987).

In the various forms of GM_2 gangliosidoses, the ERG is normal. In the infantile form of GM_2 gangliosidosis, the visual evoked potential is preserved in the early stages of the disease, but after 3–12 months the various components become increasingly poorly defined. Visual evoked responses may become abnormal late in the course of juvenile GM_2 gangliosidosis. In the various forms of GM_2 gangliosidoses, auditory evoked potentials may be abnormal in morphology and latency. EEG becomes abnormal early after birth in infantile GM_2 gangliosidosis. Hypsarhythmia and multifocal cortical spikes are frequently recorded. In the juvenile form, the EEG is usually diffusely abnormal with occasional epileptiform activity. In the adult form, EEG may be normal or show nonspecific diffuse electric abnormalities. EMG in the protracted juvenile form and in the adult-onset GM_2 gangliosidosis frequently shows evidence of denervation. Sensory nerve conduction is rarely decreased. CT scan of the head may show a diffuse atrophy or a gross cerebellar and brainstem atrophy in some patients with juvenile and adult forms of GM_2 gangliosidosis.

CSF is usually unremarkable. Urinary excretion of oligosaccharides containing N-acetylglucosamine and mannose has been observed in Sandhoff disease (Sewell 1980). The diagnosis of GM_2 gangliosidoses is confirmed by enzyme assay of Hex A and B in serum, separated white blood cells, fibroblasts, or amniotic cells. Assays for Hex A and B employing synthetic substrates (sulfated or nonsulfated) are generally sufficient to diagnose defects in α or β chains. However, mutations in the β subunit leading to heat-labile Hex B may be misdiagnosed. Furthermore, this assay procedure cannot diagnose the GM_2 activator deficiency or Hex A mutations resulting in a decreased responsiveness to activator protein. In those cases, more complicated tests are needed (Raghavan 1985; Gravel *et al.* 1991). Identification of storage material in rectal biopsy may be in helpful in such cases. Molecular DNA-based diagnostic techniques should be carried out as mutations leading to infantile, juvenile and adult GM_5 gangliosidosis can be distinguished at the molecular level. Prenatal diagnosis of Tay–Sachs disease can be accomplished in high-risk pregnancies. Discriminating features in the diagnosis of Tay–Sachs and Sandhoff disease are listed in Tables 12.4 and 12.5.

FEATURES

Table 12.4 Tay–Sachs Disease

Discriminating feature

1. Hexosaminidase: A deficiency in serum and fibroblasts

Consistent features

1. Exaggerated startle response
2. Cherry-red spot

Variable features

1. Nystagmus
2. Blindness
3. Megalencephaly
4. Hypotonia (early) and hyperreflexia (late)
5. Hyporeflexia (early) and hyperreflexia (late)
6. Difficulty swallowing
7. Seizures
8. Deafness
9. Blindness

FEATURES

Table 12.5 Sandhoff Disease

Discriminating feature

1. Hexosaminidase: A and B deficiency in serum and fibroblasts

Consistent features

1. Exaggerated startle response
2. Cherry-red spot
3. Oligosaccharides in urine

Variable features

1. Nystagmus
2. Blindness
3. Megalencephaly
4. Hypotonia (early) and opisthotonos (late)
5. Hyporeflexia (early) and hyperreflexia (late)
6. Difficulty swallowing
7. Seizures
8. Deafness
9. Blindness
10. Splenomegaly
11. Bony deformities

In Tay–Sachs and Sandhoff diseases, the consistency of the brain is firm and rubbery. Microscopically, neurons in the brain are enlarged by cytoplasmic material. Neuronal storage is found not only in the entire central nervous system (CNS) but also in the ganglion cells and amacrine cells of the retina, spiral ganglia of the inner ear, spinal ganglia, autonomic ganglia, and neurons of the myenteric plexus. Neuronal storage progressively results in death of nerve cells. In juvenile and adult GM_2 gangliosidosis, the brain weight is less than normal and there is mild to moderate cerebral atrophy visible on CT/MRI. Neuronal swelling is more selective and preferentially involves cerebellum, brainstem, and spinal cord.

Electron microscopy of the stored material in all forms of GM_2 gangliosidoses demonstrates a great number of round or oval laminated membrane-bound structures. Three forms of cytosomes are described: concentric, compound, and zebra bodies. In concentric bodies, the lamellae are arranged concentrically with a homogeneous or firmly granular zone in the center. In compound bodies, several outer concentric layers surround an inner zone filled with straight elements. In zebra bodies, a dense, double-layer, oval shell is filled with flat layers. They contain GM_2 ganglioside, cholesterol, and phospholipid. A protein component may also be present.

GM_2 gangliosidoses are autosomal recessive inherited disorders. Prior to institution of large-scale prevention programs, the infantile Tay–Sachs disease was much more frequent among Ashkenazi Jews than in other ethnic groups. The incidence of infantile Tay–Sachs disease was about 1 in 4100 among Ashkenazi Jews; in non-Jewish Americans incidence of Tay–Sachs disease is about 1:320 000 births. Extensive genetic counseling and prenatal diagnosis have reduced the incidence of infantile Tay–Sachs disease in the Ashkenazi Jews. Since the mid-1980s, more cases of infantile Tay–Sachs disease are identified in non-Jewish than Jewish infants. However, the gene frequency in heterozygotes remains unchanged. Gene frequency in Ashkenazi Jews is approximately tenfold higher than in the general population. The Sandhoff, juvenile, and adult forms of GM_2 gangliosidoses have no ethnic predilection. Management of patients with GM_2 gangliosidoses is entirely supportive.

KEY CLINICAL QUESTIONS

- Is there any Ashkenazi Jewish ancestry? If an infant presents a decreased visual attentiveness, progressive head enlargement and sudden jerks with extension of four extremities in reaction to sharp noises, Tay–Sachs disease should be suspected. Although the incidence of Tay–Sachs disease is high in Ashkenazi Jews, the disease is not restricted to this population. In any case, a funduscopic exam should be performed looking for cherry-red spots.

Menkes disease

Menkes disease is an X-linked recessive disorder of copper transport due to a deficiency in the extrahepatic transmembrane copper transporting ATPase, a glycoprotein normally localized in mitochondria and Golgi apparatus (Vulpe *et al*. 1993). This enzyme transports copper from the cytoplasm of extrahepatic cells into the mitochondria and Golgi system. Most of the symptoms of Menkes disease can be explained by copper deficiency and secondary defects of copper-dependent enzymes. For instance, decreased lumbar CSF 3-methoxy-4-hydroxyphenylglycol (MHPG), the metabolite of norepinephrine is explained by copper-dependent β dopamine-hydroxylase deficiency. The illness is characterized clinically by seizures, psychomotor retardation, failure to thrive, connective tissue findings, hypopigmentation and peculiar hair. These babies are often born prematurely. The diagnostic features of neonates with Menkes disease are subtle: feeding difficulties, temperature instability, jaundice. The characteristic alterations in the hair are usually absent. Inguinal hernia and diathesis recti abdominus may be present. Many acquire head control and responsive smile. Truncal hypotonia, progressive spasticity of the limbs, psychomotor delay and/or convulsions (partial, generalized, myoclonic) are usually reported by 2–4 months of age. The hair is hypopigmented, lusterless, and short with a steely texture. Pili torti and trichorrhexis nodosa are seen under light microscopy. Pudgy cheeks, sparse eyebrows, and depressed nasal bridge with micrognathia give these patients a cherubic appearance (Fig. 12.1). The skin is hypopigmented, hyperextensible, and joints are hypermobile. The bones are osteoporotic with flared long bone metaphyses, and there may be wormian bones on skull x-rays. The blood vessels are tortuous and elongated with irregular lumen (Fig. 12.2). Diverticula of the bladder are common. There is progressive deterioration leading to spastic quadriparesis with clenched fists and leg scissoring while axial muscles remain hypotonic. Blindness with optic atrophy is associated with vertical and horizontal nystagmus. Death occurs between 6 months and 3 years of age often from recurrent urinary tract infections.

A milder phenotype has been reported (Danks 1988; Westman *et al.* 1988). These patients present with cerebellar ataxia, developmental delay, loose skin, lax joints, and typical hair changes. Bladder diverticula, bone changes, and arterial changes are milder. Survival may extend into adulthood.

The "occipital horn syndrome" (or X-linked cutis laxa or Ehlers-Danlos syndrome type IX) is characterized by tissue and bony abnormalities, including hyperelastic skin, easy bruisability, bladder diverticula, hyperextensible joints, marked arterial tortuosity, and skeletal anomalies, as well as chronic diarrhea (defect in bowel motility). Typical radiologic features include ossified occipital exostosis, a "ham-

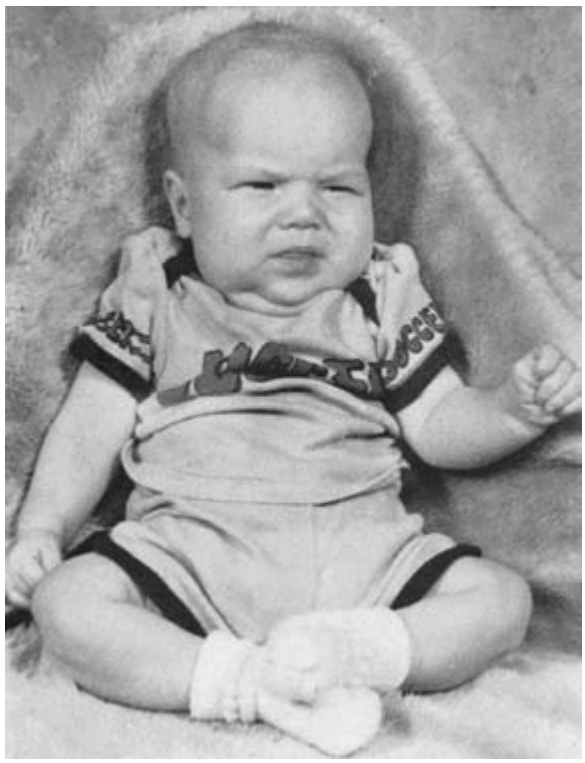

Fig. 12.1 In this 7-month-old boy the diagnosis of Menkes disease was suggested by the cherubic expression of the facies (pudgy cheeks), short, sparse, and hypopigmented hair, clenched fists and truncal hypotonia. Seizures were first reported at 3 months of age.

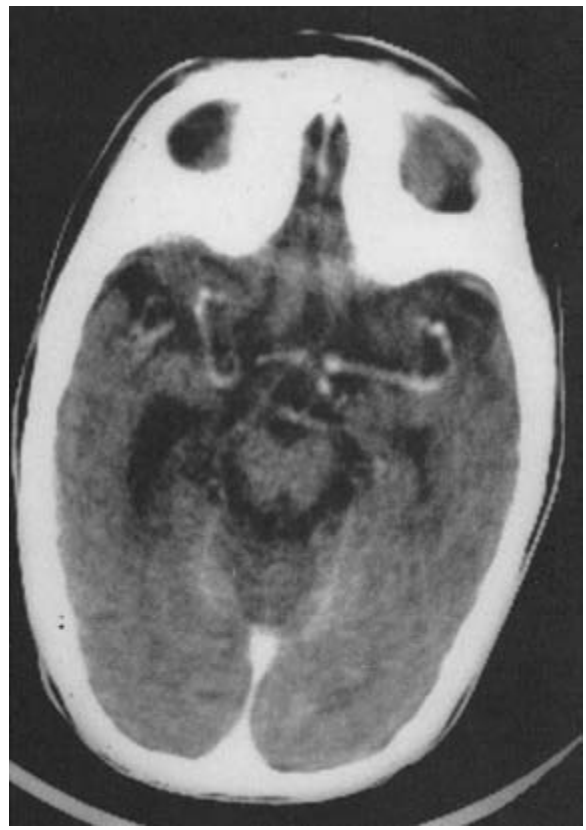

Fig. 12.2 Contrast-enhanced CT scan of the head showing brain atrophy with enlargement of the ambient cistern and tortuous middle cerebral arteries in a 2-year-old boy with Menkes syndrome who presented at 1 month of age with inguinal hernia and at 6 weeks of age with seizures, failure to thrive, and unusual hair.

merlike" extension of the lateral end of shortened clavicles, and a waxy outline of the cortex of most long bones (Sartoris *et al.* 1984). Neurologic features may include congenital myopathy, psychomotor retardation, and seizures since early childhood. In adulthood, generalized muscular atrophy and mental retardation have been reported (Wakai *et al.* 1993). There is no microcephaly. The hair appears to be normal.

In classical Menkes disease, mild Menkes disease, and occipital horn syndrome, laboratory studies typically reveal low serum copper and ceruloplasmin levels. Copper transport is affected in all tissues except the liver. In most cells (except liver), when copper is available, there is normal uptake, but reduced efflux, hence the increased copper accumulation in gut mucosa and renal tubular cells. Intestinal absorption of copper is poor. An increased uptake and an impaired efflux of copper in cultured skin fibroblasts is characteristic of various forms of extrahepatic transmembrane copper-transporting ATPase deficiency. Mild Menkes disease and occipital horn syndrome are allelic with the classic Menkes disease (Table 12.6).

Parenteral administration of copper histidinate is the treatment of choice for Menkes disease. This readily corrects the serum and liver copper levels but does not restore the levels of all copper-dependent enzymes in other organs (Danks & Catwright 1973). In particular, restoration of normal brain copper has not yet been achieved. Decreased lumbar CSF 3-methoxy-4-hydroxyphenylglycol (MHPG) persists after parenteral copper therapy. At best, patients with Menkes disease who have been treated with copper histidinate soon after birth are at the lower end of the normal range intellectually and have some residual features of the disease in hair and connective tissues. Therapeutic intervention with copper histidinate in occipital horn syndrome has a marginal af-

KEY CLINICAL QUESTIONS

- Do you know of any other boy in your family who had intractable seizures, never had a haircut and died in infancy?

Menkes Kinky Hair Syndrome

PEARLS & PERILS

- The bone changes in Menkes syndrome are easily confused with those seen in maltreated babies and the tendency for subdural hematoma to occur in this disorder adds to the risk of confusion of the two entities. Wormian bones are present in early life.
- Early diagnosis may be difficult because bony changes, hair abnormalities, and serum copper and ceruloplasmin may be normal in the very early neonatal period. In neonates with a positive family history, demonstration of an increased uptake of copper in skin fibroblasts may allow early diagnosis. Similarly, diagnosis may be achieved by demonstrating an increased uptake of copper in amniotic fluid cells in fetuses.
- Menkes disease is an X-linked autosomal recessive disorder.
- A cherubic face, hypopigmentation and frequent uncontrolled seizures in a young infant with progressive brain atrophy is not unique to Menkes disease as it is also seen in sulfite oxidase deficiencies (primary or secondary to molybdenum cofactor deficiency). Diagnosis of sulfite oxidase deficiencies is suggested when the sulfite dipstick test on fresh urine turns pink. Ectopic lenses typical of sulfite oxidase deficiencies is a late finding (Johnson & Duran 2001).

FEATURES

Table 12.6 Menkes Disease

Discriminating features

1. Increased uptake but reduced efflux of copper in cultured skin fibroblasts
2. Defects of extrahepatic transmembrane copper-transporting ATPase gene

Consistent features

1. X-linked recessive
2. Twisted, brittle hair
3. Hyperextensibility of skin
4. Pallor of skin
5. Ligament laxity
6. Psychomotor retardation
7. Myopathy
8. Low serum copper
9. Low ceruloplasmin
10. Low CSF MHPG

Variable features

1. Chronic diarrhea
2. Osteoporosis
3. Fracture of long bones and ribs
4. Subdural hematoma
5. Anemia
6. Hemochromatosis
7. Seizures
8. Bladder diverticuli
9. Recurrent bladder infections
10. Hypo/hyperthermia

fect, perhaps due to the higher susceptibility of lysyl oxidase to copper deficiency.

Alpers syndrome

Alpers syndrome, or progressive infantile poliodystrophy is a heterogeneous group of autosomal recessive, X-linked or maternally inherited (in the case of mitochondrial DNA point mutation) (Uusimaa *et al*. 2002) disorders characterized by psychomotor deterioration, convulsions, myoclonus, hypotonia or spasticity, cerebellar ataxia, involuntary movements, visual disturbances and abnormal respiration. Liver dysfunction and exacerbation during infections are consistent features. Two distinct categories can be defined. In the first group, there is a defect of selenium metabolism resulting in liver dysfunction and abnormal hair (Ramackers *et al*. 1994). In the second group, various defects of energy metabolism are reported. Those include defects in the citric acid cycle (Gabreels *et al*. 1984), pyruvate carboxylase (Atkin *et al*. 1979), pyruvate dehydrogenase (Robinson *et al*. 1987), nicotinamide-adenine dinucleotide (NADH) dehydrogenase (complex I) (Tulinius *et al*. 1991), and cytochrome c oxidase (complex IV) (Prick *et al*. 1983). Alpers syndrome has also been associated with point mutations of mitochondrial DNA (Uusimaa *et al*. 2002) and mitochondrial DNA depletion due to mutations in the nuclear-encoded mitochondrial DNA polymerase gamma (POLG) gene (Naviaux *et al*. 1999).

Clinically, three forms of the syndrome have been recognized according to age of onset: neonatal form, infantile form, and juvenile form. The neonatal form may present at birth with joint limitations, micrognathia, cryptorchidism, pulmonary hypoplasia, and intrauterine growth retardation suggesting fetal akinesia (Frydman *et al*. 1993). Micropenis and hypospadias have been described in patients with NADH dehydrogenase (complex I) deficiency and

KEY CLINICAL QUESTIONS

- Do you have videotapes showing your child before and after the onset of the visuomotor regression? Review of videotapes will allow the physician to recognize the progressive nature of the microcephaly, the rapid retrogression of developmental milestones and the characteristics of myoclonic seizures.

cytochrome c oxidase (complex IV) deficiency. Features reminiscent of fetal alcohol syndrome can be seen in pyruvate dehydrogenase E_1 α subunit deficiency. Most infants appear lethargic and floppy. Microcephaly is mild at birth and progresses with age. Refractory neonatal convulsions, swallowing difficulties, and pneumonia complicate the clinical course. Occasional features include cardiomyopathy and the de Toni–Fanconi–Debré syndrome. Most patients die before 2 years of age from respiratory arrest or liver failure. The infantile form has its onset before 2 years of age with recurrent vomiting, failure to thrive, hypotonia, and developmental delay, typically following a short period of normal development. Intractable seizures appear weeks or months later, often acutely. Other manifestations may include ataxia, involuntary movements, myoclonus, and blindness. Hair may become depigmented and brittle. Microcephaly and spasticity appear late in the illness. Some instances of terminal jaundice have been described. Most patients die between 3 and 4 years of age. The rare juvenile form has its onset in childhood with migraines, convulsions, and visual impairment. Later myoclonus, spasticity, choreoathetosis, and dementia are progressive. Death results from uncontrollable seizures.

EEG is variable yet often shows diffuse abnormalities with low-voltage background and numerous multifocal paroxysmal discharges. Visual evoked potentials are frequently abnormal. Nerve conduction studies and electromyography are usually normal. Repeated CT scans of the head document progressive cortical atrophy. Basal ganglia calcification is seen in juvenile cases (Shapira *et al.* 1975). T_2-weighted MRI of the brain may show decreased signal of the thalamus (Fig. 12.3). Liver dysfunction is an early manifestation in most cases and biochemical evidence of liver disease may precede the onset of seizures. CSF proteins are usually normal. An elevated blood and/or CSF lactate and lactate/pyruvate ratios may be found intermittently in some patients. Diagnosis of Menkes disease should be excluded. Selenium

FEATURES

Table 12.7 Alpers Syndrome

Discriminating feature

1. Spongiosis, neuronal loss, and astrocytosis which progress down through the brain cortex

Consistent features

1. Intractable seizures with myoclonus
2. Liver dysfunction

Variable features

1. Clinical evidence of liver disease
2. Failure to thrive
3. Developmental delay
4. Ataxia
5. Hypotonia
6. Progressive spasticity
7. Blindness and optic atrophy
8. Microcephaly (late)

PEARLS & PERILS

- Alpers syndrome should be distinguished from other causes of progressive microcephaly and seizures without organomegaly and without metabolic distress. Menkes disease, molybdenum cofactor deficiency and sulfite oxidase deficiency are easily recognized by their facial appearance. Abnormal hand movements suggest Rett syndrome. Unexplained hyperthermia and dystonic posturing suggest biopterin synthesis defects. Hypsarrhythmia and infantile spasm suggest West syndrome. Hypoplasia of corpus callosum and cerebellar vermis atrophy suggest nonketotic hyperglycinemia. In Schindler disease, diagnosis is suggested by abnormal urinary oligosaccharide and glycoprotein thin-layer chromatography profiles and proven by assay of the α-N-acetylgalactosaminidase activity (Linden *et al.* 1989). The diagnosis of NCL is excluded by assay of palmitoyl-protein thioesterase 1 (PPT1). In all these conditions, routine laboratory studies demonstrate a normal liver function while, in patients with Alpers syndrome, signs of liver dysfunction are typically found.

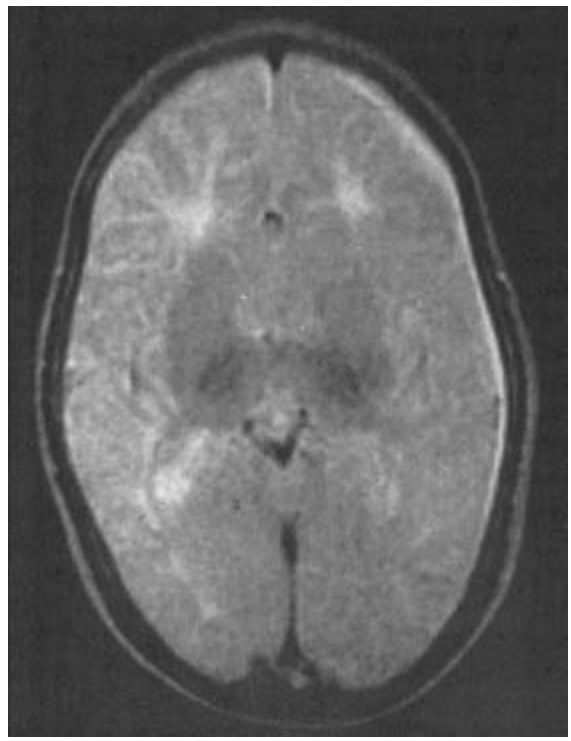

Fig. 12.3 MRI of the brain (SE 2100/100) showing low signal in thalami (suggesting iron deposits) and cortical atrophy in a 15-month-old girl with Alpers syndrome.

deficiency and glutathione peroxidase deficiency have been demonstrated in some patients (Ramacker *et al.* 1994).

Alpers syndrome is associated with characteristic neuropathologic lesions. The brain is small with a striking cerebral cortical atrophy. Histology demonstrates neuronal degeneration and loss, astrocytic gliosis, spongiosis, microglial proliferation, and capillary proliferations. These changes are most severe in the striate calcarine cortex. Neuronal loss can also be seen in cerebellum and to less extent in the basal ganglia. Alzheimer type II astrocytes are often present in the basal ganglia. White matter is relatively spared. Liver biopsy may show microvescicular fatty infiltration, necrosis of hepatocytes, inflammation and cirrhosis (Narkmick *et al.* 1991) (Table 12.7). In Alpers syndrome, the inexorable progress of liver involvement may be accelerated by anticonvulsant therapy, particularly valproate (Bicknese 1992). Selenium therapy may be beneficial in improving seizure controls and preventing liver dysfunction. A more definite therapy awaits discovery of underlying genetic defects.

PEARLS & PERILS

Niemann–Pick Disease

- Niemann–Pick cells can very easily be distinguished from Gaucher cells. Foam cells resembling those seen in Niemann–Pick disease are also observed in Wolman's disease, Tay–Sachs disease, Batten disease, sea-blue histiocyte syndrome, generalized gangliosidosis (infantile GM_1 gangliosidosis type I), and chronic granulomatous syndrome of childhood.
- Peripheral neuropathy may be demonstrated by neurophysiologic studies and nerve biopsy in NPA and NPB forms of Niemann–Pick disease.
- Infants with the NPA form of Niemann–Pick disease are typically emaciated with a protuberant abdomen. Finding a macular cherry-red spot excludes the diagnosis of Wolman's disease.
- Type II Niemann–Pick disease (NPC and NPD) should be suspected in patients with supranuclear ophthalmoplegia, dystonia, and splenomegaly. No fundoscopic abnormality is found in those patients.
- Splenomegaly is never severe enough to require splenectomy.

Niemann–Pick disease

Niemann–Pick disease is a heterogenous group of autosomal recessive lysosomal storage disorders characterized by the accumulation of varying amounts of the phosphosphingolipid, sphingomyelin, in certain tissues.

Biochemical analysis of the tissues reveals striking differences between two groups of patients. In group I, a striking increase in sphingomyelin content is found in most organs. In this group, the brain content of sphingomyelin may be increased (NPA) or normal (NPB). This group of patients is characterized by a severe and generalized acid sphingomyelinase deficiency. On the basis of somatic cell hybridization studies, NPA and NPB disease have been shown to be allelic disorders. The human acid sphingomyelinase gene has been located in the chromosomal region 11p15 and completely sequenced (Schuchman *et al*. 1992).

In group II, there is a regional variability of sphingomyelin storage. In this group of patients, sphingomyelinase activity is either partially deficient (NPC) or normal (NPD). Storage of sphingomyelin and cholesterol is observed in the liver and spleen; however no excess of sphingomyelin or cholesterol is found in the brain. The accumulated material in neurons is a glycolipid, glucosylceramide. In some patients, a partial deficiency of glucocerebrosidase has been demonstrated (Elleder *et al*. 1984). More recently cultured fibroblasts of group II patients have been shown to be deficient in their ability to synthesize cholesteryl esters during endocytic uptake of low-density lipoprotein (LDL). Instead there is lysosomal sequestration of LDL-derived cholesterol due to defects in intracellular cholesterol trafficking. NPC disease results from molecular defects in either NPC1 protein, a lysosomal permease belonging to one of the superfamilies of efflux pumps, or HE1 protein, a protein that interacts with cholesterol and is regulated by NPC1 (Yamamoto *et al*. 2000; Naureckiene *et al*. 2000). The NPC1 gene has been identified and maps to chromosome 18q11. The HE1 gene maps to chromosome 14q24. Niemann–Pick disease type C results from mutations in either the NPC1 gene (NPC1) or in the HE1 gene (NPC2). Niemann–Pick disease type D is an allelic variant of NPC1 (Greer *et al*. 1999). Most Niemann–Pick disease type D is allelic and results from mutations in the NPC1 gene.

NPA disease, or acute infantile Niemann–Pick disease, is the most common form of Niemann–Pick disease. This acute neurovisceral form is characterized by hepatosplenomegaly and severe early neurologic involvement. Feeding difficulty, failure to thrive and organomegaly are usually evident by 6 months of age. Psychomotor regression with loss of reactivity to the environment and postural hypotonia become evident by age 1 year. Seizures sometimes occur, but not as frequently as in Tay–Sachs disease. An atypical cherry-red spot is noted in 50% of cases. Some patients have clinical symptoms and pathologic findings of a peripheral neuropathy. With time, the child becomes apathetic, blind and deaf. Pupils become unresponsive to light. Death usually occurs before the fourth year of life.

NPB disease, or chronic juvenile Niemann–Pick disease, is a rare visceral or neurovisceral disorder characterized by organomegaly, diffuse infiltration of the lungs, and occasionally a decreased nerve conduction velocity. Ocular changes such as macular halo, granular pigmentation and gray discolorations of the macula do not interfere with vision. Most patients are free of neurologic symptoms until adulthood, although mental changes and extrapyramidal

KEY CLINICAL QUESTIONS

- Did the child have a prominent abdomen, jaundice and/or feeding difficulties in early infancy? If those features are absent, ask if the child has difficulties going down the stairs. This symptom resulting from vertical supranuclear ophthalmoplegia is rarely seen in other childhood neurodegenerative diseases.

signs may appear during adolescence. Most patients survive until late adulthood.

NPC disease can be classified into three major groups according to the age of onset of neurologic symptoms, that is, early infantile, late infantile, and juvenile forms. In the acute early infantile form, a transient cholestatic jaundice with hepatosplenomegaly and biliary atresia is associated with hypotonia and a rapid neurologic deterioration. In the subacute late infantile form, the patients usually seem normal until 2 years of age; psychomotor deterioration with ataxia, dysarthria, dysphagia and drooling is slow. Hepatosplenomegaly is less prominent. Most patients belong to the chronic juvenile form, also known as dystonic juvenile lipidosis. Cognitive and behavioral difficulties frequently precede the onset of motor problems. Dystonia or choreathetosis may be a presenting complaint. Dystonia starts distally and gradually becomes generalized. Some patients may never develop a visceromegaly. Most patients develop mental retardation, ataxia, dysarthria, spasticity, seizures (generalized tonic, clonic and myoclonic) and supranuclear vertical gaze paresis leading to difficulties negotiating stairs. Gelastic cataplexy has been observed in some subjects. Death usually occurs before 15 years of age.

NPD disease, or chronic adult Niemann–Pick disease, also called Nova Scotia variant (Vethamany *et al*. 1972), is a rare neurovisceral disorder characterized by a protracted course, mild organomegaly, and late onset of neurologic abnormalities (ataxia, seizures, vertical supranuclear ophthalmoplegia, intellectual deterioration), which may begin in adulthood (Elleder *et al*. 1983a).

In the NPA and NPB forms of Niemann–Pick disease, assessment of nerve conduction velocities may provide evidence of peripheral nerve involvement. ERG may show marked reduction of responses at a time when visual evoked potentials are only slightly abnormal. In NPA disease, slit lamp examination may reveal corneal and lenticular opacifications. In both NPA and NPB disease, chest radiography frequently shows diffuse bilateral interstitial infiltrates. CT scan of the head may be consistent with cerebral atrophy.

Blood chemistry may reveal some degree of liver disease. An accurate diagnosis of the NPA and NPB forms of Niemann–Pick disease is achieved by demonstrating a profound deficiency of sphingomyelinase activity in peripheral leukocytes, cultured fibroblasts, or cultured amniotic fluid cells. An in vitro assay of the enzyme is sensitive enough. For diagnosis of the NPC form, in vivo metabolic studies in cultured fibroblasts are more reliable to demonstrate partial sphingomyelinase deficiency. The dagnosis of NPC and NPD requires not only the demonstration of an impaired cholesterol esterification in the fibroblasts cultured with LDL, but also the evidence of intralysosomal accumulation of unesterified cholesterol as readily demonstrated in fibroblasts by the bright punctated fluorescence after probing with filipin, a cholesterol-binding antibiotic. Final diagnosis is confirmed by linkage analysis and sequence analysis of the mutated genes (Table 12.8).

Bone marrow examination reveals Niemann–Pick foam cells and/or sea-blue histiocytes in various types of Niemann–Pick disease. In type I diseases, foam cells are large macrophages 20–90 μm in diameter. The abundant pale cytoplasm is filled with lipid droplets, fairly uniform in size and highly refractile. On electron microscopy Niemann–Pick cells are filled with membrane-bound vacuoles containing loosely packed lamellae. In type II disease, foam cells are filled with nonuniform lipid droplets, with less birefringence than in type I. Sea-blue histiocytes are seen in NPA and type II diseases with Wright-Giemsa stain. Besides the bone marrow, foam cells and sea-blue histiocytes are found in most organs (i.e. peripheral nerves, retina, spleen, lungs). The lymphocytes of patients with NPA show cytoplasmic vacuoles, which are small and discreet by light microscopy and ultrastructurally display closely packed lamellar profiles (Elleder *et al*. 1983b).

FEATURES

Table 12.8 Niemann–Pick Disease

Discriminating feature

Type 1: Sphingomyelinase deficiency in fibroblasts and leukocytes

Type 2: Impaired cholesterol esterification and evidence of intralysosomal accumulation of unesterified cholesterol in cultured fibroblasts

Consistent features

1. Hepatosplenomegaly
2. Sea-blue or foamy histiocytes in bone marrow

Variable features

1. Failure to thrive
2. Psychomotor delay
3. Peripheral neuropathy
4. Atypical cherry-red spot
5. Vertical oculomotor apraxia
6. Seizures
7. Ataxia
8. Dystonia
9. Spasticity

The brain in patients with NPA and NPC forms of Niemann–Pick disease shows vacuolization and ballooning of neurons and microglia cells, accompanied by neuronal loss and glial proliferation. The neuronal involvement is generalized, including ganglia and intestinal plexuses.

In NPA, the stored material stains as a lipid, but in type II disease it is extremely PAS positive. In type II disease, deposition in axons results in neuroaxonal dystrophy (Braak *et al*. 1983).

Niemann–Pick disease is panethnic, but the majority of patients with the NPA form have Ashkenazi Jewish ancestry. No racial predilection is found in other types of Niemann–Pick disease. All forms are transmitted as autosomal recessive traits. The gene frequency is not well established, although NPA has been estimated to occur in about 1 in 100 Ashkenazi Jews.

As yet there is no specific treatment for Niemann–Pick disease with neurologic disease. Of the various therapy approaches, intracerebral transplantation of mesenchymal stem cell-mediated gene therapy in mice delays the onset of neurological abnormalities, providing a rationale for further investigations but remains controversial in humans (Jin *et al*. 2002).

Glucose transport protein deficiency

Glucose transport protein deficiency is an autosomal recessive progressive polioencephalopathy characterized by infantile seizures, developmental delay, and progressive microcephaly. Biochemically, the disorder has been shown to result from a defective glucose transport across the blood-brain barrier resulting in persistently low CSF glucose concentration in the absence of hypoglycemia or CNS infection. The glucose transport protein, GLUT-1-protein, is deficient in membranes of erythrocytes and brain capillary endothelial cells, which do not respond to insulin. The gene encoding the GLUT-1-protein is located on the short arm of chromosome 1 (De Vivo *et al*. 1995).

Most patients appear healthy at birth and early motor development seems to be normal. Seizures of different types start in infancy in most patients. Nonconvulsive seizures with loss of muscle tone are the most prominent clinical seizures. In addition, patients may have recurrent episodes of ataxia, unresponsiveness, or limpness. Patients display fluctuations in the motor performance through the day. Seizures are usually resistant to traditional anticonvulsants. Early recognition and prompt treatment with a ketogenic diet improve seizure control and neurologic outcome. Ketone bodies provide an alternative source of energy to the brain when supplies of glucose available to the brain are limited. Untreated, varying degrees of psychomotor retardation become evident in the first year of life. Patients may develop evidence of spasticity with or without athetoid dystonia. Cognitive and language development are frequently delayed. Hyperactive and aggressive behavior may be additional findings when diagnosis is not made. Acquired microcephaly is an inconsistent finding (De Vivo *et al*. 1991; 1994).

Most interictal electroencephalograms and neuroimaging studies including CT scans and MRI of the brain are normal. The ictal EEG typically shows generalized paroxysmal 2–2.5 Hz spike-wave discharges (Boles *et al*. 1999). Blood glucose is normal. A low CSF glucose concentration (<45 mg/dL), together with normal or low CSF lactate concentrations suggests the diagnosis. The kinetic studies of RBC glucose uptake are used as a physiological measure of the glucose transport protein integrity. The patients' RBC glucose uptake values represent approximately 50% of the parents' values. Similarly, the patients' RBC membrane immunoreactivity for GLUT-1 protein is approximately 50% of the parents' values by Western blot technique (Miller 1971) (Table 12.9).

KEY CLINICAL QUESTIONS

- Do symptoms of coordination problems and poor motor performance fluctuate during the day and do you occasionally see staring spells accompanied by loss of tone? Such patients may benefit from a ketogenic diet.

PEARLS & PERILS

- Low CSF glucose in the absence of CNS infection or hypoglycemia can be seen in mitochondrial disorders as well as in glucose transport protein deficiency; however, in mitochondrial disorders, CSF lactate is markedly elevated (6.03 ± 0.54 mM/L) if CSF glucose is low (<45 mg/dL).
- Patients responding to ketogenic diets should be suspected of having glucose transport protein deficiency.
- Patients with mental retardation and fluctuating ataxia should be assessed for GLUT-1 deficiency even when they don't have epilepsy (Overweg-Plandsoen *et al*. 2003).

Leukoencephalopathies

The progressive leukoencephalopathies result either from a primary genetic defect of myelin metabolism (primary leukodystrophies) (Table 12.10) or from glial cell damage by infectious conditions (AIDS encephalopathy, progressive multi-focal encephalopathy), immune or inflammatory phenomena (multiple sclerosis, X-linked adrenoleukodystrophy), DNA repair defects (Cockayne syndrome) or metabolic conditions resulting in the accumulation of toxic metabolites interfering with glial cell function and differentiation (nonketotic hyperglycinemia, Zellweger syndrome, Hurler disease, Pearson syndrome, glutaric aciduria) (Table 12.11).

FEATURES

Table 12.9 Glucose Transport Protein Deficiency

Discriminating feature

1. Kinetic studies of RBC glucose uptake

Consistent features

1. Fluctuation of neurological symptoms/disability through the day
2. Delayed motor and mental development
3. Low CSF/blood glucose (0.33 + 0.01) (normal: 0.65 + 0.01)
4. Low or normal CSF lactate (0.97 + 0.03 mM/L)
5. Resolution of seizures and motor fluctuation with ketogenic diet

Variable features

1. Seizures in infancy
2. Microcephaly
3. Spasticity
4. Dystonia
5. Paroxysmal fatigue, limpness, ataxia, palsy unresponsiveness, or autonomic myoclonus
6. Sleep disturbance, nocturnal myoclonus
7. Emotional outbursts
8. Fluctuating cognition

This section will discuss the primary leukodystrophies with known metabolic defects, listed by age of onset in Table 12.12. The progressive leukoencephalopathies are characterized clinically by motor manifestations that include spasticity, weakness, pyramidal tract signs and cerebellar signs. Involuntary movements are prominent in Pelizaeus–Merzbacher disease. Cognitive and behavioral deterioration are often late and overshadowed by motor disability. Seizures are absent or appear late in the course (except some cases of adrenoleukodystrophy). Macrocephaly with startle response to sound, irritability, and incessant crying is a frequent sign in Canavan disease, Alexander disease, and Krabbe disease. Peripheral neuropathy is a feature of Krabbe disease, metachromatic leukodystrophy, and some forms of adrenoleukodystrophy. High protein in the CSF is found in metachromatic leukodystrophy, Krabbe disease, and adrenoleukodystrophy.

Metachromatic leukodystrophy

Metachromatic leukodystrophy (MLD) or sulfatide lipidosis, is a heterogeneous group of autosomal recessive lysosomal storage disorders. The biochemical defect has been localized in the catabolism of a sphingolipid, sulfatide, which is a normal constituent of myelin and cellular membranes. In MLD, sulfatide is stored in the lysosomes

TABLE 12.10

Primary Leukoencephalopathies

Disorder	Chromosome	Peripheral nerve involvement	Metabolic defect
Pelizaeus–Merzbacher disease	X	-	Proteolipid protein (PLP) synthesis
Metachromatic leukodystrophy	22 or 10	+	Arylsulfatase A or sphingolipid activator protein B
Multiple sulfatase deficiency	3	+	Formylglycine generating enzyme
Krabbe's disease	14	+	ß-Galastocerebrosidase
X-linked adrenoleukodystrophy (ALD)	X	+	ALD-peroxisomal membrane protein synthesis
Alexander disease	17	-	Glial fibrillary acid protein
Canavan disease	17	-	Aspartoacylase

TABLE 12.11

Secondary Leukoencephalopathies

Disorder	Chromosome	Peripheral nerve	Metabolic defect
Zellweger syndrome	8	+	Peroxisomal assembly factor
Nonketotic hyperglycinemia	9 (glycine decarboxylase)	-	Glycine cleavage system (4 proteins)
Hurler disease	4	-	L-Iduronidase
Glutaric aciduria type I	19	-	Glutaryl-CoA-dehydrogenase
Cockayne disease	5 and 10	+	DNA repair
Mitochondrial leukodystrophy	?	+/-	Respiratory chain enzymes

TABLE 12.12

Age of Onset of Progressive Leukoencephalopathies and Leukodystrophies

Early infancy (before 12 months)
Infantile Krabbe disease
Canavan disease
Alexander disease
Pelizaeus–Merzbacher disease
Early childhood (1–5 years)
Metachromatic leukodystrophy
Late infantile forms of Krabbe disease
Late childhood and adolescence (5–15 years)
X-linked adrenoleukodystrophy
Juvenile metachromatic leukodystrophy
Juvenile Krabbe disease
Adulthood
Metachromatic leukodystrophy (ataxia, dementia)
Krabbe disease
Adrenomyeloneuropathy

of the oligodendrites and Schwann cells, as well as in many somatic tissues. The metachromasia, for which the disorder is named, results from a shift of blue stains toward red in tissues containing sulfatide. Mutations of at least three genes result in MLD. The most common mutation, in the gene for arylsulfatase-A (ASA), has been assigned to the long arm of chromosome 22 (22q13) (Hors-Cayla *et al*. 1979). Arylsulfatase-A mutations fall into two groups that correlate with clinical phenotype. Group I mutations produce no enzyme activity and no immunoreactive protein, producing the late infantile form of MLD. Group II mutations generate small amount of immunoreactive protein and low levels of functional enzymes. Individuals homozygous for type II mutation develop the adult form of MLD. Heterozygotes with type I and II mutation develop the juvenile form of MLD. Mutations within the saposin B region of the prosaposin gene on chromosome 10 (Inoi *et al*. 1985) have resulted in MLD due to loss of its sphingolipid activator protein activity. The multiple sulfatase deficiency gene that regulates in the endoplasmic reticulum the post-translational processing of all the sulfatases (SUMF1 for sulfatase modifying factor 1) has been mapped to chromosome 3p26 and encodes a formylglycine generating enzyme (FGE) (Cosma *et al*. 2003).

In the United States, the incidence of all forms of metachromatic leukodystrophy is estimated to be 1 in 100 000 births, although the true incidence may be higher because many cases remain undiagnosed.

Clinically, at least four forms of metachromatic leukodystrophy can be distinguished. The late-infantile form is the most frequent. The first clinical symptoms begin insidiously in the second year of life. Abdominal pain may be the presenting symptom. The clinical picture is characterized by progressive motor losses and dysfunction. Motor symptoms characteristically occur early and are more prominent than seizures and mental deterioration. A frequent early problem is a gait disorder with unsteadiness. Within months this leads to the loss of the ability to walk and stand. Decrease in deep tendon reflexes occurs in the early stage as the peripheral neuropathy increases and is later replaced by hyperreflexia. Bilateral extensor toe responses occur early and persist. Speech deteriorates as a result of dysarthria and aphasia. Ataxia and truncal instability become obvious. Intermittent pain is a manifestation of peripheral neuropathy. Nystagmus is present. Optic atrophy and a grayish discoloration of the macula are occasionally observed. Hypotonia is progressively replaced by rigidity and spasticity. Megalencephaly is frequently noted. Most children are bedridden by age 3 years. All meaningful contact with the surroundings is progressively lost. An opisthotonic posture with flexion of the arms and equinovarus posture, and scissoring of the legs are present in later stages of the illness, which may last for a few months to several years.

The juvenile form has its onset between age 4 and 10 years. The majority of cases develop during the first years of school with bradykinesia and poor school performance. Daydreaming, confusion, or emotional liability may be seen early. Unsteadiness of gait, usually owing to pyramidal system involvement, may occur. Extrapyramidal dysfunction, as suggested by postural abnormalities, rigidity and tremor may also develop. Seizures occur in more than half of the patients. Deep tendon reflexes are usually increased. The rate of deterioration is usually slower and more variable than in the late-infantile form. Patients often are not bedridden until 5–50 years after symptoms begin.

The adult form has its onset any time after puberty. Initial symptoms consist of personality and mental changes. Such symptoms are often misdiagnosed as attention deficit disorder, schizophrenia or manic-depressive illness. Seizures are rarely the presenting symptom. Movement disorders, ataxia, and paresis appear later. There are usually no clinical signs of peripheral neuropathy. In the final stage, the patient is mute, blind, bedridden, and unresponsive.

A rare variant of MLD combines features of the mucopolysaccharidosis with X-linked ichthyosis, X-linked chondrodysplasia punctata and those of MLD. It is now called multiple sulfatase deficiency. The mucopolysaccharidosis-like features include a mild gargoylism (facial changes with depressed bridge of the nose), hydrocephalus, growth retardation, limitation in extension of the elbows, radiologic changes of chondrodysplasia punctata, hepatosplenomegaly, heart defects and deafness. Corneal opacities do not occur. Ichthyosis, when present, develops at an early age. In general, presymptomatic development is less advanced than

that of late-infantile metachromatic leukodystrophy. Most children never achieve normal gait or speech. Neurologic regression follows the pattern of late-infantile MLD. By age 5 years, the child is profoundly retarded, with quadriplegia, pseudobulbar paralysis, and optic atrophy.

A number of laboratory tests may reinforce a clinical suspicion of metachromatic leukodystrophy. CSF studies may show an elevated protein concentration. Nerve conduction studies may demonstrate slow nerve conduction velocities or an increase in duration and number of potential components. In the adult form, nerve conduction studies and CSF proteins may be normal. EEG abnormalities are diffuse and nonspecific. Multimodality evoked potentials may reveal a latency prolongation or loss of evoked potential components that is dependent on the type of metachromatic leukodystrophy (late infantile, juvenile, or mucosulfatidosis) and in the duration of the disease. MRI is more sensitive than CT scan of the head, and allows earlier recognition and more precise characterization of areas of demyelination (Fig. 12.4). When multiple sulfatase deficiency is suspected, additional clinical laboratory tests should include skeletal x-ray series and examination of the peripheral blood smear for the characteristic lymphocytic storage vacuoles called Alder-Reilly granules.

The diagnosis of MLD is confirmed by demonstrating excess excretion of sulfatide in urine and by assay of arylsulfatase-A in leukocytes or skin fibroblasts (Table 12.13).

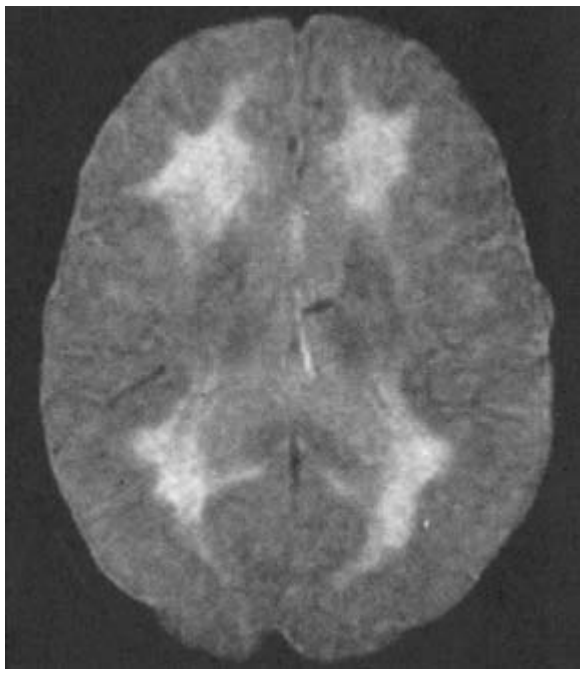

Fig. 12.4 MRI of the brain (SE2100/100) showing bilateral, symmetric, homogeneous, and diffuse elevation of the signal intensity throughout the deep hemispheric white matter (sparing U fibers) in a 3-year-old girl with metachromatic leukodystrophy.

PEARLS & PERILS

- Detection of large amounts of urinary sulfatides is essential for diagnosis. Urine should be kept at 4°C for collection.
- Low arylsulfatase-A in asymptomatic persons may be seen in two situations. Presymptomatic cases of metachromatic leukodystrophy excrete excessive amounts of urinary sulfatide. Normal amounts of sulfatide are found in pseudoarylsulfatase-A deficiency.
- Arylsulfatase-A is not always low in metachromatic leukodystrophy. Assay of arylsulfatase-A in intact cells and detection of large amounts of sulfatide in the urine allow diagnosis of saposin B deficiency.
- Arylsulfatase-A deficiency is deficient in multiple sulfatase deficiency, a rare autosomal recessive metachromatic leukodystrophy associated with combined features of mucopolysaccharidoses, X-linked ichthyosis and X-linked chondrodysplasia punctata.
- CT scan and MRI of the head typically demonstrate mild enlargement of the ventricles and demyelination bilaterally, with the maximum at the anterior and posterior poles of the ventricles.

All patients with MLD excrete large amounts of sulfatide in the urine. Most patients with MLD have, on cell-free preparations (i.e. serum, urine), a profound deficiency of arylsulfatase-A regardless of the age of onset. However, intact cells in culture are able to express subtle variations in their ability to clear sulfatide, giving a biochemical basis for variation in the age of onset in MLD. Low arylsulfatase-A activity in the cell homogenates of asymptomatic persons does not always indicate a diagnosis of MLD. Some are healthy individuals with pseudoarylsulfatase-A deficiency who excrete normal amounts of urinary sulfatide. Excessive amounts of sulfatide are however found in the urine of presymptomatic patients. In a rare variant, arylsulfatase-A activity in all homogenates is normal whereas large amounts of sulfatide are found in the urine. The molecular basis for this variant is a deficiency of saposin B, required for in vivo sulfatide catabolism. These patients present clinically with the features of juvenile MLD and show arylsulfatase-A activity in cultured fibroblasts that is in the heterozygous range but can be enhanced to normal levels by the action of the activator protein. Sulfatide loading shows deficient turnover in cultured fibroblasts. In multiple sulfatase deficiency, mucopolysaccharidoses and oligosaccharidoses are associated with sulfatiduria. In multiple sulfatase deficiency, not only is lysosomal arylsulfatase-A deficient, but also other lysosomal sulfatases acting in the catabolism of glycosaminoglycans (deficient in mucopolysaccharidoses type II, IIIA, IIID, IVA, and VII) as well as nonlysosomal sulfatases such as steroid sulfatase (deficient in X-linked ichthyosis) and arylsulfatase E (de-

FEATURES

Table 12.13 Metachromatic Leukodystrophy

Discriminating features

1. Metachromasia of peripheral nerves
2. Large amount of sulfatides in urine
3. Arylsulfatase deficiency in fibroblasts or white blood cells (type I & II)

Consistent features

1. Mental deterioration
2. Ataxia
3. Extensor toe signs
4. Reduced or absent sensory action potential

Variable features

1. Hypotonia (early) and spasticity (late)
2. Deep tendon reflexes decreased early and increased late
3. Strabismus
4. Visual impairment
5. Psychiatric symptoms
6. Extrapyramidal dysfunction
7. Seizures (rarely)
8. Elevated CSF proteins
9. Slow motor conduction velocity
10. Mucopolysaccharidosis-like symptoms (rarely)

ficient in X-linked chondrodysplasia punctata). At the genetic level, analysis of ASA, prosaposin and SUMF1 genes is now possible. Prenatal diagnosis of different forms of MLD can be accomplished.

MLD is a systemic disease affecting not only the CNS and peripheral nervous system, but also other organs such as kidneys (renal tubular epithelium), gallbladder, liver, pancreas (islets of Langerhans), adrenal cortex, ovaries, and testes. The reticuloendothelial system is never affected. In the peripheral nervous system, segmental demyelination occurs.

Treatments have been unsuccessful in correcting the progression of metachromatic leukodystrophy. Bone marrow transplantation has produced only limited success. Although it is expected to yield better results when performed at the presymptomatic stage, further clinical trials are needed to establish its value. Multiple sulfatase deficiency is expected to respond to enzyme replacement therapy.

KEY CLINICAL QUESTIONS

- Does your toddler present a visuomotor impairment and complain of abdominal pain? Eyeglasses fail to correct the alternating esotropia and funduscopic exam shows optic nerve atrophy. Decreased gallbladder function is demonstrated by appropriate imaging studies.

X-linked adrenoleukodystrophy

X-linked adrenoleukodystrophy (ALD) is a peroxisomal disorder of lipid metabolism characterized by adrenal insufficiency and neurologic disturbances. Tissues and body fluids of patients with X-linked ALD contain abnormally high levels of unbranched and saturated, very long chain fatty acids, particularly hexacosanoate (C26:0). The peroxisomes are unable to form the normal co-enzyme A derivative of very long chain fatty acids. The adrenoleukodystrophy (ALD) gene has been mapped to the terminal segment of the long arm of the X chromosome (Xq28 locus). The ALD gene is closely linked to the gene for red and green color vision pigments. The ALD gene product is a peroxisomal membrane protein which belongs to the ATP-binding cassette family of transporter. It has been postulated that a deletion or point mutation in the ALD gene results in a defective transport of the peroxisomal acyl CoA synthetase to its site of activity (Ligtenberg *et al.* 1995). The incidence of X-linked ALD is 1:20 000–1:100 000.

The clinical forms of X-linked adrenoleukodystrophy have been classified according to age of onset and presenting clinical symptoms. A first group of patients presents in childhood with Addison disease without neurologic symptoms. The primary adrenal cortical insufficiency leads to skin hyperpigmentation, intermittent vomiting and fatigue. The interval between the onset of adrenal insufficiency and neurologic disability is variable. Some patients may remain neurologically intact until adulthood while others develop a childhood or adolescent cerebral ALD. Childhood cerebral ALD, the most common form of X-linked ALD, is characterized by onset between 4 and 10 years of age of an overt neurologic disability before onset of adrenal insufficiency. The classic childhood form is characterized by behavioral, intellectual, and motor changes. Hyperactivity, withdrawal, aggressive outbursts, learning difficulties, poor memory, gait disturbances, speech difficulties, poor coordination, and impaired vision and hearing are the most common presenting symptoms. Other less common neurologic symptoms include seizures, incontinence, headaches and tics. The disease runs a relentlessly progressive course lasting between 1 and 9 years. The motor examination shows signs of upper motor unit involvement with continuing progression to quadriparesis. Signs of peripheral nerve dysfunction are never prominent. Visual disturbances include homonymous hemianopia, visual agnosia, and loss of visual acuity. Optic atrophy eventually occurs in all patients. Seizures, when present, are focal or multifocal. Duration of the illness is short. Death frequently occurs within the first 15 years of life.

The adolescent cerebral ALD is characterized by onset of neurologic disability between ages 11 and 21 years. The neurologic deterioration is rapid leading to dementia, spastic quadriparesis and vegetative state months to years after onset of symptoms.

PEARLS & PERILS

Adrenoleukodystrophy

- Clinical and laboratory signs of adrenal insufficiency may precede onset of childhood cerebral X-linked adrenoleukodystrophy.
- There are no clinical signs of peripheral neuropathy in childhood X-linked adrenoleukodystrophy, and nerve conduction velocities may be normal despite pathologic involvement.
- MRI is often pathognomonic in childhood adrenoleukodystrophy. The finding of a unilateral lesion or lesions without a perilesional enhanced rim does not exclude childhood cerebral adrenoleukodystrophy.
- Except during addisonian crisis, plasma cortisol values are normal. A provocative adrenal stimulation with ACTH is usually required to demonstrate the diminished adrenal reserve.
- In X-linked adrenoleukodystrophy, the CSF may show pleocytosis and local production of immunoglobulin G.
- Until recently, the eponym, Schilder disease, was used to describe various progressive leukoencephalopathies characterized by massive, bilateral, diffuse demyelination, more prominent in the occipital regions, and displaying histologic features of multiple sclerosis (anisomorphic gliosis and perivascular inflammatory reaction). Schilder's three cases represent three different conditions: the 1912 case probably represents a subacute (or chronic) diffuse encephaloclastic disorder, a variant of multiple sclerosis; the 1913 case probably represents X-linked adrenoleukodystrophy; and the 1924 case probably a postinfectious encephalomyelitis. The three conditions are easily differentiated using appropriate laboratory studies.

Three other phenotypes of X-linked ALD are observed in the adult. These phenotypes and childhood ALD occur in the same kindred, and are considered variant forms of the same illness.

The first phenotype, observed in adult males, is adrenomyeloneuropathy. This is the second most common form of ALD. Adrenal insufficiency may begin in childhood. Some patients have hypogonadism with azoospermia and hypotestosterononemia. Predominant neurologic manifestations reflect progressive myelopathy, beginning in the third decade with resulting progressive spastic paraparesis, sensory loss for all modalities in the lower extremities, sphincter disturbances, and sexual impotence. Clinical signs of peripheral neuropathy are discrete (dysesthesia, decreased ankle jerks and, in the early stages, spinocerebellar degeneration). Visual symptoms are absent. Late manifestations include spinocerebellar ataxia, behavioral changes or intellectual deterioration. Adrenomyeloneuropathy patients usually do not have a shortened survival.

The second adult phenotype is adult cerebral ALD. These patients have no sign of spinal cord involvement and develop psychotic symptoms or focal neurologic signs from the early 20s to the 50s.

The third adult phenotype, observed in 10% of female heterozygotes, is characterized by the onset of myeloneuropathy which is usually less severe than that observed in adult males and without adrenal insufficiency. Sensory loss is not present. The prominent features are progressive spastic paraparesis, hypotonia, and urinary symptoms. Survival is not shortened.

Recent experience has shown that MRI is superior to CT scan in demonstrating central nervous system involvement in X-linked ALD. In the childhood cerebral form of ALD, MRI shows symmetric high signal areas in the parieto-occipital white matter extending to subcortical regions on T2-weighted images. Gadolinium-enhanced MRI shows accumulation of contrast material in regions undergoing demyelination (Fig. 12.5). Brain MRI may be mildly abnormal in asymptomatic or adrenal insufficient patients with biochemical evidence of ALD. In adrenomyeloneuropathy, brain MRI may demonstrate pre-chiasmatic and post-chiasmatic visual pathway abnormalities in patients who are asymptomatic. The prognostic significance of mild MRI abnormalities in asymptomatic patients remains uncertain. Magnetic resonance

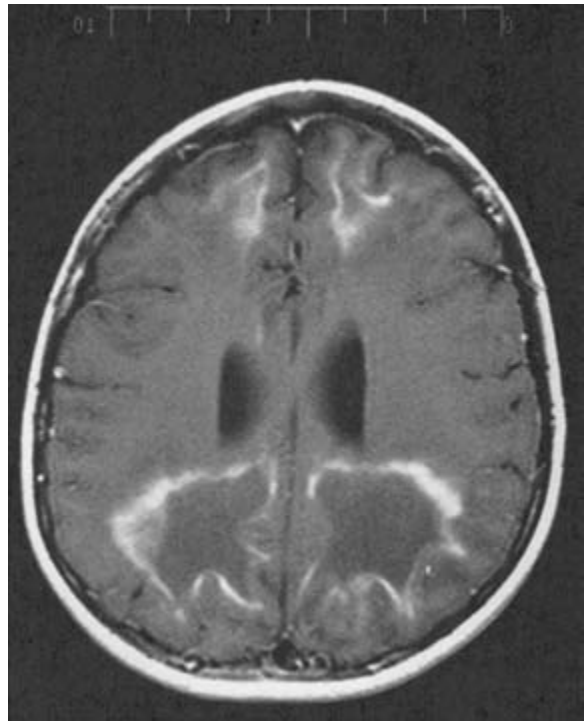

Fig. 12.5 Contast-enhanced MRI of the brain (SE 650/16) showing bilateral, symmetric low-signal inactive lesions of the subcortical white matter with typical parieto-occipital localization associated with enhancing active periphery zone of high signal in a 9-year-old boy with X-linked adrenoleukodystrophy.

spectroscopy techniques have shown, before the appearance of MRI changes, increased peaks of choline and lactate and decreased peaks of N-acetylaspartate.

Except during addisonian crisis, serum electrolyte levels and plasma cortisol values are normal. Baseline adrenocorticotropic hormone (ACTH) values may be elevated. A provocative adrenal stimulation is required in most cases to demonstrate the diminished adrenal reserve. CSF proteins are frequently elevated in the childhood form. Diagnosis of X-linked ALD is suggested by assays of very long chain fatty acids (VLCFA) in plasma, red blood cells, white cells, and cultured skin fibroblast phospholipids. Concentrations of the VLCFA, tetracosanoic (C24:0) and hexacosanoic (C26:0) acids, and the ratios of C24:0/C22:0 and C26:0/C22:0 are increased. The defects are confined to saturated VLCFA. (In neonatal ALD, both mono-unsaturated and saturated VLCFA are elevated.) Analysis of ALD gene is now possible (Ligtenberg 1995) (Tables 12.14 and 12.15).

Hormonal substitution may be necessary to correct adrenal insufficiency but this therapeutic approach does not influence the progression of the neurologic symptoms. Specific therapy for X-linked ALD is under investigation. The current dietary approach combines C26:0 restriction and a 4:1 mixture of glyceryl trioleate (GTO) and glyceryl trierutate (GTE) oils. This approach achieves normalization of plasma VLCFA but has little effect on the rate of neurologic progression. Plasmapheresis should probably be initiated early after onset of neurologic symptoms. Bone marrow transplant appears beneficial in patients with minimal neurologic involvement.

KEY CLINICAL QUESTIONS

- Does your son have intemittent vomiting and a darkening skin complexion even in unexposed skin? Addison disease should be suspected.

Krabbe disease

Krabbe globoid cell leukodystrophy, or galactosylceramide lipidosis, is an autosomal recessive lysosomal storage disease resulting from a defect in the catabolism of a sphingolipid galactocerebroside (or galactosylceramide). This lipid is exclusively a constituent of myelin and thus accumulates in Schwann cells and oligodendrocytes. Globoid cells, containing membrane-bound dense linear or curved tubular profiles, are pathognomonic in central nervous system but are not seen in the peripheral nervous system. The characteristic metabolic defect in various forms of Krabbe disease is a deficiency in galactocerebroside ß-galactosidase which is involved in the catabolism of galactocerebroside. The structural gene responsible for synthesis of galactocerebroside ß-galactosidase has been localized on chromosome 14. It has been

FEATURES

Table 12.14 X-Linked Adrenoleukodystrophy (Childhood)

Discriminating features

1. Peroxisomal lignoceroyl-CoA ligase deficiency
2. ALD gene mutations

Consistent features

1. Male
2. Adrenal insufficiency (clinical or subclinical)
3. Higher cortical function
4. Visual impairment with optic atrophy
5. Abnormal gait with pyramidal tract signs
6. Elevation of very long chain fatty acids in plasma and cultured fibroblasts
7. MRI of brain shows occipito-parietal white matter disease with perilesional enhancement

Variable features

1. CSF pleocytosis; intrathecal production of gamma-globulins
2. Elevated CSF protein
3. Skin hyper-pigmentation
4. Seizures
5. Incontinence
6. Ataxia

FEATURES

Table 12.15 X-Linked Adrenomyeloneuropathy (Adulthood)

Discriminating features

1. Peroxisomal lignoceroyl-CoA ligase deficiency
2. ALD gene mutations

Consistent features

1. Male (occasional female)
2. Spastic paraparesis
3. Distal polyneuropathy
4. Adrenal insufficiency
5. Elevation of very long chain fatty acids in plasma and cultured fibroblasts

Variable features

1. Skin hyper-pigmentation
2. Hypogonadism
3. Sphincter disturbances
4. Behavior changes
5. Dementia
6. Cerebellar
7. Focal central syndromes
8. Psychosis

PEARLS & PERILS

- The head circumference is usually normal in Krabbe disease, although hydrocephalus may occur.
- There is no visceromegaly and no cherry-red spot.
- Peripheral neuropathy and elevation of CSF protein are constant findings in infantile Krabbe disease. Those findings need not be present for the diagnosis of late-onset Krabbe disease.
- Galactocerebroside-ß-galactosidase should always be assayed with natural substrates.

shown by somatic cell hybridization studies that the classic and late-onset forms of Krabbe disease are allelic. A saposin A deficiency is suspected to be responsible for some cases of Krabbe syndrome with near normal GALC activity.

In Sweden, the incidence is about two cases per 100 000 births. In a large Druze isolate in Israel, incidence has been found to be as high as 6 in 1000 births.

Krabbe disease has been divided into two clinical subgroups according to age of onset of neurologic symptoms. Most cases are of the infantile form. The clinical onset of the disease usually occurs between 3 and 6 months of life, although a few cases with earlier (neonatal variant) or later onset have been reported. Usually, during the first months of life, the infants have a normal development. From the onset, the course of disease is steadily progressive and can be divided into three stages. Stage I is characterized by intermittent fever, hyperirritability, feeding difficulties and stimulus-sensitive, tonic extensor spasms. At the same time, stagnation in motor and mental development is noted. Seizures may occur. In stage II, rapid and severe motor and mental deterioration develops. There is marked hypertonicity with opisthotonus, scissoring of the legs, flexion of the arms, and clenching of the fists. Deep tendon reflexes are hyperactive. Optic atrophy is common, and pupillary response to light may be compromised. There are no cherry-red spots. The child remains small and may display macrocephaly. There is no visceromegaly. Various seizures (irregular myoclonic seizures, infantile spasms, major tonic–clonic seizures) frequently occur. Stage III is the "burn-out" stage. The infant is decerebrate and has no contact with the surroundings. Deep tendon reflexes are depressed. Most patients die of an intercurrent infection or bulbar paralysis before 2 years of age, although a protracted course has been observed in rare cases.

The second clinical subgroup is late-onset Krabbe disease. In most patients, the clinical manifestations appear between the ages of 2 and 6 years, although later onset has been described. The most common presenting complaint is rapidly failing vision, together with gait difficulties. The failure of vision is caused by cortical blindness with optic atrophy. Gait difficulties may be caused by hemiparesis, paraparesis, progressive cerebellar ataxia, or acute polyneuropathy. Rare individuals may first present at school age with dementia or psychotic traits. Despite the variable presentation of the disease, the clinical picture progressively becomes more uniform and is dominated by dementia, cortical blindness with optic atrophy, and spastic quadriparesis. Death usually occurs 1–3 years from the onset of symptoms, although a protracted course also occurs.

CT scan of the head early in the course of infantile Krabbe disease may be normal. Later, nonenhanced CT scan may show high signal lesions in the thalami, body of caudate nuclei, corona radiata, and cerebellum. Low attenuation in the periventricular white matter appears in the intermediate stage and in the third stage cerebral atrophy involves both gray matter and white matter. Hydrocephalus may be an additional finding. In late-onset Krabbe disease, CT of the head shows nonspecific enlargement of the lateral ventricles and low attenuation around the frontal horns. An enhancing rim may be observed between the demyelinated white matter and unaffected arcuate fibers. MRI in infantile Krabbe disease may show, on T2-weighted images, symmetric high-signal lesions in the white matter of the centrum semiovale and low-signal lesions in the thalamus and brainstem. At later stages, atrophy can been seen (Fig. 12.6). In late-onset Krabbe disease, symmetric confluent hyperintense lesions

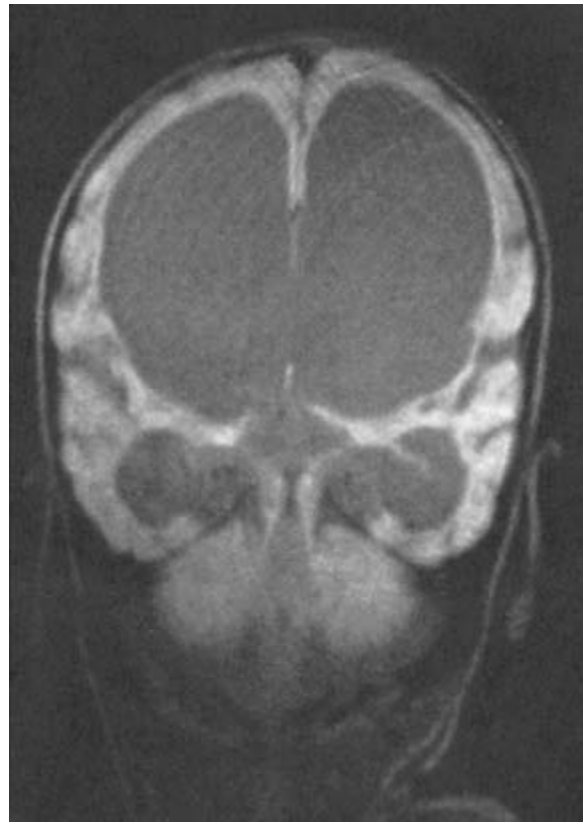

Fig. 12.6 MRI of the brain (SE 1585/40) showing hydrocephalus *ex vacuo* in a 6-year-old boy with stage III Krabbe disease.

in the peritrigonal region are associated with atrophy of the splenium of the corpus callosum. Small hyperintensity lesions can also be seen in the posterior limb of the internal capsule. There is no rim enhancement with gadolinium DTPA in late-onset Krabbe's disease.

In the first stage of infantile Krabbe disease, the CSF protein is already elevated. The electrophoretic pattern may be diagnostically helpful in that albumin and α2-globulin levels are elevated and ß1- and gamma-globulin levels are decreased. This pattern persists throughout the course of the disease. Assays of galactoceroside ß-galactosidase in white cells, serum, or cultured fibroblasts with the use of appropriate natural glycolipid substrates provide the means for antemortem diagnosis. When the enzyme ß-galactosidase is assayed with synthetic substrates, no deficiency is found. This differentiates Krabbe disease from GM_1 gangliosidosis, in which galactocerebroside ß-galactosidase activity is normal, but ß-galactosidase assayed with synthetic substrates is deficient (Table 12.16). Deficiency of galactocerebroside ß-galactosidase may be equally severe in both infantile and late-onset cases, although considerable residual activity is sometimes found in late-onset form. Prenatal diagnosis of Krabbe disease may be achieved on amniotic or chorionic cells. In heterozygotes, intermediate levels of galactocerebroside ß-galactosidase are found in serum, white cells, and cultured fibroblasts.

Treatment at this time is limited to allogenic hematopoietic stem cell transplantation that appears to slow the progression of the disease and improve magnetic resonance images. Studies using stem cells and viral vectors to transduce transplantable cells are under way (Krivit *et al*. 1999).

FEATURES

Table 12.16 Krabbe Globoid Cell Leukodystrophy

Discriminating features

1. Galactocerebroside-ß-galactosidase deficiency in leukocytes and fibroblasts
2. Globoid cells in white matter (brain biopsy)

Consistent features

1. Increased CSF proteins
2. Abnormal electrophoretic pattern of CSF proteins
3. Extensor toe signs

Variable features

1. Spasticity
2. Psychomotor retardation
3. Irritability
4. Spasticity, hyperextension
5. Hyperreflexia (early) and hyporeflexia (late)
6. Blindness (with optic atrophy)
7. Deafness
8. Failure to thrive
9. Macrocephaly
10. Ataxia
11. Focal motor deficits

KEY CLINICAL QUESTIONS

- Did your infant present an increased irritability with sudden episodes of posturing in response to minor stimuli with arching of the back, extension of the lower extremities, flexion of the upper extremities and fisting? The exam fails to show organomegaly.

Spongy degeneration of the central nervous system or Canavan–Van Bogaert–Bertrand disease

Spongy degeneration of the central nervous system or Canavan–Van Bogaert disease is an autosomal recessive leukoencephalopathy characterized by megalencephaly, axial hypotonia, peripheral spasticity, and optic atrophy. The peripheral myelin is spared. The spongy appearance of the brain results from excessive fluid accumulation in astrocytes. The biochemical basis of Canavan–Van Bogaert disease is a deficiency in aspartoacylase, an enzyme playing a role in central myelin synthesis. The human aspartoacylase locus has been mapped to the short arm of chromosome 17 and the gene cloned. Molecular genetics have revealed several specific point mutations in patients with Canavan disease (Kaul *et al*. 1994). Canavan–Van Bogaert disease is more prevalent among people of Ashkenazi Jewish descent but can also occur in other ethnic groups. The incidence of Canavan disease in the Jewish population is expected to be 1:5000 births.

Three forms of Canavan–Van Bogaert disease have been described. The infantile form is the most common. Visual attentiveness and smiling are usually noted during early development. An increasing head circumference crossing percentile lines and not explained by hydrocephalus is frequently the first clinical sign. Between 2 and 4 months of age, decreased motor activity, hypotonia, and poor head control are noted. Clinical course is variable. Deterioration is frequently rapid leading to axial hypotonia and peripheral spasticity. Some hyperreactivity is precipitated by auditory, visual, and tactile stimuli. Severe spasticity with pseudobulbar palsy and visual loss is seen in the terminal stage. Optic atrophy is demonstrated by funduscopic exam. Seizures, usually generalized tonic–clonic type, occur in about 50% of patients. Death usually occurs in the first decade from aspiration pneumonia. The congenital form is characterized by macrocephaly at birth, and severe hypotonia leading to death shortly after birth. The juvenile form is characterized by slower progression of symptoms and normal head size. Gross and fine motor development are slightly delayed. Dysarthria is frequently noted. The disorder is characterized by

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- Symmetrical areas of putaminal hypodensities can be seen in head CT scan in some cases before the appearance of subcortical leukodystrophy.
- A spongy degeneration similar to that seen in Canavan–Van Bogaert disease may be seen in some amino acidopathies (i.e. Maple syrup disease, phenylketonuria, nonketotic hyperglycinemia, arginosuccinic aciduria), organic aciduria (i.e. 3-hydroxy-methylglutaryl-CoA-lyase deficiency), mitochondrial disorders (i.e. Kearns–Sayre syndrome), infections (i.e. Creutzfeld-Jakob disease), and intoxications (i.e. triethyltin). These conditions are easily distinguishable from Canavan–Bogaert–Bertrand disease on clinical and pathological grounds.
- Macrocephaly, a characteristic feature of Canavan disease, can also be found in Alexander disease, metachromatic leukodystrophy, Krabbe disease (some cases), glutaric acidemia type I, Tay–Sachs disease (late), mucopolysaccharidosis, and disorders of glycoprotein metabolism.
- The proton MR spectroscopy shows high levels of N acetylaspartate (NAA) in the white matter. High NAA levels are also seen in patients with Salla disease, an inherited lysosomal disorder characterized by accumulation of sialic acid and in Pelizaeus–Merzbacher disease (Takanashi *et al*. 2002).

a progressive cerebellar syndrome and mental deterioration followed by generalized spasticity, seizures and visual loss. Death occurs in late adolescence.

Diagnosis is suggested by neuroimaging which shows symmetrical subcortical white matter changes (Table 12.17). Symmetric involvement of the striatum may precede appearance of white matter changes. Later in the course of the illness, diffuse atrophy is found. Nerve conduction studies and electromyogram are normal. Somatosensory, visual and brainstem auditory evoked potentials are abnormal. Spinal fluid frequently reveals elevation of CSF proteins. High concentrations of N-acetylaspartate (NAA) are found in plasma, urine and cerebrospinal fluid, analyzed by gas chromatography-mass spectrometry. Proton magnetic resonance spectroscopy of the brain white matter shows very high levels of NAA relative to other metabolites such as creatine, phosphocreatinine and choline. Aspartoacylase activity in fibroblasts of individuals with Canavan–Van Bogaert disease is absent or reduced. DNA analysis can be carried out on blood from the proband and the parents. Prenatal diagnosis combines measurements of NAA with DNA analysis. Gene therapy using a virus-based gene transfer is under investigation. Acetate supplementation may have therapeutic benefits (Kirmani *et al*. 2002). Symptomatic support includes nutritional therapy and generous use of antiepileptic drugs and antibiotics.

FEATURES

Table 12.17 Canavan–Van Bogaert Disease

Discriminating features

1. Urinary excretion of large amounts of N-acetylaspartic acid
2. High N-acetylaspartic acid signal by proton magnetic resonance spectroscopy
3. Aspartoacylase deficiency in skin fibroblasts
4. Mutations of aspartoacylase gene on chromosome 17

Consistent features

1. Macrocephaly
2. Hypotonia progressing to spasticity
3. Lack of peripheral neuropathy

Variable features

1. Generalized seizures (late)
2. Dysphagia
3. Optic atrophy
4. Leukodystrophy on neuroimaging
5. Dystonia

KEY CLINICAL QUESTIONS

- Is there any Ashkenazi Jewish ancestry or are the parents of the child closely related? The diagnosis of Canavan disease should be considered if the disease presents in early infancy with poor head control, early hypotonia and a progressive head enlargement.

Pelizaeus–Merzbacher disease

Pelizaeus–Merzbacher disease (PMD) is a slowly progressive X-linked orthochromatic leukodystrophy sparing the peripheral nervous system. Oligodendrocytes fail to deposit myelin due to decreased production of its chief protein, proteolipid protein (PLP). The PLP gene has been mapped to the human chromosome Xq22 region. In about 30% of patients, who present with a connatal phenotype of PMD, there is a point mutation in the coding portion (exons) of the PLP gene resulting in the apoptosis of maturing oligodendrocytes. In patients with classic PMD, duplications of genomic fragments containing the entire PLP gene as well as deletions or specific point mutations in one of several exons result in an abnormal myelin compaction without oligodendrocyte death. Mutations of the extraexonic PLP gene sequences or of another unknown nearby gene could be involved in rare families (Boespflug-Tanguy *et al*. 1994). PLP mutations have also been associated with X-linked spastic paraplegia 2, an allelic disorder with progressive spasticity and weakness in the lower extremities.

Clinical PMD is characterized by onset in infancy or early childhood of abnormal eye movements (slow irregular, roving eye movements interspersed with occasional rotating

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Pelizaeus–Merzbacher Disease

- Early onset stridor in association with abnormal eye movements in a newborn infant should suggest the possibility of connatal PMD.
- Some individuals affected with PMD may present with clinical and electromyographic features suggestive of neonatal spinal muscular atrophy.
- Recurrence of an apparent athetoid cerebral palsy in several males of a family following a maternal lineage should raise the suspicion for PMD. In some families an occasional female is found to have the disease (Hodes *et al.* 1993).
- In some patients, feeding difficulties and failure to thrive are so severe that child neglect may be mistakenly suspected.

searching motions) coexisting with head nodding reminiscent of spasmus nutans. The infants are usually floppy early on and have significant psychomotor delay. Most patients never learn to sit, stand or walk. As the child matures, bilateral pyramidal tract signs, athetosis, choreiform movements, facial grimacing, ataxia, intention tremor, recurrent vomiting, and feeding difficulties become apparent. Speech, when present, is slow. Optic atrophy is a frequent but not early feature of the disease and is usually recognized by 6 years of age. Some patients have seizures of the generalized tonic–clonic, partial motor, or myoclonic type. The disease often progresses to cause death in childhood or adolescence, although there are patients who survived until the sixth decade.

The onset of the disease in the first 3 months of life has been reported by several investigators and is referred to as the connatal variant. Laryngeal stridor due to floppy vocal cords has been observed in these patients. Optic atrophy can be identified early. Some individuals may present with clinical features suggestive of neonatal spinal muscular atrophy (Kayre *et al*. 1994). The connatal form has a severe course leading to death in infancy or childhood. X-linked spastic paraplegia type II, resulting from a point mutation in the PLP gene, may have its onset between toddler year and early teens[3]. The disease progresses slowly without dementia. Some patients develop a dysarthria, nystagmus and ataxia in the upper extremities. Optic atrophy is sometimes seen.

Spinal fluid studies are noncontributory. Nerve conduction velocities and muscle biopsy are normal but electromyographic changes suggestive of spinal muscular atrophy may be present in infancy[2]. Abnormalities of evoked potential responses are nonspecific indicators of central white matter disease. CT scan of the head is usually normal in the early stages of the disease and nonspecific in the late stages, showing abnormalities such as diffuse atrophy. Magnetic resonance imaging of the brain in the early stages reveals symmetrical and homogenous inversion of the signals between white matter and gray matter in T_1- and T_2-weighted images (Table 12.18). The amount of white matter is decreased and corpus callosum is thin (Fig. 12.7). Definite diagnosis is established by mutation analysis.

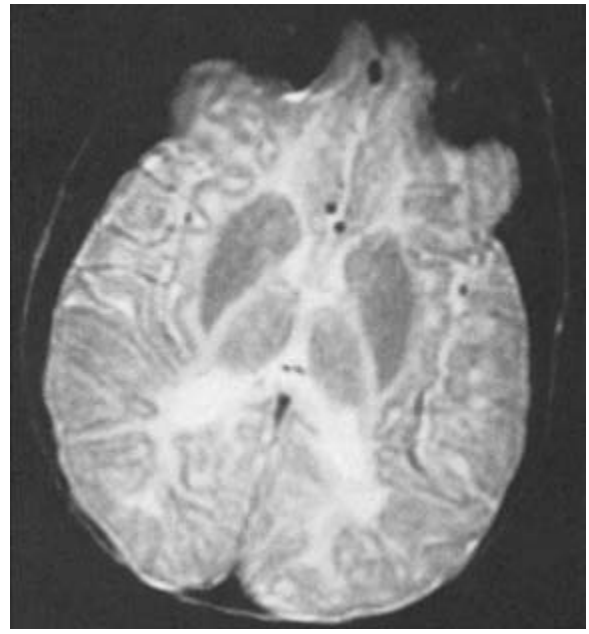

Fig. 12.7 MRI of the brain (SE 200/90) showing paucity of white matter in a 2-year-old boy with Pelizaeus–Merzbacher disease.

FEATURES

Table 12.18 Pelizaeus-Merzbacher Disease (PMD)

Discriminating features

1. Mutation in the PLP gene
2. Symmetrical and homogeneous inversion of the myelin signal on MRI of brain

Consistent features

1. Abnormal eye movements
2. Oscillatory motions of the head
3. Psychomotor deterioration
4. Male (rarely female)
5. Normal nerve conduction velocities

Variable features

1. Stridor
2. Optic atrophy
3. Bilateral pyramidal tract signs
4. Choreoathetosis
5. Vomiting
6. Ataxia
7. Seizures
8. Muscle atrophy
9. Spastic paraplegia

KEY CLINICAL QUESTIONS

- Do you know of another boy, on the maternal side of the family, who presented in infancy with abnormal eye movements, head shaking and feeding difficulties? The disease is slowly progressive with early hypotonia and involuntary movements.

Neuropathological examination may reveal cerebral and cerebellar atrophy and poor demarcation between gray and white matter. Amidst widespread dysmyelination, perivascular islets of myelin are frequently spared, a characteristic of Pelizaeus–Merzbacher disease also found in Cockayne syndrome. In the connatal form, there is a complete absence of myelin sheaths. Nerve cells and axons tend to be preserved. No involvement of the peripheral nerves is found.

Treatment of Pelizaeus–Merzbacher disease is symptomatic.

Alexander disease

This degenerative disorder is a primary genetic disorder of astrocytes, characterized pathologically by the presence in astrocytes of cytoplasmic eosinophilic hyaline bodies, called Rosenthal fibers. Rosenthal fibers result from overproduction of the glial fibrillary acid protein GFAP, an intermediate filament protein. Alexander disease has been shown to result from multiple mutations in the GFAP gene on chromosome 17 (Brenner *et al.* 2002). In all patients, the GFAP mutations are dominant. The parents are usually normal, and the disorder arises *de novo* from a spontaneous dominant heterozygous mutation or from germinal mosaicism in cases with early onset. In adults, milder mutations are autosomal dominant (Rodriguez *et al.* 2001).

Clinically one distinguishes three forms depending on age of onset. The rare neonatal form is characterized by early, often intractable, multifocal seizures, hydrocephalus due to aqueductal stenosis by the propagation of astrocytes containing excessive amounts of eosinophilic cytoplasmic material, lack of developmental maturation, and elevated CSF protein content (Springer *et al.* 2000).

PEARLS & PERILS

- Peripheral nerves sparing and macrocephaly are typical features of Alexander disease. These features are not specific as they are also seen in Canavan disease.

The most frequent form of Alexander syndrome is the infantile form, which has an average onset at 6 months of age. However, onset may occur at any time from shortly before birth to as late as 2 years of age. The average duration of disease is 2–3 years, but it can vary from a few months to several years. Predominant psychomotor retardation exists initially, and progressive spasticity and seizures develop in the context of megalencephaly, with or without frank hydrocephalus.

In the juvenile form, which is much less common than the infantile form, onset usually occurs between 7 and 14 years of age, and the duration is approximately 8 years. Bulbar and pseudobulbar dysfunction predominates, with dysphagia, dysarthria, nystagmus, ptosis, full facial palsy, and tongue atrophy (Seil *et al.* 1968). Generalized spasticity and weakness may also occur, but unlike the severe mental retardation characteristic of the infantile form, mentation tends to remain intact. The adult form of Alexander syndrome has an early stuttering clinical course mimicking multiple sclerosis and characterized by blurred vision, pyramidal tract signs, cerebellar signs, dysarthria, and dysphagia. Other reported neurologic manifestations include severe atrophy of medulla and spinal cord atrophy and palatal and ocular myoclonus (Martidis *et al.* 1999).

CT changes include low attenuation in the deep cerebral white matter, most extensively in the frontal lobes and subependymal regions. The ventricles are variably enlarged. There is inconsistent abnormal enhancement of the caudate nuclei, anterior columns of the fornix, optic radiations, and periventricular areas. MRI reveals bilateral and symmetrical white matter changes most prominent frontally. Cystic cavitation may be seen within the white matter.

Since the types of Alexander disease are phenotypically distinct, the differential diagnosis varies by age. If one encounters an infant with chronically developing megalencephaly or macrocephaly with mild regression in psychomotor milestones in the absence of any other obvious cause, Alexander syndrome is a highly probable diagnosis. Juvenile leukoencephalopathy must be considered in children and multiple sclerosis in adults. Diagnosis is suggested by the demonstration of Rosenthal fibers in subpial zone, around the blood vessels and along the ventricles in brain biopsy or at autopsy. DNA analysis of the GFAP gene confirms the diagnosis (Table 12.19).

No specific therapy is available for Alexander syndrome. Much supportive care, however, is necessary, including good nutrition and generous use of antibiotics and antiepileptics. Despite these measures, the prognosis for infants and chil-

KEY CLINICAL QUESTIONS

- Is the developmental regression accompanied by a rapid head growth?

FEATURES

Table 12.19 Alexander Disease

Discriminating features

1. Mutation in the GFAP gene

Consistent features

1. Rosenthal fibers on brain biopsy
2. Large head
3. Psychomotor deterioration
4. Normal nerve conduction velocities

Variable features

1. Nystagmus
2. Bilateral pyramidal tract signs
3. Dysphagia
4. Dysarthria
5. Seizures
6. Muscle atrophy

dren with this disease at present is poor. Recent advances in positron emission tomography (PET) scanning and single-photon emission computed tomography (SPECT) indicate that there is an abnormal flow of spinal fluid through the blood-brain barrier.

TABLE 12.20

Causes of Progressive Corencephalopathies

First year of life
Phenylketonuria due to biopterin synthesis or recycling deficiencies (Naylor *et al.* 1987; Scriver *et al.* 1987)
Pelizaeus–Merzbacher syndrome
Leigh's syndrome
Aromatic L-amino acid decarboxylase deficiency (Hyland *et al.* 1988)
Early childhood (1–5 years)
Glutaric aciduria type I
Lesch-Nyhan syndrome
Ataxia telangiectasia
Rett syndrome
Leigh syndrome
Late childhood or juvenile (>5 years)
Segawa disease
Wilson's disease
Dystonia musculorum deformans
Huntington disease
Neurodegeneration with Brain Iron Accumulation (NBIA)
Leigh syndrome
Folate and cobalamin homeostasis defects

Corencephalopathies

The progressive corencephalopathies are characterized clinically by progressive, and sometimes intermittent, extrapyramidal signs such as dystonia, dyskinesia, choreoathetosis, and parkinsonism. Progressive corencephalopathies are insidious and inherited. They differ from acute corencephalopathies which are usually acquired and nonprogressive (i.e. opsoclonus myoclonus, Sydenham chorea, hyperthyroidism, kernicterus, methemoglobinemia, hypoparathyroidism, and tardive dyskinesia (each discussed elsewhere). The age of onset of progressive corencephalopathies depends on etiology (Table 12.20). The discussion in this section will be limited to Rett syndrome, ataxia telangiectasia, Leigh syndrome and Wilson disease.

Rett syndrome

Rett syndrome is a virtually female-limited, X-linked dominant disorder characterized by a catastrophic loss of language, social and voluntary hand function with stereotyped hand-washing movements, following normal development for 5–18 months. The mapping of Rett gene to human Xq28 led to the discovery that mutations in the methyl-CpG-binding protein 2 gene (MECP2), a widely expressed transcriptional repressor with affinity for a subset of methylated genes, cause Rett syndrome (Amir 1999). Rett syndrome is the most common cause of severe mental impairment in females with a prevalence of 1 per 10 000 females. Rett syndrome is almost always sporadic, originating on the paternal chromosome. Only 1% of Rett cases are familial, originating in a female carrier suffering only from learning disability. MECP2 mutations have been identified in 80% of sporadic cases and 50% of familial cases. The same MECP2 mutations that produce the classic Rett syndrome in females lead to a severe neonatal encephalopathy with hypotonia, apnea, seizures and early death in the affected males unless the mutations are mitigated by partial or complete Klinefelter karyotype or by a somatic mosaicism, in which cases males present a classic Rett syndrome phenotype. Some other MECP2 point mutations are asymptomatic in females while males may present a nonspecific X-linked mental retardation phenotype (Shahbazian & Zhogbi 2002).

Rett syndrome exists in a classic form and in variant forms. In its classical form, birth and early development are normal. Four clinical stages have been suggested by Hagberg. Stage I, a phase of stagnation, is characterized by the appearance of early signs in infancy (5–18 months of age). Hypotonia with increased joint mobility is a frequent early symptom. Subtle abnormal signs such as facial grimacing, increased movements of the hands and tongue, locomotion changes (refusal to put feet to the ground), and equilibrium delay (lack of parachute response) are frequently noted. Head size fails to increase normally. Most girls learn to walk and say a few words. Stage II, a phase of regression, is characterized

PEARLS & PERILS

- The diagnosis of Rett syndrome is excluded if microcephaly is present at birth, if there is an obvious brain dysfunction in early infancy, or if the patient is a male.
- In both infantile autism and Rett syndrome, interaction with social environment is poor; smiling and laughing may occur without apparent reason and stereotypic movements are found. In infantile autism, elaborate actions and behaviors are possible. Rett syndrome is differentiated from infantile autism by the developmental history, the presence of acquired microcephaly, a specific constellation of neurological signs, the inability to organize purposeful activities, and the poverty of the stereotypies.
- In both Rett syndrome and NCL (i.e. infantile atypical type), hand stereotypes and loss of hand use may be present. In Rett syndrome, retinopathy and ultrastructural changes pathognomic of neuronal ceroid-lipofuscinosis are absent.
- Some children with Rett syndrome may have wounds on their hands or fingers. In contrast with Lesh-Nyhan syndrome where the lesions result from self-injurious activity, those seen in Rett syndrome result from long-lasting wetting of the hands.
- In both Rett syndrome and tuberous sclerosis, stereotyped hand movements, severe mental retardation and seizures suggestive of Lennox–Gestaut syndrome may occur. Diagnosis of tuberous sclerosis is suggested by depigmented skin lesions, normal head circumference, and tuberous lesions on CT scan or MRI of brain.
- In both Rett syndrome and happy puppet syndrome of Angelmann, unmotivated laughing, jerking, apraxic gait and limb movements and microcephaly are reported. However, stereotypic hand movements characteristic of Rett syndrome do not occur in Angelmann syndrome. Angelmann syndrome is nonprogressive.
- Fragile-X syndrome may be misdiagnosed as Rett syndrome when stereotypic hand movements, poor eye contact, and poor social interaction occur. A large head and a relatively long face with prominent ears and jaw should suggest diagnosis of Fragile-X syndrome.

by loss of acquired hand skills and speech, fluctuating attention, and appearance of intense involuntary movements (between 13 and 36 months of age). Involuntary movements are particularly prominent following emotional stimuli. Excessive flapping, wringing and patting movements are intermingled with choreiform movement and dystonic postures. Hand mouthing, tongue pulling, teeth grinding (back teeth), squinting, and jerky trunk movement increase in intensity. Emotional withdrawal is accompanied by diminished eye contact. Time spent in handling objects decreases markedly. Hands and feet remain small and cold. Gait is apraxic.

The girls look apprehensive when change of position is involved. Irregular breathing is frequently noted during wakefulness. Sleep difficulties with inappropriate laughter or screaming develop. Appetite is increased with good swallowing but decreased chewing. Seizures usually start at the end of stage II. Complex partial, atypical absence, generalized tonic–clonic, atonic, or myoclonic seizures occur in 70–80% of the patients. Stage III, or pseudostationary phase, is characterized by some resemblance of reawakening. Patients may become more communicative again and regain some of their gross motor skills. Single words can be uttered in the right context when the girls are highly motivated. However, their previous range of speech is never regained. Girls may learn eye pointing to communicate their preferences. Some girls demonstrate bloating due to extreme air swallowing. Vomiting and constipation are common. Weight loss may be extreme. With increasing age, neurogenic scoliosis, and peroneal muscular atrophy become more severe. Stage IV, or late motor deterioration, is characterized by a progressive spasticity and scoliosis leading to loss of ambulation between 4 and 31 years of age. Survival may extend past the third decade. The main causes of death are cardiorespiratory arrest and acute peritonitis.

Four Rett variant phenotypes have been described. The most common is the form fruste Rett variant. These patients fulfill most criteria for Rett syndrome but head size may be normal and some finger skills or some speech may be preserved. The early seizure onset variant of Rett syndrome is the next most common variant. In these patients, the early onset of seizures blurs the phenotypes throughout stages I to III. Congenital Rett variant is characterized by slow development in the first months of life. Late childhood regression variant is characterized by normal head circumference and gradual loss of acquired speech and fine motor skills in late childhood.

The brain may show a number of abnormalities, none of which is diagnostic of Rett syndrome. The electroencephalogram becomes progressively abnormal. During stage II, repetitive high-amplitude spike and slow wave discharges (focal, multifocal or generalized) are seen consistently during sleep. Other epileptic discharges are also present in many cases. In stage III, the epileptic discharges are less frequent, and the normal EEG morphology of sleep disappears. Bursts of irregular delta waves appear against a flat background. In stage IV, seizure activity may persist and slowing of the cortical background is found during wakefulness. Sensory evoked potentials in advanced Rett syndrome indicate involvement of the dorsal calcum and spinothalamic tracts. Investigation may show peripheral neuropathy in advanced cases. Brain weight is decreased 10–15% with greater loss of gray matter in comparison to white matter, and reduced volume of the caudate nucleus and midbrain

KEY CLINICAL QUESTIONS

- Did you have to hold the hands of your baby to take baby picture because she was constantly bringing the hands to the mouth instead of reaching for objects? Classically, stereotypic movements of the hands, bruxism, motor apraxia, dystonic posturing and cognitive regression appear later.

(Russ *et al.* 1993). Single photon emission computed tomography has indicated a frontal lobe and brainstem hypoperfusion. Metabolic studies have been consistently normal although a disturbance of mitochondrial phosphorylation can be found (Dott *et al.* 1993; Matsuishi *et al.* 1994). Electron microscopy of pyramidal neurons from the frontal cortex have shown large-appearing mitochondria, abundant ribosomal content, and some lipofuscin granules (Cornford *et al.* 1994) (Table 12.21).

The treatment remains symptomatic. Physical, occupational, and other therapy maintain and maximize function of girls with Rett syndrome. Drugs like L-dopa and haloperidol have no effect or may increase stereotyped hand movements and screaming. L-carnitine appears effective in improving social interaction in a girl with advanced Rett syndrome (Pliophys & Kasnicka 1993). Surgical inventions which may be lifesaving in selected patients include gastrostomy and spinal fusion. Sympathectomy may improve peripheral circulation.

FEATURES

Table 12.21 Classic Rett Syndrome

Discriminating feature

1 MECP2 mutations

Consistent features

1. Female sex
2. Normal head circumference at birth, acquired microcephaly
3. Normal early development
4. Loss of language, social and voluntary hand function with hand stereotypies
5. Bruxism
6. Small and cold feet
7. Late failure to thrive
8. Progressive dystonia, scoliosis

Variable features

1. Bloating, vomiting, constipation
2. Seizures
3. Overbreathing with stimulation
5. EEG abnormalities
6. Peripheral neuropathy of later onset

Subacute necrotizing encephalomyelopathy of Leigh

Subacute necrotizing encephalomyelopathy (SNE) of Leigh is an inherited neurodegenerative syndrome with an episodic or chronic clinical course characterized by ataxia, involuntary movements, hypotonia, and brainstem dysfunction. Several different defects of pyruvate and mitochondrial oxidative metabolism have been reported in association with Leigh syndrome. Inheritance of Leigh syndrome is also heterogeneous. Leigh syndrome can result from both mendelian and mitochondrial (maternally inherited) mutations (Table 12.22). Pathologically, Leigh syndrome characteristically exhibits bilateral and symmetrical areas of demyelin-

PEARLS & PERILS

Leigh Syndrome

- Patients with Leigh syndrome who exhibit in addition dermatitis and/or stridor should be suspected of having biotinidase deficiency. In biotinidase deficiency, neurologic symptoms frequently occur in the absence of aciduria and metabolic acidosis.
- The findings of low thiamine levels in blood and CSF of patients with suspected Leigh syndrome suggests the diagnosis of beri-beri (Wyatt *et al.* 1987).
- The clinical feature that usually leads to the diagnosis of SNE is the severe and rapid onset in infancy of variable neurologic signs, among which respiratory involvement, eye findings, and cranial nerve signs are most suggestive.
- Radiolucencies in the thalamus, basal ganglia, and tegmentum of the brainstem are frequently seen in SNE. A normal CT scan does not exclude the diagnosis of SNE.
- Leigh syndrome has clinical, biochemical, and pathologic features similar to other mitochondrial encephalomyopathies.
- Familial bilateral striatal necrosis closely resembles Leigh syndrome with a relatively nonprogressive course. Familial bilateral striatal necrosis may be maternally inherited with mitochondrial DNA point mutations at base pairs FBSN 3308, LHON 11696, LHON 14459 and LHON 14596 which encode for subunits of the complex I (Thyagarajan *et al*. 1995).
- The Mohr-Tranebjaerg syndrome is an X-linked disorder associated with small mitochondrial DNA deletions and due to a defect in TIMMSA gene encoding the deafness-dystonia protein (DDP-1), a component of the mitochondrial-protein-import machinery in the intermembrane space. Patients present in early childhood with sensorineuronal hearing loss and progressive dystonia associated with spasticity, mental deterioration and cortical blindness (Roesch *et al*. 2002).

TABLE 12.22

Leigh Syndrome

Inheritance	Metabolic defect	Mutation
Autosomal recessive	Complex I	11q13 (NUDFV1)
		2q33-q34 (NDUFS1)
		5q11.1 (NDUFS4)
		19p13.2 (NDUFS7)
		11q13.1 (NDUFS8)
	Complex II	5p15 (SDH Fp/SDH2)
	Complex III	2q33–37(BCS1L)
	Complex IV	9q34 (SURF-1)
	Pyruvate carboxylase	11q13
	Biotinidase	3q25
	Pyruvate dehydrogenase (lipoamide dehydrogenase)	7q31-q3 (LAD)2
X-linked recessive	Pyruvate dehydrogenase ($E_1\alpha$ subunit)	Xq22–2q22.1 (insertions, deletions, points mutations)
Maternal (mitochondrial)	Subunit 6 of ATPase (complex V)	*NARP* 8993[8]* and *LS 9176*
	$tRNA^{LYS}$	MERRF 8344[9]*
	$tRNA^{LEU}$	MELAS 3243*
	Polypeptide ND5 or ND6 of NADH dehydrogenase (complex I)	MELAS 13513 or Leber 14459

* NARP: neuropathy ataxia and retinitis pigmentosa

* MERRF: myoclonic epilepsy and ragged-red fibers

* MELAS: mitochondrial encephalopathy lactic acidosis and stroke-like episodes

LS: Leigh syndrome

ation with vascular proliferation and neuronal sparing in the putamen and brainstem.

Clinically, three syndromes can be distinguished according to age of onset. The neonatal form presents initially with disorders of sucking and swallowing, and respiratory difficulties (i.e. Ondine's curse) (Seitz *et al.*1984). Later, other symptoms of brain stem dysfunction (aberrant eye movements, facial weakness) and severe motor delay are recorded. Death occurs early. The classic infantile form presents at an age of less than 2 years and often less than 1 year. Early psychomotor development is usually normal. The early course is usually rapid. Symptoms are made worse by intercurrent infection or a carbohydrate-rich diet. Presenting complaints may include progressive psychomotor slowing, weakness, ataxia, feeding and swallowing difficulties, vomiting, poor weight gain, decreased alertness, poor visual fixation, myoclonic jerks, or generalized convulsions (Pincus 1972). On examination, clinical features that lead to the diagnosis are respiratory involvement, eye findings, and other cranial nerve signs. Respiratory irregularities, a central hyper/hypoventilation syndrome, or central apnea are remarkable. Eye findings may include nystagmus, strabismus, profound saccadic/slowing, ptosis, ophthalmoplegia, optic atrophy, and atypical pigmentary degeneration of the retina (Sedwick *et al.* 1984). Retinal pigmentary degeneration is present in about 40% of maternally inherited Leigh syndrome (Santorelli *et al.*1994). Other cranial nerve signs may include deafness, dysphagia, and facial weakness. Less specific neurologic signs may include axial hypotonia, spasticity, dystonia, choreoathetoid movements, and varying degrees of ataxia (Campistol *et al.* 1986). Deep tendon reflexes may be increased or decreased. Some patients are unusually hirsute. Other occasional features include cardiomyopathy and the renal de Toni-Fanconi-Debré syndrome of tubular renal acidosis. Death is the final outcome, occurring often rapidly within the course of a few weeks or months. However, remissions followed by further exacerbations are sometimes seen and the child may live several years.

A rare juvenile form of the disease has also been described (Grunnet *et al.* 1991). The course of the illness is often characterized by an insidious onset in childhood, leading to neurologic defects, such as mild spastic paraparesis, ataxia, exercise intolerance, nystagmus, visual impairment, and Parkinson-like features. Children with Leigh disease are usually below normal weight and height. After a long quiescent period, the illness terminates acutely or subacutely during the second decade. The terminal stage is characterized by a rapid deterioration to coma and marked respiratory depression.

The results of electrophysiologic studies change with time and vary from patient to patient. Motor nerve conduction velocities may be slow. EEG may show a generalized slowing of background activity sometimes superimposed with epileptogenic features. Brainstem auditory evoked potentials and visual evoked potentials may be abnormal. The ERG may suggest diffuse retinal dysfunction.

Neuroradiologic investigations are particularly helpful in the diagnosis of Leigh syndrome. Cranial MRI is much more sensitive in detecting lesions than CT scan (Fig. 12.8). Hyperintensive lesions on T_2-weighted images involving symmetrically the basal ganglia and brainstem, with predominant involvement of the putamen are highly suggestive of Leigh syndrome (Table 12.23). Abnormalities of the subcortical white matter can occur.

The main biochemical findings are intermittent metabolic acidosis with elevation of lactate/pyruvate ratios in the blood and CSF. An increase in blood alanine is also frequent. The absence of metabolic acidosis between acute episodes does not exclude the diagnosis of SNE. CSF protein may be elevated. Diagnosis of biotinidase deficiency, if suspected, is established by measuring biotinidase activity in the serum included in neonatal screen in some states in the United States.

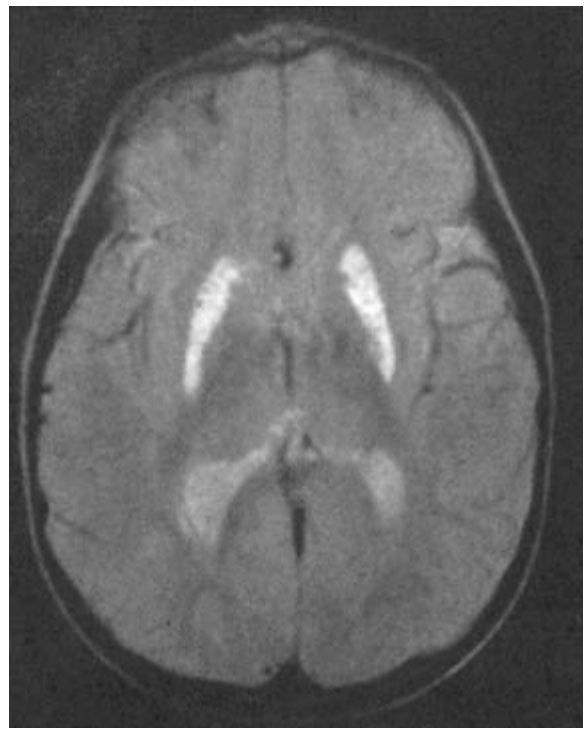

Fig. 12.8 MRI of the brain (SE 2100/100) showing increased signal in the caudate nucleus and putamen of a 5-year-old boy with autopsy-proven Leigh syndrome and cytochrome oxidase deficiency.

FEATURES

Table 12.23 Subacute Necrotizing Encephalopathy of Leigh

Discriminating feature

1. Symmetric foci of partial necrosis with associated capillary proliferation and relative sparing of neurons in putamen, brainstem, and posterior columns of spinal cord

Consistent features

1. Elevated plasma and CSF lactate and pyruvate during exacerbation
2. Symmetric hyperintense lesions of putamen and brainstem on MRI
3. No dementia

Variable features

1. Variable inheritance
2. Fulminant (intermittent) or slowly progressive course
3. Variable age of onset
4. Signs of brainstem dysfunction (respiratory, ocular motility, or swallowing disturbances)
5. Movement disorder (dystonia, myoclonus, choreoathetosis, parkinsonism)
6. Hypotonia or spasticity
7. Spasmus nutans
8. Visual impairment
9. Peripheral neuropathy with elevated CSF proteins
10. Seizures
11. Ragged-red fibers in striated muscles
12. Cardiac and renal involvement
13. Failure to thrive

Muscle and skin biopsy are often necessary to establish biochemical diagnosis. Pyruvate carboxylase and pyruvate dehydrogenase activity are best measured in tissue fibroblasts. At the time of muscle biopsy, histochemistry, electron microscopy, and oxidative phosphorylation enzymology should be performed. Ragged red fibers or striated muscles are almost never identified by light microscopy. Ultrastructural examination frequently shows discrete mitochondrial changes, such as increased size, bizarre shape, and disoriented cristae (Wyatt *et al*. 1987). Mitochondria should be immediately isolated for oxidative phosphorylation biochemistry. Deficiencies of complex I (NADH dehydrogenase), complex II (succinate dehydrogenase), complex III (cytochrome bc_1), complex IV (cytochrome oxidase) and complex V (ATP synthase) of the mitochondrial respiratory chain have been reported and several genes have been sequenced. At the time of muscle biopsy, a small portion of muscle is placed in liquid nitrogen for mitochondrial DNA testing. Muscle should be screened for the most common mitochondrial DNA point mutations (associated with NARP, MELAS and MERRF) and mitochondrial DNA depletion. If an X-linked inheritance is suspected, the PDH $E_1\alpha$ gene should be sequenced. Immunoblot techniques using anti-Surf1 antibodies are useful in detecting SURF1

KEY CLINICAL QUESTIONS

- Does the child have a history of relapsing–remitting episodes of unsteadiness, cognitive decline with floppiness, respiratory abnormalities and difficulties moving the eyes? Most children display a lactic acidosis during exacerbations.

defects in patients with Leigh's disease associated with cytochrome oxidase deficiency.

Treatment of Leigh syndrome is palliative and symptomatic as in diffuse mitochondrial encephalomyopathies. Children with Leigh syndrome due to pyruvate dehydrogenase complex deficiency can be helped by thiamine and a ketogenic diet (Di Rocco *et al*. 2000). Riboflavin may be beneficial in patients with NDUFV1 deficiency. Biotine supplementation is suggested in rare patients with biotinidase deficiency.

Wilson disease

Please refer to Chapter 9 for information on this disorder.

Ataxia telangiectasia

Ataxia telangiectasia (AT) is an autosomal recessive disorder characterized by onset in childhood of progressive neurologic symptoms, various immunologic deficiencies, premature aging, an increased frequency of cancers, endocrine abnormalities and oculocutaneous telangiectasias. These patients and heterozygotes have increased sensitivity to ionizing radiation and radiomimetic drugs (Taylor *et al*. 1975) (Table 12.24). The AT gene, localized to chromosome 11q22–23 (Gatti *et al*. 1998; Ziv *et al*. 1991), has been cloned and sequenced. The gene product, the ataxia telangiectasia mutated (ATM) protein, is related to a number of DNA-dependent protein and lipid kinases. The C-terminal region of the AT protein has strong similarities to phosphatidylinositol 3-kinase, and its N-terminal region is similar to the DNA-repair/cell-cycle-check-point gene rad3[4]. The phosphatidylinositol-3 kinase region participates in insulin-dependent glucose transport and a variety of mitogenic growth factor responses. The rad3-like region is involved in DNA repair and control of the cell cycles after irradiation, preventing damaged DNA from being reproduced. AT has a prevalence of approximately 2 per 100 000.

The clinical spectrum of AT is very wide. Neurologic symptoms are the usual presenting complaint. In severe cases, cerebellar ataxia has its onset in infancy or childhood. Ataxia is predominantly truncal with "swaying movements" of the head and trunk while sitting, walking or standing. Dysarthria usually develops simultaneously to the ataxia. Nystagmus is present on lateral gaze. Romberg sign is negative. All modalities of sensation are intact. A mild choreoathetosis frequently accompanies ataxia. Slow initiation of all voluntary movement including voluntary and involuntary saccades is characteristic of AT (Baloh *et al*. 1978) even in the earliest stages. Most patients become ambulatory and show no progression in their motor symptoms until school age. In the earliest stages, cognitive development usually remains normal. Pyramidal signs are absent.

FEATURES

Table 12.24 Ataxia-Telangiectasia

Discriminating feature

1. Defects of AT gene chromosomal instability radiosensitivity

Consistent features

1. Cerebellar atrophy
2. Elevated serum CEA and alfa-fetoprotein
3. Defects of humoral and cellular immunity
4. No pyramidal signs or symptoms

Variable features

1. Cerebellar ataxia
2. Spinocerebellar ataxia
3. Choreoathetosis
4. Spinal muscular atrophy
5. Microcephaly
6. Sinopulmonary infections
7. Malignancies
8. Early aging of skin and hair
9. Telangiectasia
10. Elevated liver enzymes

PEARLS & PERILS

Ataxia Telangiectasia

- Ataxia telangiectasia should be considered in the etiologic diagnosis of ataxic or athetoid cerebral palsy (when onset is infantile).
- Neurologic presentation is highly variable and progressive (cerebellar ataxia, spinocerebellar ataxia, spinal muscular atrophy, dystonia, choreoathetosis, and/or Parkinsonism). Abnormal voluntary eye movements are a common finding which is highly suggestive of the diagnosis.
- Slow viscous eye movements are present in most patients with ataxia-telangiectasia. Similar eye movements are seen in early-onset ataxia with oculomotor apraxia, a progressive cerebellar ataxia with peripheral axonal neuropathy lacking systemic symptoms which is caused by a deficiency in aprataxin, a protein involved in the postmitotic DNA repair (Date *et al*. 2001).
- The severity of the neurologic features is not directly related to the severity of the systemic symptoms.

In adolescence, ataxia, which was truncal earlier, involves the limbs, with incoordination and intention tremor. Myoclonic jerks, particularly on intention, may result in frequent falling and make the patient nonambulatory. Other patients with AT who have a relatively benign course and prolonged survival may present in adolescence or early adulthood with extrapyramidal involvement, spinocerebellar ataxia, or spinal muscular atrophy. The extrapyramidal signs are difficulties in initiating movements, dull, expressionless facies as in Parkinson's disease, slow eye movement, stooping posture, drooling, and seborrheic dermatitis. Smile is delayed and protracted. Rigidity is usually absent. Dystonic posturing of the fingers is frequent. In the predominant spinocerebellar form, there is diminution and even loss of position and vibratory sense. Romberg sign is positive. Plantar responses are usually flexor in contrast to Friedreich ataxia (Barbieri *et al.* 1986) (see Table 12.25).

In the predominant spinal muscular atrophy variant, patients show generalized muscle weakness with marked distal atrophy and gross fasciculations of muscles. Flexion contractures of the fingers and bilateral foot drop are present (Goodman *et al.* 1969). Spinocerebellar ataxia and spinal muscular atrophy may develop simultaneously (Rosen & Harris 1987) in AT.

Nonneurological features have a variable age of onset. Telangiectasias, which are dilations of venous capillaries, are usually evident by age 6 years. Some patients, however, lack telangiectasias (Willems *et al.* 1993). Telangiectasias are usually symmetrical, appearing initially on the bulbar conjunctiva and later on exposed areas of the skin (nasal bridge, eyelids, ears, lobes, antecubital and popliteal areas, flexor folds of the neck and mucosa of nose and mouth). Telangiectasias are frequently in the liver and, in elderly patients, in the central nervous system. They are rarely associated with hemorrhage, unlike the telangiectasias of Osler–Rendu–Weber disease. Skin and hair show premature aging (Smith & Conerey 1985). Bodily growth and sexual development are frequently retarded. There is a strong tendency to develop sinopulmonary infections and malignancies, the two leading causes of early death. Fifteen per cent of patients with AT die from malignancies, particularly lymphomas and lymphocytic leukemia. Primary carcinomas of the stomach, liver, ovary, salivary glands, oral cavity, breast, and pancreas have also been reported (Morrell *et al.* 1986).

KEY CLINICAL QUESTIONS

- Has your child been hospitalized for recurrent pneumonia and is there a family history of breast cancer? Patients with ataxia telangiectasia frequently suffer from sinopulmonary infections. In addition the ataxia telangiectasia carrier has a shortened lifespan and an elevated risk of breast cancer.

Half the patients with AT have mild elevation in liver enzymes. More than 50% of patients display glucose intolerance. The most constant biochemical markers of AT are elevated serum levels of alfa-fetoprotein (AFP) and carcinoembryonic antigen (CEA). Immunological deficiency is very common, but its pattern is highly variable. Defects in both humoral and cellular immunity have been described. About 75% of patients with AT have an absence or extreme deficiency of serum IgA and 80% manifest extreme IgE deficiency. IgG2 and IgG4 may be deficient or absent. Autoimmune phenomena are common in AT. Forty-five per cent of AT patients show one or more auto-antibodies to muscle, mitochondria, bile canaliculi, basement membrane, thyroglobulin, parietal cells, and even immunoglobulin G. Impaired function of T lymphocytes is suggested by delayed rejection of skin grafts and cutaneous anergy to delayed hypersensitivity skin testing. *In vitro*, T lymphocytes show a poor response to T-cell mitogens and a defective cytotoxic response to viral pathogens (Waldmann *et* al. 1982). T-cell levels are usually low while B-cell levels are normal or elevated. Gamma/delta T-cell levels are usually elevated. Cytogenetic abnormalities are frequently found in AT patients and include a variety of chromosomal aberrations reflecting a general "chromosomal instability." They are less frequent in young children and are not commonly observed in fibroblasts. More than 95% of patients fail to make the ATM protein as detected by immnunoblotting of cell line extracts (Becker-Catania *et al*. 2000).

Presently, no specific treatment has been found to halt the progression of the disease. Avoidance of undue exposure to sunlight is recommended. Radiologic procedures should be limited. The use of radiation therapy in conventional doses is contraindicated. Radiomimetic agents such as bleomycin, actinomycin D, and cyclophosphamide should be avoided. Immunotherapy may decrease the frequency and severity of infections. Trihexyphenidyl may improve dystonia and parkinsonism. Propranolol may improve ataxia.

Spinocerebellopathies

Spinocerebellopathies are a heterogeneous group of inherited neurologic disorders characterized by variable degrees of degeneration of the cerebellum, brainstem, and spinal cord. Peripheral nervous system may be involved. An autosomal dominant pattern of inheritance is characteristic of adult onset in spinocerebellar ataxia. An earlier childhood onset occurs in subsequent generations of dominantly inherited spinocerebellar ataxia (Zoghbi & Balladio 1995). This phenomenon known as anticipation is due to an increased number of an unstable trinucleotide repair in the affect gene. An autosomal recessive pattern of inheritance is seen in most childhood onset spinocerebellar ataxia (Table 12.25). Not every progressive spinocerebellopathy is due to a genetic defect. Nutritional, toxic, and immune causes are discussed in other chapters.

TABLE 12.25

Differential Diagnosis of Childhood Slowly Progressive Spinocerebellopathies

Type	C*	Age of onset	Ataxia	Sensory	Dtr	Babinski	Muscle	Mental	Eye	Heart	Other
IOSCA	10	Infancy	Severe	Moderate and late	Absent	+	Hypotonia	Late	Ptosis, optic atrophy, ophthalmoplegia	No	Hypogonadism athetosis, seizures, hearing loss
RL	17	Infancy	Moderate	Mild	Absent	+	Atrophy (legs)	Normal	Normal	No	Pes cavus
SLO	7	Infancy	Severe	Moderate	↓	+	Hypotonia	Abnormal	Ptosis, cataract	Congenital defects	Failure to thrive
FA	9	1st decade	Severe	Moderate	↓ in LE	+	Atrophy (legs)	Normal	Normal	Cardiomyopathy	Pes cavus
BKS	4	1st decade	Severe	Moderate	↓	+ late)	Atrophy (legs)	Normal	Degenerative retinopathy	Rare cardiomyopathy	Pes cavus
Refsum	10	1st decade	Severe	Severe	↓	+	Atrophy	Normal	Degenerative retinopathy	Hypertrophic cardiomegaly	Pes cavus, deafness, ichthyosis
AVED	8	1st or 2nd decade	Severe	Moderate	↓	+	Late atrophy	Normal	Cataract, retinopathy	Normal	Pes cavus, scoliosis
NARP	M*	1st decade or later	Mild	Mild	↑-early ↓-late	+	Proximal weakness	Deterioration	Degenerative retinopathy	No	Seizures
SCD		1st or 2nd decade	Moderate	Paresthesia	↓	+	Weakness and atrophy (legs)	Frequent deterioration	Macular changes	No	Microcephaly, seizures
CDG	16	1st decade or later	Moderate	Mild	↑-early ↓-late	+	Weakness and atrophy (legs)	Deterioration	Retinopathy, strabismus	Pericarditis, hypertrophic cardiomegaly	Skeletal deformity
AT	11	1st decade	Severe	Mild	↓-late	-	Atrophy (late)	Late deterioration	Slow eye movements	No	Telangiectasia, immune deficiency
AOA1	9	1st decade	Severe	Mild	↓-late	-	Atrophy (late)	Mild	Slow eye movements		Dystonia
MS	5	1st decade	Moderate truncal	Mild	↑-early ↓-late	+ in 50%	Atrophy (legs)	Deterioration	Cataracts (congenital)	No	Skeletal deformity, short stature
CX	2	2nd decade	Mild-early	Mild-early	↑	+	Later	Deterioration, early at times	Cataracts	Myocardial infarction	Tendon xanthomas, fractures

IOSCA: infantile onset spinocerebellar ataxia; C*: Abnormal chromosome; RL: Roussy–Levy syndrome; M*: Mitochondrial DNA; SLO: Smith–Lemli–Opitz; FA: Friedreich ataxia; BKS: Bassen–Kornzweig syndrome; AVED: Ataxia with isolated vitamin E deficiency; NARP: Neuropathy, ataxia, retinitis pigmentosa syndrome; SCD: Subacute combined degeneration; CDG: Carbohydrate deficiency glycoprotein; AT: Ataxia–telangiectasia; AOA1: Early-onset ataxia with oculomotor apraxia; MS: Marinesco–Sjögren; CX: Cerebrotendinous xanthomatosis

Spinocerebellar ataxia and vitamin E deficiency

Vitamin E deficiency is a significant cause of spinocerebellar ataxia and/or neuropathy. Most disorders causing vitamin E deficiency produce a chronic steatorrhea (Bassen–Kornzweig syndrome, hypobetalipoproteinemia, cystic fibrosis, celiac disease, intestinal lymphangiectasia, α1-antitrypsin deficiency, Wilson disease, biliary atresia and defects of bile acid synthesis). Ataxia with isolated vitamin E deficiency is not associated with steatorrhea (Table 12.26).

Bassen–Kornzweig syndrome

Bassen–Kornzweig syndrome (BKS) or abetalipoproteinemia is an autosomal recessive-inherited disorder of lipoprotein metabolism characterized by steatorrhea, hypocholesterolemia, hypotriglyceridemia, lack of all apo B-containing lipoproteins (chylomicrons, VLDL, LDL), hematologic changes, and progressive neurodegeneration with cerebellar ataxia, degenerative retinitis pigmentosa, and peripheral neuropathy. Biochemically, the disorder is caused by absence of microsomal triglyceride transfer protein (MTTP). The MTTP gene locus is on chromosome 4q24. Both point mutaions and deletions in the MTTP gene are responsible for abetalipoproteinemia (Xiao Ping *et al.* 1999; Ohashshi *et al.* 2000).

The infant with BKS is usually normal at birth. Failure to thrive and abdominal distention, along with steatorrhea, are the first symptoms in infancy. The diagnosis of cystic fibrosis and celiac diseases typically are entertained, and later excluded by laboratory tests and failure to respond to appropriate therapy. Endoscopy reveals a yellow discoloration of the duodenum and jejunal biopsy is generally pathognomonic, showing extensively vacuolated mucosal cells packed with lipid droplets. The earliest neurologic finding is the loss of deep tendon reflexes at an early age. Neurologic symptoms typically develop toward the end of the first decade of life as a spinocerebellar degenerative disorder. Position and vibratory sensation are lost, and a positive Romberg's sign typical of sensory ataxia can be elicited. Clinical evidence of pyramidal tract lesions usually appears later. Weakness and muscle atrophy are progressive. Most subjects are unable to walk by their mid-20s. Pes cavus and scoliosis are common findings. Athetosis has been observed. Some degree of mental retardation may become apparent in 20% of the patients. Behavioral and cognitive changes may occur. Degeneration of the retina may develop during infancy, but more often it occurs later. Pigmentary retinopathy is a constant finding. Reduced electroretinographic amplitudes precede visual decline. Oscillating, vertical, horizontal, and dissociated nystagmus are concomitant with the progressive loss of with vision. Ophthalmoplegia may result from both supranuclear and nuclear involvement.

Laboratory findings suggestive of BKS include a very low plasma concentration of cholesterol (<100 mg/mL) and triglycerides (<30 mg/mL), and acanthocytosis of the peripheral erythrocytes. (Acanthocytes are crenated red blood cells of normal size exhibiting spiny processes of various sizes in thick smears. Their formation is attributed to changes in the lipid composition of erythrocyte membranes.) Severe anemia may occur. Hyperoxaluria is one consequence of fat malabsorption. Vitamin E is undetected in the serum of symptomatic patients. The diagnosis of BKS depends on the confirmation of the absence of apoprotein B.

Treatment consists of providing a low fat diet, supplementing the fat-soluble vitamins A and K, and pharmacologic doses (100–200 mg/kg/day) of standard vitamin E preparations. Much smaller doses of d-alfa tocopherol polyethylene glycol-1000 succinate (15–25 mg/kg/day), a new form of vitamin E, inhibits progression of neurologic symptoms (myopathy, neuropathy, ataxia) more rapidly. Some regression of neurologic symptoms may also be seen.

Hypobetalipoproteinemia

Hypobetalipoproteinemia is an autosomal dominant-inherited disorder of lipoprotein metabolism characterized by hypocholesterolemia with low levels of LDL and with a number of mutations resulting in the synthesis of truncated apoprotein B. The apoprotein B gene locus is on chromosome 2q24.

The condition is usually asymptomatic in simple heterozygotes except for reduced levels of plasma LDL. Compound heterozygotes and homozygotes may show steatorrhea, hematologic manifestations and neurologic signs and symptoms similar to Bassen–Kornzweig syndrome (Scott *et al.* 1979). These conditions differ from abetalipoproteinemia by identification of truncated apoproteins.

FEATURES

Table 12.26 Spinocerebellar Ataxia caused by Vitamin E Deficiency

Discriminating feature

1. Vitamin E deficiency

Consistent features

1. Spinocerebellar ataxia
2. Vibratory sense loss

Variable features

1. Peripheral neuropathy
2. Decreased myotatic reflexes in LE
3. Retinopathy
4. Cataract
5. Myopathy
6. Steatorrhea
7. Weight loss, failure to thrive
8. Facial dysmorphism
9. Hepatomegaly
10. Jaundice
11. Acanthocytosis

Treatment for the homozygotes and compound heterozygotes is the same as for BKS. In simple heterozygotes, restriction of fat is initiated when malabsorption and oxalate urolithiasis is present.

Steatorrhea

Steatorrhea caused by disorders other than BKS or hypobetalipoproteinemia (i.e. cystic fibrosis, celiac disease, intestinal lymphangiectasia, biliary atresia) may result in variable neurologic symptoms, including spinocerebellar degeneration, proprioceptive loss, areflexia, weakness, delayed motor and cognitive development, ophthalmoplegia, and retinal pigmentation. The clinical progression of neurologic symptoms is variable and depends on the etiology (Table 12.27).

Vitamin E deficiency is common in unsupplemented patients with cystic fibrosis, but rarely causes a spinocerebellar degeneration (Sokol *et al.* 1989). Disorders that interfere with biliary excretion (bile acid synthesis defects (Clayton 1995), Alagille's syndrome (Alagille *et al.* 1987), Åagenes syndrome (Åagenes 1974), and peroxisomal disorders) are not only frequently complicated by steatorrhea, vitamin E deficiency, and other fat-soluble vitamin deficiencies (Rosenblum *et al.* 1981), but also may result in copper retention with subsequent lenticular degeneration (Danks 1991). Disorders of biliary excretion frequently present in infancy with pruritus.

TABLE 12.27 Causes of Vitamin E Deficiency

Chronic pancreatic insufficiency
Cystic fibrosis
Reduced intestinal bile salt concentration
Liver disease: α_1 antitrypsin deficiency
Wilson disease
Biliary atresia
Deficient bile synthesis
Smith–Lemli–Opitz syndrome
3-β hydroxy C27 steroid dehydrogenase/isomerase deficiency
3-oxo steroid 5 β-reductase deficiency
Peroxisomal disorders
Chronic intestinal mucosal absorption defects
Celiac sprue (gluten-induced enteropathy)
Short bowel syndrome
Bassen–Kornzweig disease
Hypobetalipoproteinemia
Lymphatic obstruction
Whipple disease
Intestinal lymphangiectasia
Familial isolated vitamin E deficiency

Smith–Lemli–Opitz syndrome

The Smith–Lemli–Opitz syndrome (SLOS) is an autosomal recessive disorder of cholesterol biosynthesis characterized by specific congenital anomalies, developmental retardation and failure to thrive. The patients have a low plasma cholesterol and a high 7-dehydrocholesterol level by gas chromatography. The disorder has been shown to result from a microsomal 7-dehydrocholesterol reductase deficiency (Shefer *et al.* 1994). The gene of the SLOS has been assigned and mapped to chromosome 7q32 (Wallace 1994). The incidence of this disorder has been estimated to be 1:20 000 births.

The facial features are pathognomic with microcephaly, a narrow high forehead, ptosis, cataract, low-set posteriorly rotated ears, broad anteverted nares, inner epicanthal folds, micrognathia and often alveolar ridging. Limb anomalies include polydactyly and syndactyly of the toes. Simian creases and high frequency of digital whorl patterning are common. Genital anomalies include cryptorchidism or hypospadias in males and labial hypoplasia in females. The most severely affected patients present at birth with hepatomegaly, renal cysts, adrenal enlargement, and epiphyseal dysplasia. Affected patients are usually small and hypotonic. Failure to thrive is the rule. Many patients have problems with gastrointestinal dysmotility or Hirschsprung's disease. Developmental anomalies of the central nervous system such as colpocephaly and delayed myelination are common. Most patients have significant developmental delay. Most patients who survive the first year of life become hypertonic, severely retarded and display self-injurious, aggressive, and destructive behaviors. Seizures are occasionally reported.

Treatment of SLOS consists of providing cholesterol, bile acids, and fat-soluble vitamins, except for vitamin D. Photosensitivity and polyneuropathy improve with cholesterol supplementation. In SLOS, dehydrocholesterol which is stored in the skin is rapidly converted to vitamin D_3 leading to hypervitaminosis D (Acosta 1995).

Ataxia with isolated vitamin E deficiency

Ataxia with isolated vitamin E deficiency (AVED) is an autosomal recessive neurodegenerative disease due to free radical damage and characterized by spinocerebellar ataxia with peripheral neuropathy. AVED results from a defect in liver cells of α-tocopherol transfer protein (αTTP) (Afif Hentati *et al*. 1985). The αTTP incorporates the α-tocopherol form of vitamin E into VLDL. This leads to a vitamin E deficiency which occurs in the absence of steatorrhea. The AVED locus has been mapped to chromosome 8q13 (Doerflinger *et al*. 1995).

Clinically, patients with AVED have a normal early development. Some patients develop an intention tremor, head titubation and impaired vibratory sensation in childhood

PEARLS & PERILS

- Areflexia is not present in all patients with vitamin E deficiency.
- Ophthalmoplegia may be found in fat malabsorption but is not a feature of isolated vitamin E deficiency.
- Smith–Lemli–Opitz syndrome should be distinguished from peroxisomal disorders. Very long chain fatty acids are normal in Smith–Lemli–Opitz syndrome.
- AVED differs from Friedreich ataxia by the absence of cardiomyopathy and diabetes and by the occasional presence of head titubation or dystonia.

KEY CLINICAL QUESTIONS

- Does your child have chronic diarrhea with vomiting and failure to thrive? If there is steatorrhea, AVED is unlikely. AVED should be considered in the differential diagnosis of Friedreich ataxia.

while others remain asymptomatic until adulthood. Proprioceptive loss, weakness, gait disturbances, kyphoscoliosis, and pes cavus develop later. Areflexia and dysarthria are not present in all patients[14]. An extensor plantar response is generally found in the lower extremities. Head titubation is reported in 28% of patients and dystonia is present in 13% of patients. Ophthalmoplegia is not a feature of isolated vitamin E deficiency. Visual impairment and retinitis pigmentosa have been reported in some families (Benomar *et al*. 2002).

Diagnosis of AVED is suggested by low-fasting serum vitamin E concentrations, absence of steatorrhea, normal lipoprotein electrophoresis, and normal intestinal absorption of vitamin E as demonstrated by oral vitamin E tolerance test (OVETT). An accelerated decline of serum tocopherol after the OVETT peak represents the effects of the liver clearing the circulating chylomicron remnant containing tocopherol, combined with a failure to adequately secrete tocopherol into hepatic-derived lipoproteins (Sokol *et al*. 1988). Red blood cell morphology is normal. Genetic diagnosis can now be achieved.

Treatment with 800–900 IU/day of oral DL-α-tocopherol normalizes vitamin E status and stabilizes or improves neurologic status.

Subacute combined degeneration of the spinal cord

In children, subacute combined degeneration of the spinal cord may result from a familial malabsorption of cobalamin (congenital intrinsic factor deficiency or cubilin deficiency) (Yang *et al*. 1985; Aminoff *et al*. 1999), an inadequate dietary intake (Maclean & Graham 1980), a congenital cobalamin transport defect (transcobalamin II defiency) (Hall 1992) or from inborn errors of folate and cobalamin metabolism (Dillon *et al*. 1974; Shinnar & Singer 1984; Clayton *et al*. 1986; Beckman *et al*. 1987; Carmel *et al*. 1988). The human gene for methylene-tetrahydrofolate reductase has been localized to chromosome 1p36.3 (Goyette *et al*. 1994). Defects of adenosylcobalamin synthesis are not associated with combined degeneration.

The clinical features of this disorder vary with age of onset and underlying metabolic defect. Classically, sensory signs are combined with motor signs. Loss of proprioception and vibratory sensation lead to a sensory ataxia and positive Romberg's sign. The motor signs include loss of strength, spasticity, and extensor plantar responses. Deep tendon reflexes may be diminished. Disturbances of sphincter function are uncommon. Mental and personality changes are frequent. Visual impairment may occur. Funduscopic exam may reveal a hypopigmented perimacular zone surrounded by a hyperpigmented ring (Goyette *et al*. 1994). In severe cases, lethargy, feeding difficulties, and seizures are the usual presenting symptoms. Head growth may be delayed (Beckman *et al*. 1987; Clayton *et al*. 1986). Parkinsonism has been reported in 5,10-methylenetetrahydrofolate reductase (Clayton *et al*. 1986). Some children, however, may only have a mild developmental delay (Carmel *et al*. 1988).

Serum vitamin B12 level is lower in nutritional deficiency or malabsorption, but normal in inborn errors of folate and cobalamin metabolism. Homocystine is increased and methionine reduced in the plasma. Homocystinuria with methylmalonic aciduria is found in defective cytosolic processing of hydroxycobalamin (cobalamin C and D disorders [Shinnar & Singer 1984]), in severe nutritional B12 deficiency and in defective B12 absorption. Homocystinuria without methylmalonic aciduria suggests impaired function of methionine synthase (Carmel *et al*. 1988) or 5,10-methylenetetrahydrofolate reductase (Clayton *et al*. 1986; Beckman *et*

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- In patients with combined degeneration of the spinal cord, signs suggestive of Friedreich ataxia are always accompanied by mental changes or developmental delay.
- If there are signs of stomatitis or atrophic glossitis, an inborn error of cobalamin absorption should be suspected.
- Megaloblastic anemia, the hallmark of cobalamin deficiency, may be absent in errors of folate and cobalamin metabolism.
- Homocystinuria and homocystinemia are consistently seen in all patients.
- Defects of adenosylcobalamin synthesis are not associated with subacute combined degeneration. Such patients have a severe methylmalonic acidemia and no homocystinuria.

KEY CLINICAL QUESTIONS

- Is there any sign of mental decline? Dementia frequently accompanies other signs of myelopathy and peripheral neuropathy.

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Table 12.28 Subacute Combined Degeneration of Spinal Cord

Discriminating feature

1. Enzyme deficiency in skin fibroblasts

Consistent feature

1. Homocystinuria

Variable features

1. Sensory ataxia
2. Spasticity
3. Mental changes
4. Seizures
5. Microcephaly
6. Parkinsonism
7. Megaloblastic anemia
8. Methylmalonic acidemia

al. 1987). Megaloblastic anemia, the hallmark of cobalamin deficiency, is also seen in hereditary folate malabsorption and functional methionine synthase deficiency (cobalamin E and G disorders). The Schilling test shows a cobalamin malabsorption in inborn errors of cobalamin absorption and transcobalamin II deficiency (Table 12.28).

Early diagnosis and treatment may be the only way to prevent permanent neurologic damage. Methylenetetrahydrofolate reductase deficiency is very resistant to treatment, but some response has been seen with methionine, folates and betaine. Betaine in conjunction with hydroxycobalamin has been effective in treating patients with cobalamin C disorder[9] and methionine synthase deficiency. Treatment with reduced folates has been successful in hereditary folate malabsorption and inadequate dietary intake.

Carbohydrate-deficient glycoprotein syndrome

Carbohydrate-deficient glycoprotein (CDG) syndrome is a newly described group of autosomal recessive disorders of glycoprotein glycosylation characterized by post-translational defects in the addition of carbohydrates to the amide group of selected asparagines residues of glycoproteins before their transfer into the rough endoplasmic reticulum (Yamashita *et al*. 1993). Patients with N-glycosylation disorders have a cathodal shift of their serum transferrin isoelectrofocusing (IEF) profile. In CDG I, the hypoglycosylation of the high-mannose type lysosomal enzymes causes a cellular mis-sorting with targeting of the lysosomal enzymes to the secretory pathway and deficient uptake in the lysosome. Plasma levels of lysosomal enzymes are elevated. Storage lysosomes containing hypoglycosylated glycoproteins is found in hepatocytes. In CDG II, there is no defect in the sorting of lysosomal enzymes. Plasma lysosomal enzymes are not elevated and no abnormal lysosomal inclusion is seen in hepatocytes. So far 12 enzyme defects have been identified (Jaeken 2003). The most common is CDG Ia due to phosphomannomutase (PMM) deficiency. The gene has been mapped to chromosome 16p13 and multiple mutations have been reported in the sequenced gene.

Clinically, most patients present in infancy with prominent neurologic symptoms such hypotonia, muscular weakness, psychomotor retardation, strabismus, and failure to thrive. In childhood, cerebellar ataxia, and mental retardation (mild to severe) may be associated with retinitis pigmentosa, and axonal peripheral neuropathy involving particularly the lower limbs suggesting in these later cases diagnosis of NARP. Acquired microcephaly is seen in 50% of patients. Some patients may walk unaided. Most attend special schools. In adolescence and adulthood, ataxia and mental retardation remain stable while lower extremity weakness and atrophy increase slowly. Multivisceral involvement is suggested in younger patients by mild to moderate hepatomegaly, diarrhea, vomiting and failure to thrive and in older patients by hypogonadism, and skeletal abnormalities (kyphoscoliosis, extensor defects of the joints, pigeon breast deformity). Relative specific symptoms of CDG Ia including dysmorphic features (prominent forehead, large ears and jaw, thin upper lip), inverted nipples and lipocutaneous abnormalities (prominent fat pads on buttocks and thighs) are occasionally absent. In addition to these chronic symptoms, the patient may present acutely at any age with stroke-like episodes, seizures and cerebral hemorrhage. Most patients with this syndrome have been reported to survive into early adulthood. Some patients with a more severe multivisceral

PEARLS & PERILS

- CDG syndrome is an infantile autosomal recessive form of olivopontocerebellar atrophy with remarkable systemic manifestations involving the liver and kidney. CDG syndrome is a hepatocerebellorenal syndrome which should not be confused with hepatocerebrorenal syndrome of Zellweger.
- Abnormalities of transferrin and other glycoproteins similar to CDG syndrome are reported in untreated galactosemia, chronic alcoholism, and hemolytic uremic syndrome.
- CDG may mimic mitochondrial diseases. Early screening for CDC may be helpful in preventing an unnecessary muscle biopsy.
- Relatively specific symptoms of CDG Ia include dysmorphic features, inverted nipples and abnormal fat pads. Such features are not always present.

KEY CLINICAL QUESTIONS

- Are there signs of a multisystemic disease in this child with cerebellar atrophy, hypotonia, cognitive decline and peripheral neuropathy?

involvement succumb in the neonatal period from severe hepatocellular failure, protein-losing enteropathy, proximal tubular proteinuria, pericardial and pleural effusions, or hypertrophic cardiomyopathy.

CT and MRI of the brain show varying degrees of cerebellar and brainstem hypoplasia. EEG is usually unremarkable. Nerve conduction velocities are decreased in virtually all patients. Nerve biopsy shows absence of myelin sheaths and presence of multivacuolar myelinoid-bodies in Schwann cells. Abnormalities of the electroretinogram are present in the majority (Andréasson *et al*. 1991). CSF analysis may transiently show increases of protein content. Liver dysfunction is frequently suggested by elevated AST and ALT. Liver biopsy consistently shows the presence in hepatocytes of lysosomal vacuoles containing membranous myelin-like inclusions. Kupffer cells are normal or show signs of cholestasis. Low serum levels of thyroxine-binding globulin, haptoglobulin, albumin, apoliprotein B, cholesterol, and coagulation factors (factor XI, antithrombin III, and protein C) have been reported repeatedly. Serum lysosomal enzymes are consistently elevated in CDG I patients. Deficiencies of transferrin sialylation may be detected quantitatively by carbohydrate-deficient transferrin analysis or qualitatively by IEF. PMM activity is preferably measured in leukocytes, as patients with a mild presentation may show a high residual activity in their fibroblasts. Screen for mutations in the PMM2 gene has shown that most patients are compound heterozygous. (See Table 12.29.)

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Table 12.29 Carbohydrate-Deficient Syndrome

Discriminating feature

1. Elevation of carbohydrate-deficient transferrin

Consistent features

1. Mental retardation
2. Liver dysfunction
3. Cerebellar ataxia (olivopontocerebellar atrophy)
4. Peripheral neuropathy

Variable features

1. Stroke-like episodes
2. Lipocutaneous abnormalities
3. Pericardial and other effusions
4. Retinitis pigmentosa
5. Epilepsy

Treatment is symptomatic. The pathologic characteristics of this syndrome are (1) hepatic micronodular cirrhosis, (2) renal microcysts affecting exclusively tubules and sparing glomerular spaces, (3) olivopontocerebellar atrophy with sparing of the cerebrum. Ultrastructural examination of the Purkinje cells reveals dendrite expansions containing membranous cytoplasmic body-like inclusions (Chang *et al.* 1993).

Friedreich ataxia

Friedreich ataxia is an autosomal recessive progressive neurodegenerative disease characterized by early age of onset of a spinocerebellar ataxia with corticospinal tract signs and areflexia. Skeletal deformity and hypertrophic cardiomyopathy are additional features. At the cellular level, the syndrome is caused by the death of neurons with long axons. The gene locus is on chromosome 9q13–9 (Duclos *et al*. 1994). The incidence of Friedreich ataxia is approximately 1:50 000 individuals. Clinical heterogeneity among family members is common with some family members exhibiting only extraneural findings. The syndrome is caused primarily by a deficiency in frataxin, small mitochondrial matrix protein which binds to Fe^{2+} (like ferritin), decreases the rate of oxidation of Fe^{2+} and promotes the iron export to the cytosol. Frataxin deficiency results in mitochondrial iron accumulation, enhancing the sensitivity of mitochondria to oxidative stress, and leading eventually to free radical-mediated cell death. Frataxin deficiency is caused primarly by expansion of a trinucleotide (66–1800 GAA triplets) in the first intron of the frataxin gene (Adinolfi *et al*. 2002). Friedreich ataxia is the most frequent nuclear encoded mitochondrial encephalopathy.

The onset of Friedreich ataxia is anywhere between 4 and 20 years of age. Peak age of onset is 12 years. The usual presenting symptoms are weakness, gait instability, and difficulty with running. Postexertional cramps and aching in the legs are occasionally reported. If the patient is examined at this stage, ataxia is found to be worse in the legs than in the arms. Tandem walking and standing on one leg for more than a few seconds are impossible. Position sense and vibration sense are impaired in the lower limbs. Romberg sign is usually present. The patellar reflexes are absent. Few patients with Friedreich ataxia have preserved lower limb deep tendon reflexes (Harding 1981). Bilateral extensor toe signs are easily elicitable. Pes cavus and kyphoscoliosis are early findings. As the child grows older, the ataxia progresses, arm dysfunction and dysarthria occurring later. Intention tremor of the upper extremities becomes evident. Muscle weakness predominantly involves the distal muscles and is mild compared with that seen in the hereditary motor and sensory neuropathies. Distal muscle wasting tends to appear and may result in a mild atrophy of peroneal muscles. Diagnosis of Roussy-Levy syndrome should

be considered if abdominocutaneous reflexes are abolished or if peroneal muscle wasting is severe. Claw deformity of the hand is sometimes present in Friedreich ataxia. Speech becomes dysarthric and slurred, and gradually evolves into a severe scanning staccato type of speech. Head titubation is sometimes observed. By the end of the third decade of life, most patients are wheelchair-bound or are bedridden.

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- In many cases of hereditary motor and sensory neuropathy type I (HMSN I, the Roussy–Levy variant of Charcot–Marie–Tooth disease), features of spinocerebellar degeneration may include dysarthria, limb and gait ataxia, nystagmus, areflexia, pes cavus, extensor plantar responses, and sensory changes. HMSN I can be distinguished from Friedreich disease by virtue of its autosomal dominant inheritance, its benign course, its early age of onset before 2 years of age, and its severely reduced motor conduction velocities.
- Hyporeflexia, Romberg sign, extensor plantar response, cerebellar ataxia, and loss of position and vibration sense in the first decade are the hallmarks of Friedreich ataxia. A clinical syndrome similar to Friedreich ataxia is seen in vitamin E deficiency. This condition is associated with pigmentary retinal degeneration, which is absent in Friedreich ataxia. In ataxia-telangiectasia, peripheral sensory degeneration is a secondary factor that exacerbates the ataxia of cerebellar origins during the second decade.
- In Refsum disease, there is no extensor plantar response, and pigmentary degeneration of the retina is a prominent feature.
- In tabes dorsalis, there is no peripheral neuropathy.
- Clinical features of B12-deficient polyneuropathy are somewhat similar to those of Friedreich ataxia. A megaloblastosis and methylmalonic aciduria are typical of B12 deficiency.
- An atypical form of NCL with juvenile ataxia predominating can be distinguished by hyperreflexia in NCL and hyporeflexia in Friedreich ataxia. An atypical spinocerebellar degeneration with hyperreflexia is also found in juvenile GM2 gangliosidosis.
- Adrenomyeloneuropathy may present as a spinocerebellar syndrome.
- Leigh syndrome may present as a spinocerebellar syndrome that can be distinguished from Friedreich ataxia if its course is intermittently progressive and if eye involvement is present.
- A CT scan of the head is usually normal in Friedreich ataxia (cerebellar atrophy is demonstrated in Marinesco-Sjögren-Garland syndrome and ataxia-telangiectasia).
- An echocardiogram permits recognition of heart disease in Friedreich ataxia before the onset of cardiac symptoms.

Bladder dysfunction may manifest at any time during the illness. Symptoms of spastic bladder are most common. Ophthalmologic findings more frequently include horizontal nystagmus (Harding 1981) and optic atrophy (Geoffrey *et al.* 1976). Higher cortical functions remain intact until later stages of the illness. Cardiac arrhythmia or congestive heart failure are major complications (Hewer 1968). Diabetes mellitus has been reported in 20% of patients (Finocchiarro *et al*. 1985). The mean age of death is 30 years old. Somatosensory evoked potentials are impaired in all patients regardless of the duration or the severity of the illness. The features of Friedreich ataxia are outlined in Table 12.30.

The motor conduction velocity of peripheral nerves is usually normal. Sensory nerve conduction, however, is practically absent in the lower limbs, and considerably slowed in the upper. On electromyography, fasciculation and an impaired interference pattern indicate denervation. Patients with Friedreich ataxia have no or only minor abnormalities on cranial CT scan. MRI of the spine may be helpful in assessing spinal cord atrophy. The CSF is usually normal.

Laboratory investigation reveals an abnormal glucose tolerance test in about 40% of cases, and an abnormal insulin response to glucose in more than 60% of cases (Finocchiaro *et al.* 1985). Abnormalities of mitochondrial enzymes are

FEATURES

Table 12.30 Friedreich Ataxia

Discriminating feature

1. Trinucleotide GAA repeat expansion of frataxin gene

Consistent features

1. Ataxia of limbs
2. Decreased or absent vibratory sense
3. Extensor plantar responses
4. Normal or mildly slow motor nerve conduction velocity
5. Absent or reduced sensory nerve potentials
6. Impaired somatosensory evoked potentials
7. Abnormal echocardiogram and EKG

Variable features

1. Absent myotatic reflexes in lower extremities (distal first)
2. Muscle atrophy and weakness (distal)
3. Truncal ataxia
4. Dysarthria
5. Loss of position sense
6. Cramp and aching in legs
7. Pes cavus and kyphoscoliosis
8. Claw hands
9. Optic atrophy
10. Nystagmus
11. Cranial nerve palsies, neurosensory hearing loss
12. Intellectual difficulties
13. Seizures
14. Palpitation or shortness of breath
15. Diabetes mellitus

KEY CLINICAL QUESTIONS

- Does your child complain of shortness of breath or palpitations? Although heart disease is frequently asymptomatic, shortness of breath is reported in 40% of patients and and palpitation in 10%.

frequently found (Sorbi *et al.* 1989). However, no specific metabolic defect or enzyme deficiency has been found to date. Dunn and Dolman (1969) reported a case resembling atypical Friedreich ataxia with a fluctuating course and elevated serum lactate and pyruvate levels. Subacute necrotizing encephalomyopathy of Leigh was diagnosed at autopsy. Vitamin E levels should be obtained in order to exclude one of the few treatable causes of spinocerebellar degeneration. Documentation of cardiomyopathy confirms the diagnosis of Friedreich ataxia. The best early indicators of myocardial involvement appear to be the presence of ECG and echocardiographic abnormalities (Salih *et al*. 1990). In most patients ECG shows inverted T-waves. Echocardiography demonstrates concentric hypertrophy of the ventricles in 60% of patients or asymmetric septal hypertrophy in 30% of patients. A molecular diagnosis of Friedreich ataxia can be made by demonstration of homozygosity for the GGA repeat expansion in the frataxin gene by polymerase chain reaction.

No treatment halts the progression of the disease. Free radical scavengers such as idebenone have been shown to decrease the rate of neurologic decline and improve the cardiomyopathy (Rustin *et al*. 1999). Congestive heart failure secondary to cardiomyopathy is generally treated with digitalis and diuretics. Increased taurine intake and administration of calcium channel blockers have been suggested to prevent the progression of cardiomyopathy. Scoliosis should be observed before deciding on surgical intervention in order to assess the rate of progression of the deformity, because in some patients the deformity may remain mild throughout the course of the illness.

Neuropathy, ataxia and retinitis pigmentosa syndrome

Neuropathy, ataxia and retinitis pigmentosa (NARP) syndrome is a maternally inherited multi-system disorder characterized by development delay, retinitis pigmentosa, ataxia, and proximal weakness. The disease is associated with a mitochondrial DNA (mtDNA) point mutation at base pair 8993 causing a substitution of a thymidine by a guanine in the gene coding for the subunit 6 of ATPase (Holt *et al.* 1990). More than 20 families have been published with this mutation (Tatuch *et al.* 1992). These families have shown similar clinical features and marked intrafamilial variability. Clinical phenotypes such as "cerebral palsy" and Leigh's syndrome may coexist with NARP in the same family. The

PEARLS & PERILS

- Ragged-red fibers are not essential for diagnosis of NARP.
- Recurrence of cerebral palsy in multiple family members should raise suspicion for NARP.
- A maternal mode of inheritance is always seen in NARP.
- Maternal relatives of NARP patients may present with Leigh syndrome.

Leigh's syndrome phenotype is seen in patients with abundant (above 90% of the mtDNA) mtDNA mutation (see Table 12.31).

Symptoms associated with the NARP mutation are highly variable. Some individuals are hypotonic from birth and have a psychomotor retardation. Microcephaly can be an occasional feature (Freyer *et al.* 1994). These individuals frequently carry the diagnosis of cerebral palsy. Other individuals present intermittent episodes of drowsiness, ataxia and hyperventilation suggesting a diagnosis of Leigh syndrome. Other individuals have a normal early development. By school age or early adulthood, they develop a dysarthria, a progressive limb and gait ataxia, and night blindness. Deep tendon reflexes are frequently decreased. Babinski signs are extensor. Sensory exam reveals decreased position sense and a positive Romberg sign. There is frequently a progressive loss of peripheral and sometimes central vision. Ophthalmologic examination reveals a retinitis pigmentosa with "bone spicule" and optic atrophy. Even asymptomatic individuals may show a retinal degeneration. Seizures, dementia, and proximal muscle weakness with wasting are other variable features. A cardiomyopathy is seen in some

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Table 12.31 Neuropathy, Ataxia, and Retinitis Pigmentosa Syndrome

Discriminating feature

1. Mitochondrial NARP point mutation

Consistent features

1. Retinitis pigmentosa
2. Ataxia (sensory)
3. Axonal neuropathy

Variable features

1. Leigh syndrome
2. Cardiomyopathy
3. Convulsion
4. Mental retardation or dementia
5. Muscle wasting and weakness
6. Short stature

KEY CLINICAL QUESTIONS

- Does the mother, her sister or the maternal grandmother suffer or has children suffering from migraine-like headache, seizures, night blindness, proximal weakness, unsteady gait, cerebral palsy, dementia or cardiomyopathy? If no family member is found, examination of the maternal retina may reveal an asymptomatic retinitis pigmentosa.

individuals (Freyer *et al.* 1994). Long-term outcome remains unknown.

Lactic acid and pyruvate in blood and CSF are usually normal (unless patient presents severe phenotype reminiscent of Leigh's syndrome). Brain CT and MRI may disclose brainstem and cerebellar atrophy (Holt *et al.*1990). Electroretinogram may show attenuated responses. Nerve conduction velocities suggest an axonal sensorimotor neuropathy (low amplitude motor and/or sensory responses). EEG may show a slow background and paroxysmal activity. Analysis of blood usually shows the NARP point mutation.

Muscle biopsy may show ragged-red fibers on Gomori trichrome or signs of chronic denervation. Ultrastructural studies may show large mitochondria with abnormal branching cristae. Polarographic analysis of isolated muscle mitochondria shows ATP synthase (complex V) deficiency (DiMauro 1993). NARP point mutation is more easily detected in muscle than blood.

Palliative treatment may be beneficial (see Generalized Mitochondrial Encephalomyopathies).

FEATURES

Table 12.32 Refsum Disease

Discriminating features

1. Phytanic oxidase deficiency in fibroblasts
2. Elevated phytanic acid levels in blood with normal hydroxyphytanic and pristanic acid levels

Consistent features

1. Pigmentary degeneration of the retina w/night blindness
2. Chronic progressive sensorimotor polyneuropathy: hypertrophic demyelinating neuropathy with onion bulb formation
3. Decreased motor and sensory nerve conduction
4. Hyporeflexia (ankle)
5. Distal muscular atrophy
6. Ataxia (sensory and cerebellar)
7. Elevated CSF proteins
8. Normal intelligence
9. No pyramidal tract signs

Variable features

1. Age of onset and presenting symptoms
2. Neural hearing loss
3. Anosmia
4. Cataracts
5. Cardiomyopathy
6. Ichthyosis
7. Bony changes
8. Renal tubular involvement
9. Enlarged palpable peripheral nerves
10. Improved with dietary restriction

Refsum disease

Refsum disease (or heredopathia atactica polyneuritiformis) is a rare autosomal recessive peroxisomal disorder of branched-chain lipid metabolism characterized by progressive onset in first or second decade of the tetrad of retinitis pigmentosa, cerebellar ataxia, chronic progressive sensorimotor polyneuropathy, and elevated cerebrospinal fluid protein concentration. Refsum disease is characterized biochemically by accumulation of phytanic acid in body fluids and tissues. Pristanic acid, the end product of phytanic acid's alfa-oxidation, is not elevated in Refsum disease (Table 12.32). It has been shown that the phytanic acid accumulation is due in most cases to a deficiency of the peroxisomal phytanoyl-CoA alpha hydroxylase. (PAHX). The sequence of PAHX gene is known and localized on chromosome 10p13. Both point mutations and deletions have been described in the PAHX associated with Refsum disease (Waterman *et al*. 2000).

Most patients with classical Refsum disease are normal during the first few years of life. However, congenital skeletal malformations are recorded in more than half of the patients (Skjeida *et al.* 1987). The most common finding appears to be bilateral shortening or elongation of the metatarsal bones, particularly the third and fourth. Other common skeletal malformations include symmetrical epiphysial dysplasia of large joints, syndactyly, shortened and elongated metacarpal bones and phalanges, hammer toes, and pes cavus. Age of onset of symptoms is highly variable. Some rare patients present in infancy with hypotonia and development delay (Herbert & Clayton 1994). Infantile onset of photophobia, night blindness, and anosmia have been noted in other patients (Gibberd *et al.* 1985). Childhood onset of symptoms is usually insidious and characterized by loss of appetite, an unsteady gait, dryness and desquamation of the skin, and progressive deafness. Nystagmus and intention tremors are frequently observed. Dysarthria is not a feature of the illness. Deep tendon reflexes are absent. Romberg sign is positive. The plantar responses are indifferent or flexor. In some families, children with Refsum disease have multiple attacks following viral infections of an illness that is indistinguishable from Guillain–Barré syndrome. In between attacks, there may be complete clinical remission.

PEARLS & PERILS

- Infantile onset Refsum disease should be distinguished from "infantile Refsum disease" (see Peroxisomal disorders). Infantile onset Refsum disease is not associated with hepatomegaly. The accumulation of phytanic acid in plasma is due to a defective hydroxylation of phytanic acid; therefore, there are normal plasma levels of alfa-hydroxyphytanate and pristanate in infantile onset Refsum disease.
- Childhood onset Refsum disease should be distinguished from Friedreich ataxia. Generally, the plantar responses are flexor or absent in childhood onset Refsum disease. Dysarthria is not found in Refsum disease. Night blindness, anosmia, deafness, ichthyosis, and elevated CSF protein are not found in Friedreich ataxia.
- Mental deterioration, seizures, pyramidal and extrapyramidal signs and symptoms are not features of Refsum disease.
- Some patients with Refsum disease may present with a clinic picture resembling that of relapsing or chronic polyneuropathy, or Guillain–Barré syndrome. Other patients present with a neurologic disorder resembling other hypertrophic neuropathies (e.g. Charcot–Marie–Tooth disease or Dejerine Sotos syndrome). A pigmentary degeneration of the retina distinguishes Refsum disease.
- The clinical course of Refsum disease may be improved by dietary restriction of phytanic acid.
- Mutations in the PEX7 gene (normally causing rhizomelic chondrodysplasia type I) are found in some rare patients with Refsum disease (van den Brink *et al*. 2003). Such patients have a decreased plasmalogen synthesis in their skin fibroblast while in classic Refsum disease plasmalogen synthesis is normal.

KEY CLINICAL QUESTIONS

- Do you suffer from difficulties walking in the dark and/or did you lose your sense of smell?

Juvenile and adult onset sensorimotor polyneuropathy is sometimes preceded for many years by night blindness, anosmia and/or deafness. In some cases onset is acute and frequently precipitated by infection, surgery, pregnancy or delivery. Most often, onset is slowly progressive. Most patients improve spontaneously and significantly after an acute exacerbation. The neuropathy is generally symmetrical and, at the onset, chiefly affects the distal parts of the limbs with muscle weakness, atrophy, and sensory disturbances. Myotatic reflexes are decreased or absent. Vibration and position senses are impaired distally, more than superficial sensory modalities. Paresthesias, dysesthesias, and spontaneous pains occur in some cases. Many adult-onset cases have no skin changes.

The clinical course of Refsum disease is highly variable. An early onset of the disease does not necessarily indicate a particularly poor prognosis. Dementia and epileptic seizures are not part of the clinical picture. In a few cases, psychosis, particularly paranoid psychosis, has occurred. Sudden death among patients with Refsum disease has been reported in children as well as adults. Sudden death has been related to cardiomyopathy. Half the untreated patients have died before the age of 30 years.

Ophthalmologic manifestations of Refsum disease include retinal changes, lenticular opacities, and nystagmus. Retinal changes are variable. Some patients present the typical "bony spicules" of retinitis pigmentosa. In others, the pigmentation appears as fine, small granules giving a "salt and pepper" appearance to the retina. In some cases, areas of retinal depigmentation associated with attenuation of the retinal vessels and prominence of the choroid vasculature have been described. The optic disks are slightly yellowish. Night blindness and constriction of the visual field result from retinopathy. Cataract has been described in one-third of the cases, usually of the posterior subcapsular kind. Nystagmus appears more frequent in children.

In Refsum disease, nonspecific electrocardiographic changes are found. Electrophysiologic studies may reveal reduced motor and sensory nerve conduction velocity. Electromyography may show evidence of denervation. The ERG shows reduction or complete absence of rod and cone responses. The EEG is normal in most cases.

Laboratory findings suggestive of classic Refsum disease include increased CSF protein content without a corresponding increase in the number of cells (albuminocytologic dissociation), and increased plasma phytanic acid level (normally less than 0.3 mg/100 mL). Phytanic acid is a fatty acid derived from phytol, a component of the chlorophyll molecule. It cannot be synthesized endogenously; therefore, the only source is diet. In Refsum disease, phytanic acid normally present in the diet cannot be metabolized owing to a defect of the alfa-oxidative pathways, the initial step in catabolism of phytanic acid. In some patients with a typical clinical picture of Refsum disease, a diet low in phytanic acid will normalize the pattern of fatty acid in the serum. Accumulation of phytanic acid cannot be considered diagnostic for Refsum disease, as this acid has also been elevated in patients with peroxisomal disorders, such as neonatal adrenoleukodystrophy, Zellweger syndrome, and chondrodysplasia punctata (rhizomelic type). Normal plasma levels of alfa-hydroxyphytanate and pristanate differentiate Refsum disease from peroxisomal disorders other than rhizomelic chondrosdysplasia punctata type I. The demonstration of a deficient activity of the phytanic acid oxidase and phytanoyl-CoA hydroxylase in skin fibroblasts does not differentiate Refsum disease from rhizomelic chondrodysplasia type I.

Measurement of plasmalogen synthesis in cultured fibroblast is necessary for the differential diagnostis: in Refsum's disease it is normal while in rhizomelic chondrodysplasia puncta type I it is decreased. Mutation analysis of the PAHX gene in most cases confirms the diagnosis.

A restricted dietary intake of phytanic acid is achieved by avoiding fats obtained from herbivores (e.g. milk, beef, rabbit), fish, pork and green vegetables. It is important to maintain sufficient caloric intake to avoid release of phytanic acid from body stores. Vitamin and mineral supplementation is required. Carefully supervised dietary restriction can lower the plasma phytanic acid levels in a few weeks, with a concomitant improvement in peripheral nerve conduction, muscle strength, and skin abnormalities. In patients with severe exacerbations of symptoms, plasmapheresis reduces plasma phytanic acid levels rapidly, reversing most clinical symptoms. Central neurologic damage, however, is permanent (Lundberg *et al.* 1972).

Infantile onset spinocerebellar ataxia

Infantile onset spinocerebellar ataxia (IOSCA) is a slowly progressive autosomal recessive neurodegenerative disease characterized by acute or subacute infantile onset of ataxia. As the disease progresses, cerebral symptoms, ophthalmoplegia, hearing deficit and sensory neuropathy are additional manifestations. No biochemical markers of this disorder have been found. The IOSCA gene locus is on chromosome 10q23.3-q24.1 (Nikali *et al.* 1995).

Early development is usually normal until the acute or subacute onset of clumsiness and ataxic gait between 9 and 18 months of age. In addition to ataxia, the clinical examination reveals loss of deep tendon reflexes, hypotonia with pes planus, athetoid movements of hands and face and on occasion, ptosis. By school age, ophthalmoplegia and hearing loss are diagnosed. Babinski sign appears with the progression of the disease. In adolescence, most patients become wheelchair bound. Proprioception and kinesthetic sensation are impaired. There is progressive atrophy of thighs, legs, and distal hand muscles. Scoliosis may appear. Optic atrophy is demonstrated on funduscopic exam. Seizures may be a late manifestation. The height of the patients is normal. In females, hypogonadism is suggested by amenorrhea and poorly developed secondary sex characteristics (Koskinen *et al.* 1994) (refer to Table 12.33).

Slowing of sensory nerve conduction velocities occurs early. Latencies of somatosensory evoked potentials are also frequently delayed. In older patients, moderate slowing of motor nerve velocities, delayed latencies of visual evoked potentials, and abnormal EEG are additional findings. Neuroimaging studies may show cerebellar atrophy late in the course of the illness. The main pathologic features are sensory axonal neuropathy (with severe loss of large myelinated fibers) and progressive spinocerebellar atrophy. Treatment is still purely supportive.

FEATURES

Table 12.33 Infantile Onset Spinocerebellar Ataxia

Discriminating feature

1. Gene locus on chromosome 10

Consistent features

1. Spinocerebellar ataxia onset in infancy
2. Ophthalmoplegia, areflexia, hearing deficits, hypotonia, athetosis in childhood
3. Cerebellar atrophy in adolescence

Variable features

1. Hypogonadism
2. Peripheral neuropathy
3. Ptosis
4. Optic atrophy
5. Seizures
6. Muscle atrophy
7. Scoliosis

KEY CLINICAL QUESTIONS

- Does the patient have Finnish ancestry? Most patients with IOSCA originate from Finland.

PEARLS & PERILS

- The clinical symptoms are very similar to those found in mitochondrial encephalomyopathies.
- Distinguishing features are normal growth pattern and lack of mitochondrial abnormalities in muscle biopsies.

Diffuse encephalopathies

In this section, the discussion will be limited to peroxisomal disorders, mitochondrial encephalopathies, Lafora disease and cerebrotendinous xanthomatosis. This group of disorders is obviously heterogeneous. Common clinical features are dementia, seizures, involuntary movements, and ataxia.

Peroxisomal disorders

Peroxisomes are single membrane subcellular organelles with important function in cellular catabolic and anabolic processes. Catabolic peroxisomal function involves various

oxidases that produce H_2O_2. Peroxisomes have the ability to decompose H_2O_2 via catalase which is present in high concentration in peroxisomes. Peroxisomes also contain superoxide dismutase and glutathione peroxidase (Singh *et al.* 1994), suggesting importance of this organelle in free radical metabolism. Peroxisomes are the site of beta-oxidation of various fatty acids such as very long chain fatty acids, long chain dicarboxylic acids, and side chains of cholesterol (important in synthesis of bile acids). Peroxisomes also catabolize pipecolic acid (an intermediate in lysine catabolism) and polyamines. Anabolic peroxisomal functions include certain steps in plasmalogen (an ether phospholipid), bile acids, steroid hormones and isoprenoid biosynthesis (cholesterol, dolichols, coenzyme Q, squalene, farnesylated proteins, and the isoprenoid moiety of heme a).

Peroxisomal disorders can be subdivided into three categories (Table 12.34): the disorders of peroxisomal biogenesis or assembly (class 1), disorders involving a single peroxisomal enzyme (class 2) and CADDS, an X-linked contiguous deletion syndrome with a critical region spanning the genes ABCD1 and BAP31 that presents with a phenotype mimicking peroxisomal biogenesis disorders (Corzo *et al*. 2002).

Class 1 disorders are characterized pathologically by a reduced number of peroxisomes (disorders of peroxisomal biogenesis) or by the finding of ghost peroxisomes (disorders of peroxisomal assembly). Biochemically, class 1 disorders are characterized by the concomitant loss of activity in both membrane (plasmalogen synthesis) and matrix peroxisomal enzymes. As a result, the hallmark of class 1 disorders is the concomitant decrease in plasmalogen synthesis with multiple biochemical abnormalities such as the increased plasma very long chain fatty acids (VLCFA), phytanic acid, and trihydroxy-cholestanoic acid (THCA). Clinically, most class 1 disorders are not separate disease states but represent phenotypes differing in their severity with Zellweger syndrome the most severe, infantile Refsum disease the least severe, and neonatal adrenoleukodystrophy (NALD) of intermediate severity. Rhizomelic chondrodysplasia punctata type I and rare cases of Refsum-like disease are the only class 1 disorders that represent a separate disease state. Genetically, the class 1 disorders are transmitted in an autosomal recessive mode of inheritance. Since the genetic heterogeneity was elucidated in 1989 (Roescher *et al*. 1989), complementation studies have shown that class 1 disorders can be classified in at least 12 complementation groups. Class 1 dis-

TABLE 12.34

Classification of Peroxisomal Disorders

Defect	Disorder	Enzyme defect	Peroxisomes	VLCFA	Phytanic	THCA	Plasmalogen
Class 1 peroxisomal biogenesis or assembly	Zellweger syndrome	Generalized defect	Absent/ghosts	Increased	Increased	Increased	Decreased
	Infantile Refsum	Generalized defect	Ghosts	Increased	Increased	Increased	Decreased
	Neonatal ALD	Partial defect	Ghosts	Increased	Normal	Normal	Decreased
	RCDP type 1	Partial defect	Ghosts	Normal	Increased	Increased	Decreased
	Refsum type 2	Partial defect	Ghosts	Normal	Increased	Increased	Decreased
Class 2 single enzyme defect	RCDP type 2	DHAP-AT	Normal	Normal	Normal	Normal	Increased
	RCDP type 3	Alkyl-DHAP synthase	Normal	Normal	Normal	Normal	Increased
	X-linked ALD	ALDP	Normal	Increased	Normal	Normal	Normal
	Pseudo-neonatal ALD	Acyl CoA-oxidase	Large	Increased	Normal	Normal	Normal
	Pseudo-Zellweger syndrome	Bifunctional enzyme Thiolase	Normal or large	Increased	Increased	Increased	Normal
	Mevalonic aciduria	Mevalonate kinase	Normal	Normal	Normal	Normal	Normal
	Classical Refsum	Phytanoyl hydroxylase	Normal	Normal	Increased	Normal	Normal
	THCA acidemia	THCA CoA oxidase	Normal	Normal	Normal	Increased	Normal
CADDS	Contiguous ABCD1 DXS1357E deletion	*ABCD1* and *BAP31*	Normal	Increased	Normal	Increased	Normal

ALD, Adrenoleukodystrophy; DHAP-AT, dihydroxyacetone phosphate acyltransferase; DHAP-S, dihydroxyacetone-phosphate synthase; RCDP" rhizomelic chondrodysplasia punctata; mCA, trihydroxy-cholestanoic acid; VLCFA, very long chain fatty acids; CADDS: contiguous ABCD1 DXS1357E deletion syndrome

PEARLS & PERILS

Peroxisomal Disorders

- Analysis of very long chain fatty acids is a highly reliable test to establish whether or not one is dealing with a peroxisomal disorder.
- Peroxisomal morphology is frequently abnormal in peroxisomal disorders. However, a normal morphology does not exclude a peroxisomal disorder.

orders result from mutations in PEX genes. The Pex genes encode peroxins, proteins involved in and necessary for peroxisomal biogenesis or assembly. The absence of detectable peroxisome is seen exclusively in patients with Zellweger syndrome and results from defects in "chaperone" proteins lacking peroxisomal targeting signals (PTS) but required for proper assembly of membrane vesicles before targeting of all peroxisomal membrane proteins (PMP). These "chaperone" proteins, including peroxin 3 (chromosome 6q23–24), peroxin 16 (chromosome 11p12-p11.2), and peroxin 19 (chromosome 1q22), are essential for peroxisomal biogenesis. Ghost peroxisomes may result from targeting defects of newly synthesized peroxisomal proteins or from defects in the process of peroxisomal matrix enzyme import. Matrix and membrane protein targeting requires the presence of either peroxin 5 (chromosome 12p13) which acts as receptor for the proteins containing the peroxisomal targeting signals 1 (PTS 1), or the presence of peroxin 7 (chromosome 6q21) which acts as receptor for PTS 2. Mutations of at least seven other genes encoding peroxins result in defects of the peroxisomal protein import (Matsumoto *et al*. 2003) (see Table 12.35). The prevalence of peroxisomal biogenesis disorder is estimated to be 1:50 000 with PEX1 mutations associated with about 65% of all cases. PEX6, PEX 10, PEX 12 and PEX 26 mutations account for another 25% of the cases.

Disorders involving a single peroxisomal enzyme (class 2) are characterized by a normal morphology and number of peroxisome and, in most cases, by a normal plasmalogen synthesis. A single peroxisomal enzyme is deficient and therefore metabolic abnormalities are selective, involving in general only one metabolic pathway. However when the deficient peroxisomal enzyme is necessary for the normal function of multiple metabolic pathways, the finding of multiple metabolic derangements may suggest a PBG disorder: both bifunctional enzyme deficiency and oxoacyl CoA thiolase deficiency are associated with VLCFA and THCA and present with the clinical phenotype of "pseudo-Zellweger." Class 2 disorders can result from a defect in the transport of the enzyme to its site of action or from a structural defect (deletion, point mutation) of the gene encoding for the enzyme. For example, X-linked adrenoleukodystrophy (ALD) results from a defect in the transport of the peroxisomal acyl CoA synthetase. Large deletion of the peroxisomal acyl CoA synthetase gene produces the pseudo-NALD phenotype (Fournier *et al.*1995).

Disorders involving a single peroxisomal enzyme do not always cause an elevation of very long chain fatty acids. At least 15% of patients presenting with a clinical phenotype resembling Zellweger syndrome and demonstrating increased plasma very long chain fatty acids have no mutation in the PEX gene and the defect is in one of the genes encoding fatty acid beta-oxidation enzymes (acyl CoA oxidase, bifunctional enzyme, thiolase). However, elevation of very long chain fatty acid is absent in other defects such as a variant of rhizomelic chrondrodysplasia punctata with isolated dihydroxyacetone phosphate acyltransferase deficiency, mevalonate kinase deficiency, and trihydroxy-cholestanoic

TABLE 12.35

Categories of Peroxisomal Disorders

CG KG	CG J	Protein	Gene	Chromosome	Phenotype
1	E	ABC protein (AAA ATPase)	PEX1	7q21-q22	ZS, NALD, IRD
2		PTS-1 receptor	PEX5	12p13.3	ZS, NALD, IRD
3		Ring finger membrane protein (19PXMP3)	PEX12	17q21.1	ZS, NALD, IRD
4	C	ABC protein (PAF-2)	PEX6	6p21.1	ZS. NALD
7	B	Ring finger membrane protein	PEX10	1p36	ZS, NALD
8	A	Interacts with PEX1-PEX6 complexes	PEX26	22q11.2	ZS, NALD, IRD
9	D	"Chaperone"	PEX16	11p12-p11.2	ZS
10	F	Ring zinc finger membrane protein (PAF-1)	PEX2	8q21.1	ZS, IRD
11	R	PTS-2 receptor	PEX7	6q21	RCDP. RD
12	G	Anchor for Pex19	PEX3	6q23-q24	ZS
13	H	Docking site for PTS-1	PEX13	2p15	ZS, NALD
14	J	"Chaperone"	PEX19	1q22	ZS

CG: complementation group; KG: Kennedy Greiger; J: Japanese; PEX: peroxine; PAF: peroxisomal assembly factor; PTS: peroxisomal targeting signal

acyl CoA oxidase (THCA-CoA oxidase) deficiency. Multiple other isolated peroxisomal enzyme deficiencies remain to be described. Most of these disorders are autosomal recessively inherited except for X-linked ALD. The mevalonic aciduria gene is localized to human chromosome 12.

Patients with peroxisomal encephalopathies have various signs and symptoms depending on the severity and complexity of biochemical defect(s) resulting from a specific mutation. In neonates, the most common neurologic findings are seizures, hypotonia, generalized weakness, feeding difficulties and blindness. Multi-system involvement is common as suggested by dysmorphic features, short stature, cataract, glaucoma, hepatomegaly, diarrhea and bleeding tendencies. In infants more than 6 months of age, neurologic features are psychomotor retardation, seizures, visual and hearing impairment. Systemic findings include hepatomegaly, osteoporosis, ichthyosis and hyperpigmentation of skin. In children, ataxia, developmental regression, peripheral neuropathy, behavior changes, speech difficulties, deafness, loss of vision and hearing, and spastic quadriparesis are common neurologic findings. Systemic findings include nausea, vomiting, hyperpigmentation of skin and ichthyosis. In adults, spastic paraparesis, ataxia, peripheral neuropathy, dementia, deafness and visual loss are frequently seen with minimal systemic manifestation. However, cardiac arrythymia can result in sudden death. X-linked ALD (see White matter diseases) and Refsum disease (see Spinocerebellopathies) will not be discussed in this section.

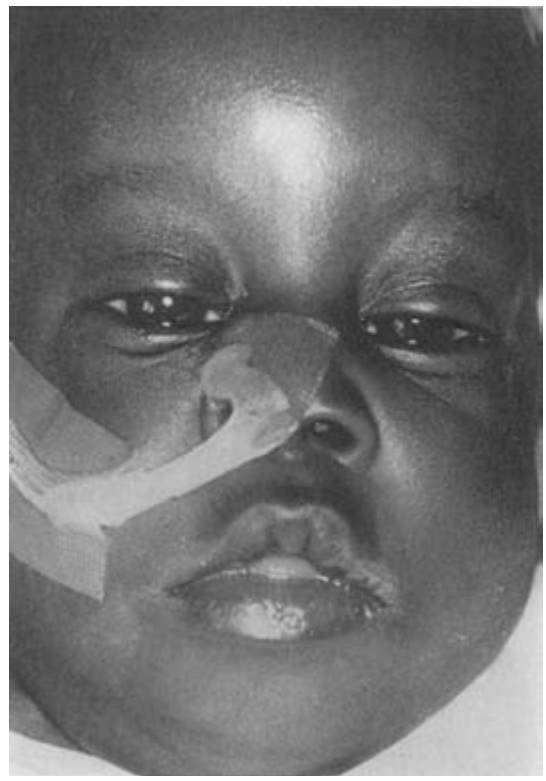

Fig. 12.9 Characteristic facial features – such as flat supraorbital ridges, high forehead, ptosis, epicanthal folds, depressed nasal bridge, short anteverted nose, tented mouth, and micrognatia – in a 2-month-old girl with Zellweger syndrome who has to be gavage fed.

Cerebrohepatorenal syndrome of Zellweger

Zellweger syndrome is characterized by typical dysmorphic features and cerebrohepatorenal involvement (Figs 12.9 and 12.10). Multiple gene defects can result in Zellweger phenotype. The appearance of newborns with Zellweger syndrome is characteristic: the forehead is broad; the supraorbital ridges and bridge of the nose are flat; the anterior fontanelle is large with splitting of the metopic suture; the eyes may show bilateral glaucoma with corneal clouding, cataracts, and retinal pigmentary degeneration; the mouth is triangular with the upper lip shaped like an inverted V; the infants generally show micrognathia, high-arched palate, and full cheeks; ears are low-set with abnormal pinna; clitorimegaly, hypospadias, and undescended testes are common features; neck webbing may be noted; limbs may display simple transverse palmar creases, syndactyly, camptodactyly, clubfeet, and stippled chondral calcifications of the patella and acetabulum.

Early onset of cerebral involvement may be indicated by a history of paucity of intrauterine movements and polyhydramnios. At birth, respiration is spontaneous but apneic episodes may occur. Sucking and swallowing difficulties necessitate gavage feedings. The infants are paretic and severely hypotonic. Deep tendon reflexes are difficult to elicit. Seizures of various types are frequent. Psychomotor development is limited. Hepatomegaly is nearly a constant finding. Postnatal weight gain is poor. Bleeding tendency, osteopenia, retinal pigmentary degeneration, and poor wound healing are caused by fat-soluble vitamin deficiency. Jaundice may develop before death. Most patients die within the first 3 months of life.

Small subcapsular renal cysts are a constant finding and can be detected by abdominal ultrasound. Skeletal x-rays may show osteoporosis or scattered calcified stippling in the patellar areas, acetabular synchondrosis, and proximal epiphyses of femur and humerus. The epiphyses are generally spared but may be retarded in development.

Neuroimaging may show cysts in the subependymal region of the germinal matrix, hypoplasia of corpus callosum,

KEY CLINICAL QUESTIONS

- Did your baby appear more premature than expected for the gestational age? The premature appearance of a newborn with Zellweger syndrome is suggested by the posture, poor activity and feeding difficulties, head shape and inspection of genitalia.

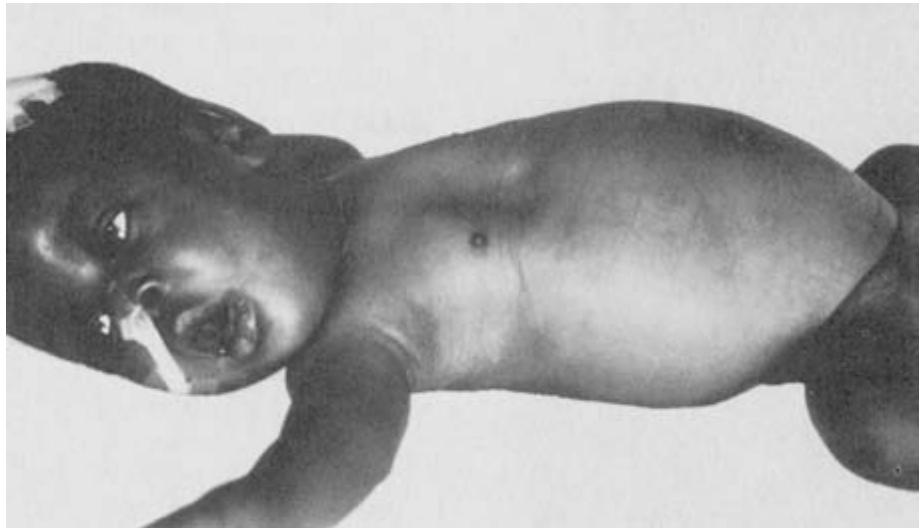

Fig. 12.10 In this 2-month-old girl, the diagnosis of Zellweger syndrome was suggested by a generalized muscle wasting and weakness with bifacial involvement, hyporeflexia, and severe hypotonia with frog-leg position. In addition the liver was enlarged and multiple dysplastic features were noted.

gyral malformations, hypomyelinization and cerebellar hypoplasia. The electroretinogram is grossly abnormal. EEG demonstrates seizure activity.

Laboratory studies in Zellweger syndrome show low serum cholesterol (due to mevalonate kinase deficiency), high serum iron levels with low iron binding capacities (due to a derangement in the reduction and delivery of ferric iron in transferrin to the ferrous iron in heme), and microcytic nonhemolytic anemia. A functional deficiency of the adrenal cortex may be evidenced by ACTH stimulation. There is liver (elevated liver enzymes, hyperbilirubinemia, and abnormal bile acids in blood and urine) (Van Eldere *et al*. 1987) and kidney (nonspecific aminoaciduria) involvement. Pipecolic acid is typically found in the plasma and urine. Very long chain fatty acids (C26:0 and C26:1) are elevated in plasma, body fluids, and tissues with increased C26/C22 and C24/C22 ratios. Other biochemical marker suggesting diagnosis include an elevation of plasma phytanic acid and pristanic acid, an elevation of plasma/urine dihydroxycholestanoic acid and trihydroxy-cholestanoic acid. In addition, C16 and C18 plasmalogens are severely diminished in the erythrocyte membranes (Wanders *et al*. 1986 1994; Fauler 1994).

Pathologic changes occur in the liver, the kidney, and the nervous system. The liver is large, cirrhotic and dysgenetic. The kidneys show dysgenetic parenchyma and small subcapsular cysts. No peroxisomes can be recognized in the liver and kidneys. The brain shows macrogyria, polymicrogyria, hypoplasia of the corpus callosum, bilateral subependymal cysts in the area of the head of the caudate nuclei, and olivary dysplasia (Table 12.36).

Treatment with oral plasmalogen normalizes erythrocyte plasmalogen levels and may result in clinical improvement. Bile acid therapy may reduce burden on cholesterol synthesis and help fat-soluble vitamin absorption. Supplementation with coenzyme Q10, vitamin E, vitamin K, and vitamin A may be beneficial. Replacement of adrenal steroids should be considered, particularly under stress.

FEATURES

Table 12.36 Cerebrohepatorenal Syndrome of Zellweger

Discriminating features

1. Disorder of peroxisomes biogenesis
2. Mutations in PEX1, PEX2, PEX3, PEX5, PEX6, PEX10, PEX12, PEX13, PEX16, PEX19 or PEX26 gene

Consistent features

1. Seizures
2. Hypotonia
3. Characteristic facies with flat supraorbital ridges
4. Widely patent fontanelles and sutures
5. Hepatomegaly
6. Failure to thrive
7. Subcapsular renal cysts
8. Nonspecific aminoaciduria
9. No or ghost peroxisomes in liver and renal tubular epithelia
10. Multiple defects of peroxisomal functions; dihydroxyacetone phosphate acyltransferase deficiency in fibroblasts; pipecolic aciduria and acidemia; elevated very long chain fatty acids in serum and plasma; abnormal bile acid metabolites; abnormal plasmalogen synthesis

Variable features

1. Cataracts, retinitis pigmentosa, glaucoma, cloudy cornea
2. Congenital heart lesions
3. Cryptorchidism or cliteromegaly
4. Limb abnormalities
5. Calcific stippling of epiphysis and patellae
6. Redundant skin on the neck
7. Osteoporosis
8. Jaundice
9. Gastrointestinal bleeding
10. Elevated serum iron and total iron-binding capacity
11. Hypoglycemia
12. Vitamin E, A, D, and K deficiency

PEARLS & PERILS

Cerebrohepatorenal Syndrome of Zellweger

- Zellweger syndrome should be suspected in newborns with craniofacial dysmorphism, seizures, and hypotonia. Cataracts and hepatomegaly may not be present at birth.
- Renal cysts and subependymal cysts may be demonstrated by ultrasound.
- X-rays of the lower extremities may demonstrate osteoporosis and/or chondral calcifications, most marked in the patellas.
- Laboratory findings typical of Zellweger syndrome include hyperpipecolicacidemia, elevated levels of C26 very long chain fatty acids and the C26:0/C22:0 ratio, elevated levels of C27 bile acid intermediates, and sometimes elevated levels of phytanic acid.
- Dihydroxyacetone phosphate acyltransferase defects and absence of peroxisomes in the liver prove the diagnosis.

Infantile Refsum disease

Infantile Refsum resembles Zellweger syndrome but with milder muscular hypotonia and less feeding difficulties. Patient have minor dysmorphic features such as simian creases, pectus excavatum, redundant skin folds in the neck, epicanthal folds, low set ears, flattened facial profile, high arched palate, undescended testes, and/or contractures. Most patients learn to walk, although gait may be ataxic and broad based. Diarrhea and vomiting with mild hepatomegaly, weight loss and failure to thrive may precede onset of neurologic symptoms. Bilateral ptosis and generalized hypotonia are frequently observed during first year of life. Between 6 and 36 months of age, neurologic deterioration leads to progressive hearing loss, poor vision, nystagmus, and severe mental retardation. Late in the course of the illness, seizures and increased spasticity dominate the clinical picture. A prolonged survival into the second and third decade is the rule.

X-rays of long bones demonstrate osteoporosis in the absence of chondrodysplasia punctata. No renal cysts are found by abdominal ultrasound. CT scan of brain may show atrophy or subdural hematoma. MRI demonstrates leukodystrophy. ERG is extinguished and VEP shows only feeble responses. Nerve conduction studies may be normal or demonstrate a polyneuropathy (Poll-Thé *et al.* 1987) (for biochemical features see Table 12.37). Therapeutic trials suggest that a phytanic acid restricted diet, fat-soluble vitamin supplementation and bile acid therapy may be beneficial in selected patients.

KEY CLINICAL QUESTIONS

- Did you have your child's hearing tested? All patients with infantile Refsum syndrome have a sensorineuronal hearing loss. Most patients are floppy at birth, show mild dysmorphic features, acquire the ability to walk and remain severely retarded but stable until mid-teens.

FEATURES

Table 12.37 Infantile Refsum

Discriminating features

1. Disorder of peroxisomal biogenesis
2. Mutations in PEX1, PEX2, PEX5, PEX6, PEX12 or PEX226 gene

Consistent features

1. Early systemic symptoms: hepatomegaly, failure to thrive, hypocholesterolism
2. Hypotonia
3. Minor dysmorphic features
4. Late neurologic deterioration with deafness, retinitis pigmentosa, microcephaly, severe mental retardation
5. No aminoaciduria
6. No peroxisomes in liver and renal tubular epithelia
7. Dihydroxyacetone phosphate acyltransferase deficiency in fibroblasts
8. Elevated phytanic, hydroxyphytanic, and pristanic levels
9. Elevated VLCFA, pipecolic acid and bile acid intermediates
10. Abnormal plasmalogen synthesis

Variable features

1. Seizure
2. Polyneuropathy
3. Subdural hematoma
4. Vitamin K responsive coagulation defects
5. Hyperbilirubinemia
6. Spasticity
7. Vitamin E deficiency

PEARLS & PERILS

- Protracted diarrhea with low cholesterol levels appear during the first months of life in infantile Refsum syndrome.
- Patients with infantile Refsum syndrome can survive until adolescence or adulthood.
- Neurosensory hearing loss and elevation of phytanic acid differentiate infantile Refsum from X-linked ALD.
- Mental retardation and elevation of VLCFA differentiate infantile Refsum from Refsum disease.

Neonatal adrenoleukodystrophy

In neonatal adrenoleukodystrophy (NALD) dysmorphic features are less striking and more variable than in Zellweger syndrome, including mid-facial hypoplasia with depressed nasal bridge, epicanthal folds, ptosis, short philtrum, prominent forehead, and abnormal ears (Fig. 12.11). In addition, patients may have simian creases and/or cryptorchidism. Some infants appear severely ill at birth with hypotonia, stridor, poor respiratory efforts and seizures while others appear near normal at birth. Half are macrocephalic at birth. NALD patients show initial, slow psychomotor development, rarely advancing beyond mental age of 12 months. Some may walk and say a few words. Hypotonia is the rule before regression sets in. Hearing and vision are frequently impaired. Cataract and retinopathy are common. Hepatomegaly, when present, is mild.

Severe growth retardation is usually noted by 2 years of age. Some patients develop subdural hematoma. The age at which regression begins varies from 12 months to more than 7 years of age (Kelly *et al.* 1986) Intention tremor, ataxia, hyporeflexia and sensory defects develop while truncal hypotonia persists. Survival into the second decade has been reported. If not present neontally, seizures usually develop during the degenerative period.

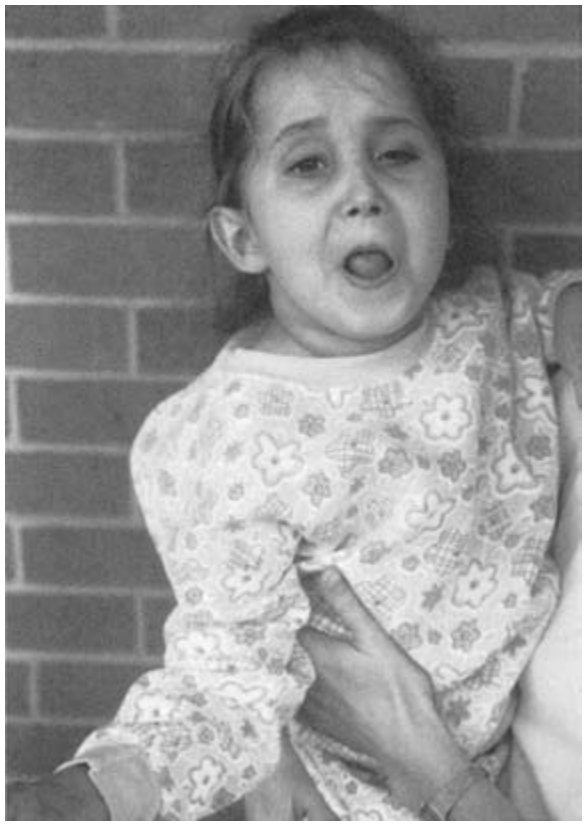

Fig. 12.11 In this 12-year-old girl, the diagnosis of neonatal adrenoleukodystrophy was suggested by loss of acquired motor skills, unusual facial features and generalized muscle wasting and weakness with bifacial involvement, truncal hypotonia, and limb spasticity. There was no hepatomegaly.

X-rays of long bones demonstrate osteoporosis but no sign of chondrodysplasia punctate. No cysts are found on renal ultrasound. MRI of brain demonstrates a leukodystrophy. ERG is extinguished. Brainstem auditory evoked responses are abnormal. Nerve conduction studies may demonstrate polyneuropathy.

Hypocholesterolenemia, vitamin E deficiency, vitamin D deficiency, and clotting factor deficiencies are frequently demonstrated. Most patients have subnormal adrenal cortical response to ACTH stimulation. CSF may show elevation of proteins. Saturated VLCFA (C26:0) are usually elevated while mono-unsaturated C26:1 VLCFA are normal (Kelly *et al*. 1986) C26:C22 ratio is increased. Extremely low levels of docosahexanoic acid (DHA) are found (Martinez *et al*.1993). Pipecolic acid may be normal or elevated. Plasmalogen may be normal or decreased (Sakai *et al.* 1986). DHAP-AT activity in fibroblasts may be normal or decreased. Peroxisomes are usually presenting but decreased in liver (Table 12.38). It

FEATURES

Table 12.38 Autosomal Recessive Neonatal Adrenoleukodystrophy (NALD)

Discriminating features

1. Disorder of peroxisomal biogenesis
2. Mutations in PEX1, PEX5, PEX6, PEX10, PEX13 or PEX26 gene

Consistent features

1. Autosomal recessive
2. Hypotonia and hyporeflexia
3. Failure to thrive
4. Psychomotor retardation
5. Dysmorphic features less severe than in Zellweger syndrome
6. Osteoporosis
7. Abnormal BAER
8. Decreased number and size of liver peroxisomes
9. Increased VLCFA (C26:0) and low C26:C22 ratio
10. Normal phytanic and bile acids
11. DHAP-AT normal or decreased
12. Abnormal plasmalogen synthesis

Variable features

1. Enlarge liver and impaired liver function
2. Adrenal insufficiency
3. Pigmentary retinal disturbances
4. Cataracts
5. Nystagmus
6. Ataxia
7. Seizures
8. Deafness
9. Subdural hematoma

PEARLS & PERILS

- Perilesional enhancement usually does not occur in NALD, as in X-linked NALD.
- NALD may be misdiagnosed as cerebral palsy in patients who show little or no progression of symptoms.

KEY CLINICAL QUESTIONS

- Did your infant make any maturation gains after 1 year of age? Most infants with NALD are floppy and poor feeders at birth. Dysmorphic features are mild. Maturation is slow reaching a plateau phase around 1 year of age. The plateau phase may last several years. Phase of regression is frequently heralded by seizures.

has been suggested that docosahexanoic (DHA) deficiency causes visual and brain dysfunction. Therapy with pure DHA ethyl ester appears to produce good results (Martinez *et al.*1993).

Rhizomelic chondrodysplasia punctata type I

Rhizomelic chondrodysplasia punctata (RCDP) type I is characterized clinically by short limb dwarfism, affecting especially the proximal parts of the limbs (rhizomelic shortening of knees and hips), dysmorphic facial features, congenital cataract, contractures of knees and hips, profound psychomotor retardation, spastic quadriparesis and epilepsy. Dysmorphic facial features include depressed bridge of the nose, flat supraorbital ridge, upturned nostrils, short nose, hypertelorism, epicanthal folds, high arched palate, and long philtrum. The anterior fontanel is large with an open metopic suture. The head is small. External ears are dysplastic. Neck and proximal limbs are short. Hands may exhibit camptodactyly with abnormal palmar creases. Chest is long and narrow. Intrauterine growth retardation is the rule. The eyes may show corneal changes and evidence of cataract formation (70%). Skin changes, such as those observed in ichthyosiform erythroderma, are demonstrated in about 25% of patients (Bodian 1966). Other malformations may include pulmonary stenosis (Gray *et al*. 1992) and laryngeal atresia (Storm & Fassa 1991). Sucking is poor, leading to failure to thrive. In 40% of patients, recurrent infections in infancy cause death in the first year of life. A milder phenotype mimicking noninfantile Refsum disease has been described in some patients presenting congenital cataract.

Radiologic abnormalities include punctate stippling of epiphyses at the knees, hips, elbows, shoulders, and vertebrae visible in late infancy. CT scan and MRI of the brain show cortical and subcortical atrophy (Williams *et al*. 1991). EEG may demonstrate seizure activity (Gray *et al*. 1992). The electroretinogram is grossly abnormal. Brainstem auditory evoked responses may be delayed. Ultrasound fails to show renal cysts.

Plasma phytanic acid level in RCDP is equal to that seen in classic Refsum disease. Plasma VLCFA, bile acids, and pipecolic acid levels are normal. Plasmalogen synthesis in cultured fibroblasts is deficient, distinguishing RCDP from

KEY CLINICAL QUESTIONS

- Did you notice in your newborn a proximal shortening of the limbs and was there evidence of cataract shortly after birth? If long bone x-ray shows stippled calcifications of the epiphysis and eye evaluation reveals cataract within the first few months of life, diagnosis of rhizomelic chondrodysplasia punctata type I should be suspected.

PEARLS & PERILS

- Rhizomelic chondrodysplasia punctata should not be confused with autosomal recessive (multiple sulfatase deficiency) and X-linked recessive (defect in arylsulfatase E) nonrhizomelic chondrodysplasia punctata. The recessive nonrhizomelic chondrodysplasia punctata shares with rhizomelic chondrodysplasia punctata the evidence of ichthyosis, deafness and progressive neurodegeneration (see metachromatic leukodystrophy). There is no limb shortening but instead hypoplasia of distal phalanges is noted.
- Rhizomelic chondrodysplasia punctata (autosomal recessive) should not be confused with X-linked dominant.
- Chondrodysplasia punctata (Conradi–Hünermann syndrome). In rhizomelic chondrodysplasia punctata, the limbs are short proximally and bilaterally and both sexes are affected. In Conradi-Hünermann syndrome, limb shortening is asymmetrical and not always proximal. This disorder of cholesterol biosynthesis is lethal in males. Cataract is sectorial. In severely affected individuals, bilateral findings may mimic rhizomelic chondrodysplasia. Diagnosis is confirmed by measuring the plasma concentration of sterols and assay of sterol-Δ8-isomerase.
- Plasmalogen biosynthesis defects are found in all cases of rhizomelic chondrodysplasia punctata. If plasma phytanic acid is elevated suspect PEX7 gene defects. If plasma phytanic acid is normal, suspect rarer isolated defects of peroxisomal bile acid synthesis.
- PEX7 gene mutations may cause a noninfantile Refsum phenotype. A deficiency in plasmalogen synthesis is consistently found.

classic Refsum disease. Hepatocytes lack peroxisomes or contain an increased number of large, irregular shaped peroxisomes (Heymans *et al*. 1986) (Table 12.39). Molecular analysis of the PEX7 gene (chromosome locus 6q22-q24) is available. Present treatment consists of palliative orthopedic care, cataract removal, and dietary restriction of phytanic acid.

Pseudoneonatal adrenoleukodystrophy

Pseudoneonatal adrenoleukodystrophy (pseudo-NALD) is an autosomal recessive isolated defect of peroxisomal acyl CoA oxidase, the first enzyme of beta-oxidation system, resulting in a phenotype mimicking NALD. Dysmorphic features when present may include hypertelorism, depressed nasal bridge, low set ears, polydactyly (Suzuki *et al.* 1994). Profound hypotonia and areflexia are present at birth. Intrauterine growth retardation is the rule. Early onset seizures and slow psychomotor development are the rule. Some patients walk and say a few words. Hearing and vision are impaired. Age of death is variable up to 5 years of age.

Plasma VLCFA are elevated while bile acid intermediates, pristanic acid, and phytanic acid levels are normal. DHAP-AT activity in skin fibroblasts is normal (Poll-Thé *et al.* 1988). In some patients a large deletion of the acyl CoA oxidase gene is found while other cases probably result from a point mutation (Suzuki *et al.* 1994). This disorder is associated with enlarged hepatic peroxisomes (Table 12.40).

KEY CLINICAL QUESTIONS

- Was there any perinatal complication? Both pseudo-NALD and pseudo-Zellweger clinically present with neonatal seizures and hypotonia, mimicking perinatal asphyxia. Plasma VLCFAs are elevated and fibroblast plasmalogen synthesis is normal in both conditions. The clinical course and urine bile acid intermediates differentiate the two syndromes.

FEATURES

Table 12.39 Rhizomelic Chondrodysplasia Punctata

Discriminating features

1. Disorder of peroxisomal biogenesis (complementation group 11)
2. PEX7 gene defects

Consistent features

1. Rhizomelic dwarfism
2. Dysmorphic features
3. Failure to thrive
4. Psychomotor delay
5. Contractures
6. Absent hepatomegaly liver dysfunction & malabsorption
7. Cataract
8. Elevated phytanic acid
9. Normal VLCFA and bile acids
10. Deficiencies in the enzymes related to plasmalogen synthesis
11. Abnormal peroxisomes

Variable features

1. Microcephaly
2. Corneal clouding
3. Retinopathy
4. Stippled calcifications of epiphyses
5. Ichthyosis
6. Epilepsy
7. Laryngeal atresia
8. Pulmonary stenosis

Pseudo-Zellweger syndrome

Pseudo-Zellweger syndrome results from a group of autosomal recessive, isolated defects of peroxisomal beta-oxidation that affect either bifunctional enzyme or peroxisomal thiolase, and resulting clinically in a phenotype mimicking Zellweger syndrome (see Table 12.41) (Goldfischer *et al.* 1986; Suzuki *et al.* 1994).

Trihydroxycholestanic acidemia

Trihydroxycholestanic acidemia is an autosomal recessive isolated defect of peroxisomal bile acid metabolism due to trihydroxycholestanoic acyl-CoA oxidase deficiency presenting with progressive ataxia in the second or third year of life (Christensen *et al.* 1990; Vanhove *et al.* 1993). Patient

FEATURES

Table 12.40 Pseudo-NALD

Discriminating feature

1. Peroxisomal acyl CoA oxidase deficiency

Consistent features

1. Slow development precedes regression
2. Seizures
3. Visual and hearing impairment
4. Survival up to 5 years of age
5. Large peroxisomes in liver
6. Elevated VLCFA levels
7. Normal plasmalogen synthesis
8. Normal bile and phytanic acid levels

Variable features

1. Facial dysmorphic features
2. Retinal degeneration

FEATURES

Table 12.41 Pseudo-Zellweger Syndrome

Discriminating feature

1. Peroxisomal thiolase or bifunctional enzyme deficiency

Consistent features

1. Severe hypotonia
2. Minimal development progress
3. Seizures
4. Visual and hearing impairment
5. Brain dysplasia
6. Death in infancy or early childhood
7. Abundant peroxisomes in liver
8. Elevated VLCFA and bile acid intermediates
9. Normal plasmalogen synthesis

Variable feature

1. Facial dysmorphic features
2. Hepatomegaly
3. Osteopenia
4. Stippled patella
5. Renal microcysts
6. Bleeding tendency
7. Adrenal insufficiency
8. Ventricular septal defect
9. Retinitis pigmentosa

is found to be hypotonic without deep tendon reflexes and hearing is impaired. Biochemical studies show an accumulation of di- and trihydroxycholestanoic acid in urine.

Rhizomelic chondrodysplasia punctata type II and type III

Rhizomelic chondrodysplasia punctata type II is caused by an isolated defect of peroxisomal dihydroxyacetonephosphate acyltransferase (DHAP-AT) while type III results from an isolated defect of peroxisomal alkyl-DHAP synthase (alkyl-DHAP synthase) (Wanders *et al*. 1994). Rhizomelia may be absent. Mental retardation, hypotonia and stippled epiphysis are consistent features. Cataract and skin changes are consistently seen. In all forms of RCDP plasma VLCFAs are normal and plasmalogen synthesis in fibroblasts is decreased. In RCDP variants, unlike classic RCDP type I, phytanic acid metabolism is normal and liver biopsy shows mature peroxisomes. The diagnosis is confirmed by measurement of the specific enzyme activity in cultured skin fibroblasts.

Mevalonic aciduria

Mevalonic aciduria is an autosomal recessive disorder of peroxisomal cholesterol and nonsterol isoprene biosynthesis associated clinically with two clinical phenotypes which

PEARLS & PERILS

- Mevalonate kinase deficiency can be seen in peroxisomal biogenesis disorders such as Zellweger syndrome.
- Mevalonic aciduria should be suspected in patients with visual impairment and development delay anytime there is a history of recurrent inflammatory crisis. Some patients survive in adulthood.

may overlap. The subacute classic neurologic form is characterized by psychomotor retardation, hypotonia, failure to thrive, recurrent crisis with fever, and gastrointestinal symptoms. The chronic "systemic" form is a hyperimmunoglobulin D (hyper IgD) and periodic fever syndrome. The human gene for mevalonate kinase has been localized to chromosome 12q24 (Schafer *et al*. 1992). Compound heterozygosity can result in mevalonic aciduria.

Patients with subacute neurologic mevalonic aciduria consistently present in infancy with psychomotor retardation, and failure to thrive. Dysmorphic features such as microcephaly, dolichocephaly, frontal bossing, hypertelorism, down-slanted eyes, large fontanels, hypoplasia alae nasi, low-set ears, and syndactyly have been reported in some patients (Mancini *et al*. 1993; Hoffman *et al*. 1993). Typically, noninfectious recurrent crisis characterized by fever, diarrhea, and vomiting develop in most patients. These episodes are accompanied by arthralgia, edema, morbiliform rash, lymphadenopathies, hepatomegaly, hypotonia, lethargy, and seizures. Severely affected patients die in infancy. A cardiomyopathy with heart block may develop in some patients. Survivors have a mild mental retardation, sometimes accompanied by hypotonia and cerebellar ataxia. Cataract is found in half of the patients.

The hyperimmunoglobulin D (hyper IgD) and periodic fever syndrome is an autoinflammatory disease beginning in infancy and characterized by lifelong recurrent episodes of fever accompanying signs and symptoms such as abdominal distress, erythematous rash, aphtous ulcers, arthralgia and lymphadenopathies. Most patients have no neurologic symptom, although some patients exhibit mild to severe mental retardation, cerebellar ataxia and a progressive blindness due to tapetoretinal degeneration and cataract. Seizures have been reported in two cases. Survival to adulthood is common (Simon *et al*. 2004).

Bone age and skull suture closure are frequently delayed. Brain imaging demonstrates cerebral and cerebellar vermis atrophy. White and gray matter signals are normal. Nerve conduction velocities and EMG are normal. EEG findings are variable.

Blood cholesterol is normal or low. A deficiency in plasma ubiquinone-10 (Q_{10}) is demonstrated in plasma of patients

KEY CLINICAL QUESTIONS

- Does your child with unsteady gait have developmental delay, failure to thrive, and appears susceptible to infections? In such a child, look for unusual facial features, cataract, hepatomegaly and cerebellar hypoplasia. Organic acids should be tested in the urine.

who develop a cardiomyopathy, hypotonia (Hübner *et al*. 1993) and cerebellar atrophy. The excretion of fat in the feces, when present, results from a deficient synthesis of bile acids (Gibson *et al*. 1993). Liver enzymes may be normal or elevated. Anemia and increased sedimentation rate can be found during recurrent crisis. Hyperimmunoglobulinemia D is found in patients with episodic fever. Urinary excretion of leukotriene E_4 is elevated in most patients (Mayateke *et al*. 1993).

The diagnosis can be made readily by analysis of urine organic acids which demonstrate mevalonic aciduria. Plasma levels of mevalonate are also elevated, although the elevation may only be transient in patients with episodic fever. Mevalonate kinase deficiency is proven by assay of the enzyme in fibroblasts or lymphocytes (Table 12.42).

Treatment with lovastatin, an inhibitor of hydroxy methyl glutaryl CoA reductase, to reduce mevalonate production, exacerbates symptoms. Supplementation with cholesterol, coenzyme Q10, vitamins E, D, and A may be beneficial. Corticosteroid therapy prevents death during clinical crisis.

FEATURES

Table 12.42 Mevalonic Aciduria

Discriminating feature

1. Mevalonic kinase deficiency

Consistent features

1. Mevalonic aciduria
2. Recurrent "inflammatory" crisis

Variable features

1. Cataract
2. Tapetoretinal degeneration
3. Mental retardation
4. Failure to thrive
5. Myopathy with elevated CK
6. Cerebellar atrophy
7. Cardiomyopathy
8. Dysmorphic features
9. Seizures
10. Coenzyme Q10 deficiency

Diffuse mitochondrial encephalomyopathies

The mitochondrial encephalomyopathies are hereditary neurodegenerative disorders characterized by multiple features indicating dysfunction of mitochondrial aerobic oxidative metabolism: elevated levels of lactate and pyruvate in the blood and CSF, alteration of mitochondrial morphology in various tissues, and diminished activity of oxidative mitochondrial enzymes (Table 12.43).

The mitochondrial encephalomyopathies are clinically, biochemically, and genetically heterogeneous. Many mitochondrial encephalomyopathies have been discussed in various sections of this chapter based on the most prominent neuropathologic features: Menkes disease and Alpers disease are examples of polioencephalopathies; Leigh syndrome, familial bilateral striatal necrosis (BFSN), Mohr–Tranebjaerg syndrome (MTS) and Wilson disease are corencephalopathies; neuropathy, ataxia and retinitis pigmentosa syndrome (NARP) and Friedreich ataxia are spinocerebellopathies. In this section, seven diffuse mitochondrial encephalopathies will be discussed. It has been demonstrated that the nature of a given clinical syndrome depends not so much on the exact oxidative enzyme that is defective but rather on the degree to which flux through oxidative pathways is impaired. Therefore, affected individuals within a single kindred may display different clinical syndromes (i.e. Leigh and NARP; Leigh being seen in the most severely affected individuals). Similarly, in different kindreds the same mitochondrial biochemical defect may lead to various clinical syndromes. Additionally, the same clinical syndromes can be caused by various biochemical defects. Organs other than the brain and muscle are frequently involved. Systemic involvement

FEATURES

Table 12.43 Mitochondrial Encephalomyopathies

Discriminating feature

1. Defective mitochondrial oxidative phosphorylation due to defective nuclear or mitochondrial DNA

Consistent features

1. Increased lactate in areas of brain involved by acute process (by proton magnetic spectroscopy)
2. Increased lactate in the blood after exercise or glucose loading test

Variable features

1. Ragged-red fibers in muscles
2. Histochemical changes
3. Morphological changes of mitochondria
4. Elevated lactate and pyruvate in CSF

may result in renal tubular, cardiac, pancreatic, and bone marrow dysfunction, endocrinopathy, neuropathy, hearing loss, and retinopathy.

The mitochondrial encephalomyopathies can result from nuclear gene defects (mendelian inheritance) or abnormal mitochondrial DNA. Nuclear gene defects may result in mutations in the genes encoding the structural components of the respiratory chain (e.g. ND genes in Leigh syndrome), the genes required for the mitochondrial protein importation (TIMM8A gene in Morh-Tranebjaerg syndrome), the genes required for the assembly of active complexes (SURF-1 gene in Leigh syndrome), the genes required for transport of protein cofactors (ATP7B gene, encoding the Golgi and mitochondrial hepatic transmembrane copper-transporting ATPase, in Wilson disease), and the genes required for the intramitochondrial cofactor homeostasis (FRDA gene in Friedreich ataxia). In addition, mitochondrial DNA defects may result from abnormalities in communication between nuclear and mitochondrial genome. Mitochondrial DNA "depletion," a quantitative alteration in mitochondrial DNA, results from a defective nuclear-encoded protein controlling mitochondrial replication (deoxyguanosine kinase gene in lethal infantile mitochondrial disease of Boustany). Qualitative alterations in mitochondrial DNA such as multiple mitochondrial DNA "deletions" result from defective nuclear-encoded proteins required for maintenance (ANT1 gene, an ADP/ATP carrier protein in CPEO or thymidine phosphorylase gene in mitochondrial neurogastrointestinal encephalopathy) and repair (mitochondrial DNA polymerase gamma gene in autosomal dominant CPEO) of mitochondrial DNA. Other qualitative alterations such as mitochondrial "deletions" and duplications are sporadic. Mitochondrial DNA point mutations are always maternally inherited due to exclusive maternal transmission of mitochondrial DNA. Mitochondrial DNA point mutations are homoplastic when intracellular mitochondrial DNA is purely mutant. Such mutations are, of necessity, only mildly deleterious and affect structural gene of the respiratory chain. Mitochondrial DNA point mutations are heteroplasmic when mixed populations of mutant and normal mitochondrial DNA coexist in each cell. Such mutations frequently affect tRNA. The patient's clinical symptoms and survival depend on amount of normal mitochondrial DNA present in each tissue. The neurologic syndromes associated with abnormal mitochondrial DNA are summarized in Table 12.44. Mitochondrial encephalopathies due to nuclear DNA mutations are summarized in Table 12.45.

One of the most encouraging aspects of this group of diseases is the fact that preventive/palliative therapy can be achieved if the basic pathophysiology is understood. Prevention of exacerbation can be achieved simply by rapid

TABLE 12.44

Neurologic Syndromes Associated with Abnormal Mitochondrial DNA

Syndrome	Abnormal mitochondrial DNA	Inheritance
MELAS	Heteroplasmic point mutations in genes ecoding $tRNA^{LEU}$ (3243,3260,3271,3291,3308,4271,5601,3291, 8344,13513)	Maternal
	Deletion/duplications	Sporadic
	No defect (defects of mitochondrial oxidative metabolism)	Nuclear
MERRF	Heteroplasmic point mutations in genes encoding $tRNA^{LYS}$ (3243,3256,7512,8296,8344,8356,8363)	Maternal
CPEO/KSS	Heteroplasmic point mutations in genes encoding tRNA (3243,4285,4298,5692,5703,5877,8344 12308,12311,12315)	Maternal
	Deletion/duplication	Sporadic
	Multiple deletions	Nuclear
NARP	Heteroplasmic point mutations encoding complex V (8993)	Maternal
Leigh	Heteroplasmic point mutations in genes encoding tRNA (3243,8344), complex I, complex V (8851,8993,9176)	Maternal
	No defect (defects of mitochondrial oxidative metabolism)	Nuclear
FBSN	Heteroplasmic point mutations (14459,14596,11696)	Maternal
LHON	Heteroplasmic *and/or* point mutations in genes encoding complex I (3394,3460,4216,4160,4917,5244, 7444,9101,11696,11778,13708,14459,14484,14498,15257,15812)	Maternal
MNGIE	Multiple deletions	Nuclear
LIMD	Heteroplasmic point mutation (15923,15924)	Maternal
	Depletion	Nuclear
Alpers	Heteroplasmic point mutation in COX II (7706)	Maternal
	Deletions	Nuclear

MELAS: mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MERRF: myoclonic epilepsy with ragged-red fibers; CPEO: chronic progressive external ophthalmoplegia; KSS: Kearns-Sayre syndrome; NARP: neurogenic muscle weaknessa, ataxia, retinitis pigmentosa; FBSN: familial bilateral striatal necrosis, LHON: Leber hereditary optic neuroretinopathy; MNGIE: mitochondrial myopathy, peripheral neuropathy, gastrointestinal, and encephalopathy disease; LIMD: lethal infantile mitochondrial disease

TABLE 12.45

Mitochondrial Encephalopathies due to Nuclear DNA Mutations

Syndrome	Gene function	Chromosome
CPEO with multiple	Adenine nucleotide translocator 1 (Ant1)	4
mitochondrial DNA	Mitochondrial DNA polymerase gamma (POLG)	15
deletions	Twinkle (C10orf2)	10
MNGIE	Thymidine phosphorylase (multiple mitochondrial DNA deletions)	22q13.32-qter
MSMA	Thymidine kinase 2 (mitochondrial DNA depletion)	16
LIMD	Deoxyguanosine kinase (mitochondrial DNA depletion)	2p13
Leigh	Complex I – NDUFS8 N-2 FeS	9q33.2–34.11
	Complex I – NDUFS7	11q13.1
	Complex II – flavoprotein subunit (SDH2)	5p16
	Complex II – iron-sulfur protein (SDH1)	1p35–36
	Complex IV – SURF-1	9q34
	PDH-E1α	X
DDS	TIMMSA gene encoding a component of the mitochondrial-protein import machinery	X
Friedreich	Frataxin, Fe transport	9q13
AD HSP 13	Mitochondrial import chaperonin HSP60	2q24-q34
AR HSP7	Paraplegin, mitochondrial metalloprotease with ATPase associated activities	16q24.4l
Wilson	Hepatic transmembrane copper ATPase, Cu transport	13q14.3-q21.1
Menkes	Extrahepatic transmembrane copper ATPase, Cu transport	Xq13.33
Alpers	Mitochondrial DNA polymerase gamma (POLG)	10

CPEO: chronic progressive external ophthalmoplegia; MNGIE: mitochondrial myopathy, peripheral neuropathy, gastrointestinal, and encephalopathy disease; MSMA: myopathy and spinal muscular atrophy; LIMD: lethal infantile mitochondrial disease; DDS: deafness-dystonia syndrome of Mohr-Tranebjaerg; HSP: hereditary spastic paraplegia

treatment of infections and fever and avoidance of fasting and strenuous exercise. Frequent or continuous feeding during night and/or high caloric intake may be necessary to avoid catabolic state. Drugs which inhibit mitochondrial protein synthesis (tetracyclines, chloramphenicol), sequestrate carnitine (valproic acid), and inhibit respiratory chain (barbiturate, phenytoin) should be avoided. Other palliative therapeutic measures include removal of toxic products, reduction of the load of substrate presented to the mutant enzyme, coenzyme supplementation at pharmacologic levels, replacement of products (important intermediates in metabolism) that are missing due to enzyme deficiencies, and pharmacologic therapy. Detoxification strategies are summarized in Table 12.46.

Restricting dietary precursors decreases production of toxic metabolites. A low-carbohydrate, high-fat diet (essentially a ketogenic diet) is effective in preventing lactic acidosis in patients with deficiency in the El subunit of pyruvate dehydrogenase complex, whereas a high-carbohydrate diet has favorable effect in the deficiency of E3 subunit of pyruvate dehydrogenase complex and pyruvate dehydrogenase phosphatase deficiency.

Coenzyme supplementation at pharmacologic levels should be tried (Table 12.47). Sodium succinate is a product

TABLE 12.46

Detoxification Strategies in Mitochondrial Encephalomyopathies

Drugs	Dosage	Route	Conditions
Dichloroacetate	15–150 mg/kg/day	IV/PO	Lactic acidosis
Coenzyme Q10	4.3 mg/kg/day	PO	Complex I or II deficiency
Phytonadione	0.36 mg/kg/day	PO	Complex III deficiency
Menadione	1.1–1.5 mg/kg/day	PO	Complex III deficiency
Ascorbic acid	57 mg/kg/day	PO	Complex III deficiency
Idebenone	5 mg/kg/day	PO	Mitochondrial disorders
L-Carnitine	50–300 mg/kg/day	PO/IV	Mitochondrial disorders
Lipoic AcidM	10–50 mg/kg/day	PO/IM	Respiratory chain defects
Vitamin E	200–400 mg/kg/day	PO	Respiratory chain defects

TABLE 12.47

Coenzyme Therapy in Mitochondrial Encephalomyopathies

Drugs	Dosage	Route
Biotin	10–50 mg/day	PO
Thiamine	150–300 mg/day	PO/IV
Riboflavin	30–300 mg/day	PO/IV
Pyridoxine	50–500 mg/day	PO/IV
Hydroxycobalamin	1–10 mg/day	IV/IM

that is favorably replaced in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS) and chronic progressive external ophthalmoplegia (CPEO). Corticosteroids have been reported to be effective in MELAS.

Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes syndrome

Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is a maternally inherited or sporadic progressive, neurodegenerative disease that is characterized by migraine headaches, focal neurologic defects, and focal or generalized seizures. Lactic acidosis is an inconsistent feature. Many cases of MELAS have been reported to be associated with isolated deficiency of NADH dehydrogenase (complex I) activity (Koya *et al.* 1988). Maternal inheritance is suggested by detection of mitochondrial DNA' point mutations encoding for mitochondrial RNA. In sporadic patients combining features of MELAS and Kearns–Sayre syndrome (KSS), mitochondrial deletions can be found (Zopanc *et al.* 1991).

Patients with MELAS syndrome are usually asymptomatic in infancy and have normal early development. Most patients are short. Some patients display muscle weakness, fatigability, and myalgia before the onset of central neurologic dysfunction. Chronic asthma may be an unusual presentation of MELAS (Shanske *et al.* 1993). Central neurologic symptoms begin between infancy and young adulthood. The mitochondrial angiopathy may manifest early in the skin as purpura (Horiguchi *et al.* 1991). Most patients have recurrent epileptic seizures, which are partial or generalized. Myoclonic seizures are uncommon. Attacks of prolonged migraine headaches with vomiting are prominent in some patients. In the wake of headaches or partial seizures, patients may abruptly develop stroke-like episodes. Episodes of cortical infarction lead to the gradual decline of motor, sensory, and mental functioning.

There is usually a history of bilateral hemiparesis with corticospinal tract signs, dysarthria, visual impairment with hemianopia, and decline in cognitive function. Patients progressively become bedridden, quadriparetic, deaf, blind, and demented. A progressive myoclonus epilepsy can be seen late in the course of the illness. Ocular signs and symptoms may include posterior subcapsular cataract, bilateral ptosis, chronic external ophthalmoplegia, diffuse choroidal atrophy, atypical pigmentary retinopathy with macular involvement, and optic atrophy (Rumelt *et al.* 1993). Myocardial involvement may produce mitral regurgitation (Suzuki *et al.* 1993), hypertrophic or dilated cardiomyopathy (Inui *et al.* 1992), and cardiac conduction defects, including ventricular arrhythmias, pre-excitation syndromes, and cardiac conduction block (Ciafaloni *et al.* 1992). Renal involvement may result in nephrotic syndrome (lnui *et al.* 1992) or renal tubular dysfunction (Ciafaloni *et al.* 1992). Endocrine involvement may include diabetes mellitus, pituitary dwarfism, and hypothyroidism (Inui *et al.* 1992). Death usually occurs within a few years from onset.

Laboratory findings of MELAS syndrome are variable. Most patients present with elevations of lactate and pyruvate in the blood and CSF. However, lactic acidosis may be intermittent and glucose tolerance tests may fail to produce lactic acidemia (Breningstall & Lockman 1988). CSF proteins may be elevated (Shapira *et al.* 1975). Mitochondrial DNA point mutation analysis should evaluate 3243, 3271, and 3252 MELAS point mutations in blood. Patients with MELAS syndrome may develop autoantibodies, such as rheumatoid factor and antimitochondrial antibodies (Shapira *et al.* 1990).

PEARLS & PERILS

- Approximately 80–90% of MELAS patients have a point mutation in the mitochondrial gene encoding for the $tRNA^{Leucine(UUR)}$, either at the base pair 3243 or at base pair 3271.
- Patients suffering from recurrent migrainous strokes and progressive dementia should be tested for mitochondrial DNA point mutations. Most patients with hemiplegic migraine do not have a defect in mitochondrial DNA.
- Cardiac manifestations of MELAS are major determinants of prognosis.
- Most patients with MELAS have elevated blood lactate concentrations, but it may be intermittent, and is not mandatory for diagnosis of MELAS.
- CT scan and MRI of brain are less sensitive than SPECT scan in visualizing stroke-like episodes in the early stages of the illness.
- The absence of ragged-red fibers does not exclude MELAS.
- MELAS point mutations are maternally inherited. Maternal relatives of MELAS patients may be normal or may have migraine, deafness, diabetes mellitus, limb-girdle myopathy, cardiomyopathy, or other mitochondrial encephalomyopathy (CPEO, Leigh syndrome).

Cardiac abnormalities can be shown on chest x-ray study, electrocardiography, and echocardiography. Electromyogram and nerve conduction studies may be normal or show various myopathic and neuropathic patterns (Breningstall & Lockman 1988). EEG may show focal or diffuse slowing with or without epileptogenic potentials. Neuropathology demonstrates infarct-like lesions in cortex and subcortical white matter and mitochondrial abnormalities are found in the endothelial cells smooth muscle cells of blood vessels.

The strokes in MELAS can be seen as hypoperfusion by single proton emission computed tomography (SPECT) even when MRI and CT are normal (Satoh *et al.* 1991).

CT scan of the head may show hypodensity and swelling of the cerebral cortex in multiple vascular tortuosities with a predilection for parieto-occipital regions. Sequential scans may show resolution and subsequent reoccurrence of the abnormal areas. Calcifications or hypodensities of the basal ganglia are found in some patients. Gyriform enhancement can be demonstrated on contrast studies (Allard *et al.* 1988). Some patients may show multifocal white matter hypodensities (Fujii *et al.* 1990). In advanced cases there is sulcal and ventricular prominence. In one patient with infantile-onset MELAS syndrome the author found diffuse white matter calcifications (Fig. 12.12) (Maertens *et al.* 1988). MRI of brain reveals the lesions more distinctively and precisely than CT scan. Lesions have high-signal intensities on T_2-weighted MRI (Fig. 12.13). MRI may reveal cerebellar lesions that could not be detected on CT scan (Fujii *et al.* 1990). Proton MR spectroscopy shows high lactate levels in the affected areas of the brain (Barkovich *et al.* 1993).

KEY CLINICAL QUESTIONS

- Does any one on your mother side of the family have a history of hemiplegic migraine, cerebral palsy, epilepsy, weakness, hearing loss or diabetes?

Muscle biopsy is particularly useful in reaching morphologic, biochemical, and genetic diagnosis of MELAS syndrome. Ragged red fibers are observed in some patients. Ultrastructural studies may reveal aggregates of mitochondria, which may contain paracrystalline bodies. Muscle biopsy should be performed in individuals showing MELAS phenotype and negative blood testing for point mutation analysis (Table 12.48). Treatment of MELAS syndrome is palliative and symptomatic.

Myoclonic epilepsy and ragged-red fiber

Myoclonic epilepsy and ragged-red fiber (MERRF) disease is a maternally inherited disease characterized by progressive myoclonic epilepsy, mitochondrial myopathy with ragged-red fibers, and slowly progressive dementia (Rosing *et al.* 1985; Fukuhara *et al.* 1991). Elevations of lactate and pyruvate

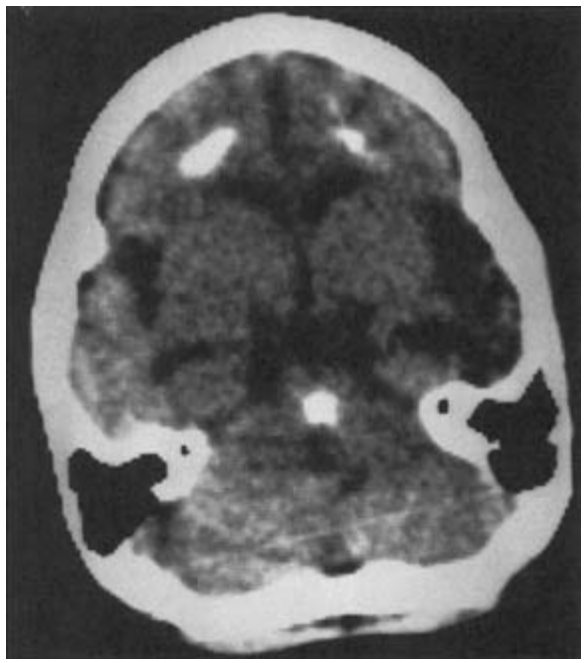

Fig. 12.12 Noncontrast CT scan of the brain showing diffuse brain atrophy with white matter calcifications in the pons and the frontal white matter in a 23-month-old girl with MELAS and cytochrome oxidase deficiency.

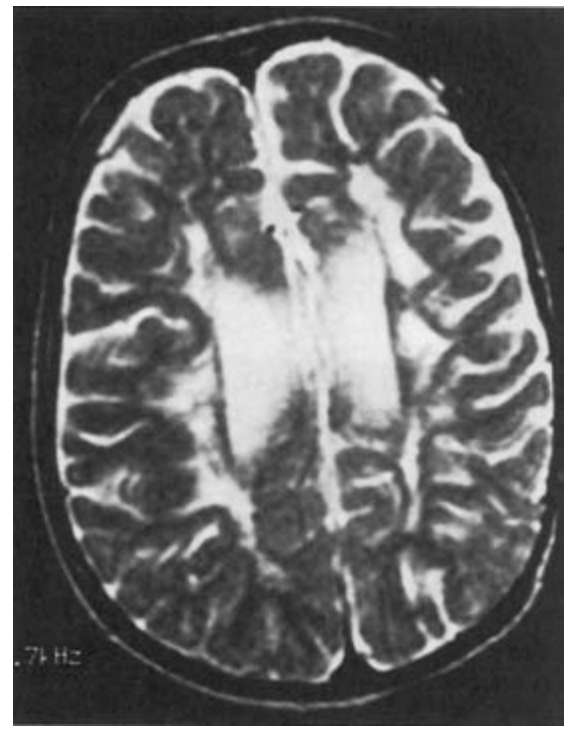

Fig. 12.13 MRI of the brain (SE 3000/80) showing bilateral, asymmetric, irregular areas of high signal involving both gray and white matter in an 18-year-old woman with MELAS.

FEATURES

Table 12.48 Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-Like Episodes

Discriminating features

1. Point mutation of mitochondrial DNA (or mitochondrial DNA deletion in patients combining MELAS and KSS phenotype)
2. Maternal inheritance

Consistent features

1. Hemiparesis or hemianopsia
2. Migraines or convulsions

Variable features

1. Lactic acidosis
2. Cortical blindness
3. Short stature
4. Hearing loss
5. Gastrointestinal symptoms
6. Dementia
7. Muscular atrophy and weakness/proximal
8. Hypertrophic or dilated cardiomyopathy
9. Renal dysfunction
10. Endocrine dysfunction
11. Ophthalmoplegic findings
12. Ragged-red fibers

PEARLS & PERILS

- Approximately 80–90% of MERRF patients have a point mutation in the gene encoding for the tRNA-^{Lysine} gene, either at the base pair 8344 or at base pair 8356.
- Ragged-red muscle fibers are not invariably found in MERRF disease.
- MERRF point mutations are maternally inherited. Maternal relatives of MERRF patients may be normal or have a mild, partial clinical syndrome.
- MERRF syndrome causes progressive myoclonus epilepsy. Other conditions causing progressive myoclonus epilepsy include Lafora disease, NCL, Gaucher disease, Unverricht–Lundborg syndrome, Huntington disease and cherry-red spot myoclonus syndrome.

in the blood and CSF suggest an oxidative phosphorylation defect. Biochemical analysis has revealed deficient activity of complex I and IV in most pedigrees (Wallace *et al.* 1988; Bindoff *et al.* 1991). Maternal inheritance is suggested by the detection of mitochondrial DNA point mutations encoding for mitochondrial tRNA.

The onset of symptoms ranges from late childhood to adulthood. Typically MERFF patients have normal early development, although the most severely affected individuals have pes cavus at birth and deafness in childhood. The cardinal triad of symptoms is myoclonus, spinocerebellar ataxia, and convulsions. The onset of this triad is between 5 and 42 years of age. Myoclonus involves the neck, trunk, and proximal portions of limbs, and is not associated with loss of consciousness. These involuntary movements are triggered by attempted postures and actions, emotional reactions, or photic and auditory stimulation. They disappear at rest and during sleep. Spinocerebellar ataxia leads to dysarthria, intention tremor, and gait ataxia. Myoclonic epilepsy and other forms of seizures are frequent. Various other findings less commonly seen in this syndrome include muscle weakness associated with easy fatigability and muscle wasting (Lance & Evans 1984), dementia (Rosing *et al.* 1985), hearing loss (Lance & Evans 1984), accumulation of lipomas (Holme *et al.* 1993), short stature, sleep apnea with respiratory failure (Byrne *et al.* 1985), and stroke-like episodes (McKelvie *et al.* 1991). Typically patients with MERRF syndrome do not have ophthalmoplegia, retinal pigmentary degeneration, or heart block. However, optic neuropathy, ophthalmoparesis with ptosis, retinopathy, and diabetes have been associated with MERFF 8356 mutation (Moraes *et al.* 1983).

Elevation of lactate and pyruvate levels in the blood and CSF is commonly intermittent. Mitochondrial DNA analysis should evaluate 8344 and 8356 MERRF point mutations in blood. However, replicative segregation of leukocyte and platelets may create false-negative values. EEG may show generalized spike-wave discharges. Photic stimulation may induce 2- to 5-Hz diffuse spike-wave epileptiform activity of posterior predominance or even a photomyoclonic response. Giant visual evoked potentials are usually demonstrated (Roger *et al.* 1992). Imaging studies of patients with MERRF are nonspecific. Some patients may present with intracerebral calcification on CT scan (Fukuhara *et al.* 1983). MRI of the brain almost always demonstrates cerebellar atrophy (Iwanga *et al.* 1992).

Although patients with MERRF generally have ragged-red fibers on muscle biopsy, some individuals with progressive myoclonic epilepsy and ataxia without ragged-red fibers show the MERRF mitochondrial DNA point mutation. Muscle biopsy, however, is useful in demonstrating mitochondrial oxidative phosphorylation defects and allowing a detailed mitochondrial DNA analysis (Table 12.49). Treatment of MERRF is no different from that of other mitochondrial encephalomyopathies.

KEY CLINICAL QUESTIONS

- Is there any sign of deafness? Deafness is common and should suggest the diagnosis. Other suggestive features include diabetes, short stature, migraine, and fatigue.

FEATURES

Table 12.49 Myoclonic Epilepsy and Ragged-Red Fiber

Discriminating features

1. Mitochondrial myopathy with defects of mitochondrial oxidative metabolism and point mutation of mitochondrial DNA.
2. Maternal inheritance

Consistent features

1. Myoclonus
2. Cerebellar ataxia
3. Epilepsy
4. Ragged-red fibers

Variable features

1. Short stature
2. Dementia
3. Hearing loss
4. Peripheral neuropathy
5. Pes cavus
6. Optic atrophy
7. Retinitis pigmentosa
8. Ophthalmoplegia
9. Diabetes
10. Stroke-like episodes
11. Lipoma

Kearns–Sayre syndrome and chronic progressive external ophthalmoplegia

Kearns–Sayre syndrome (KSS) and Ophthalmoplegia (CPEO) are sporadic, autosomal dominant, or maternally inherited neurodegenerative disorders. KSS is characterized by onset before 20 years of age of: ophthalmoplegia (paralysis of eye muscles), ptosis (droopy eyelids), atypical retinitis pigmentosa, mitochondrial myopathy, and one of the following: cardiac conduction defect, cerebellar syndrome, or a CSF protein elevated above 100 mg/dL (Rowland 1983). Individuals whose symptoms are less severe and present in childhood or adolescence with extraocular muscle weakness with ptosis are classified as having CPEO. CPEO is often accompanied by limb weakness, dysphagia, or dysarthria (mitochondrial myopathy). Patients with an intermediate disorder, less severe than KSS and more severe than CPEO, are referred to as having CPEO Plus. CPEO Plus patients have complex and variable clinical manifestations. KSS and CPEO Plus may overlap with other mitochondrial encephalopathies because CPEO has been seen in patients with otherwise typical MELAS syndrome (Fang *et al.* 1993), MERFF (Silvestri *et al*. 1993), and mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) (Threlkeld *et al.* 1992). Biochemical analysis of blood and biopsied skeletal muscles suggest deficiencies in oxidative phosphorylation in most patients with CPEO or KSS.

Genetic analysis suggests heterogeneity. KSS, CPEO Plus, and CPEO cases have been associated with various defects of mitochondrial DNA. The great majority of KSS and CPEO cases are due to spontaneous mitochondrial DNA rearrangements (combinations of duplications and deletions), which are not inherited. Despite extensive heterogeneity in deletion size and breakpoint positions, the two origins of the mtDNA replication are spared, thus defining two areas in which mitochondrial deletions occur. Over 90% of the deletions occur in the large arc and can remove 9–50% of mitochondrial genome. One-third of all KSS/CPEO patients harbor the same deletion[6]. Approximately 6% of CPEO cases have multiple mitochondrial DNA deletions in all tissues and show most often an autosomal dominant inheritance pattern although an autosomal recessive inheritance can also be seen. At least three genes are known to cause the autosomal dominant CPEO: adenine nucleotide translocator 1 (Ant1, chromosome 4), DNA polymerase (POLG, chromosome 15) and Twinkle (C10orf2, chromosome 10) (Lewis *et al*. 2002). Those KSS OR CPEO patients who have no mitochondrial DNA deletion are likely to have a mitochondrial DNA point mutation. Maternal inheritance of CPEO is suggested by discovery of a mitochondrial DNA point mutation in variable amounts in various tissues of some patients. Patients with one mitochondrial DNA point mutation or more present combined features of Kearns–Sayre disease or chronic progressive ophthalmoplegia with features of MELAS (Fang *et al*. 1993) and MERRF syndromes (Silvestri *et al*. 1993). All the mutations seen in patients with CPEO or KSS alter or remove one or more mitochondrial tRNA genes. The result is a defect in the synthesis of proteins necessary for oxidative phosphorylation.

The presenting manifestations of KSS are frequently the same as diseases such as Pearson syndrome (a disorder presenting in infancy with a unique combination of bone marrow and pancreatic exocrine dysfunction) (Bernes *et al*. 1993), renal tubular acidosis (Mori *et al*. 1991), and Lowe syndrome (congenital cataract, hypotonia, mental retardation, and progressive renal tubular dysfunction) (Moraes *et al*. 1991). Before 20 years of age, most patients develop a combination of ophthalmoplegia, ptosis, retinal degeneration, and heart block or cerebellar ataxia. The KSS may also include signs and symptoms of myopathy, hearing loss, pyramidal and extrapyramidal dysfunction, seizures, and dementia. KSS has also been associated with a variety of endocrine and metabolic disorders, in particular short stature, gonadal failure, hypothyroidism, hypoparathyroidism, and hyperaldosteronism (Harvey & Barnett 1992). Patients with KSS may deteriorate rapidly and die from heart block or brainstem dysfunction.

The clinical features of sporadic chronic progressive external ophthalmoplegia are restricted to eye and proximal

PEARLS & PERILS

- CPEO can be associated with MELAS, MERRF, and MNGIE.
- Edrophonium test should not be performed in KSS due to the risk of arrhythmia. Patients presenting with external ophthalmoplegia frequently undergo edrophonium chloride testing to rule out myasthenia gravis. Ptosis in CPEO does not respond to edrophonium test.
- Blood for mitochondrial deletions is frequently negative in Kearns–Sayre syndrome. Muscle is the tissue of choice for the evaluation of mitochondrial genome. If no mitochondrial DNA rearrangement/deletion is found, mitochondrial DNA point mutations should be considered.
- Kearns–Sayre patients should be followed carefully with serial EKG and Holter monitoring. At the first indication of serious conduction defect, a pacemaker should be placed.
- KSS patients typically have a higher proportion of mitochondrial DNA deletion in more tissues than do CPEO patients.

muscles without other organ involvement. Rarely, weakness becomes severe. Chronic progressive external ophthalmoplegia plus may combine features of MELAS, MERRF, MNGIE, and KSS. Patients with autosomal CPEO may present during the second decade with symptoms other than ptosis and ophthalmoplegia. Those symptoms vary greatly between and within families and may include dysarthria, depression, mental retardation, sensory ataxic neuropathy, deafness, exercise intolerance, muscle pain, gastrointestinal dysmotility, cardiac conduction defects and hypogonadism. Four patterns of retinal degeneration are encountered in KSS and CPEO Plus: (1) generalized, (2) "salt and pepper", (3) "bone spicule" and (4) complete atrophy of choroid and sclera (Herzberg *et al*. 1993).

Elevated blood lactate and pyruvate are frequently found at rest or after exercise in patients with CPEO or KSS. Renal tubular dysfunction can be suggested by hypermagnesemia, hypophosphatemia, hypocalcemia, hypokalemia, glycosuria, and aminoaciduria. Endocrine abnormalities are suggested by impaired glucose tolerance, insufficient rise of growth hormone following administration of growth hormone releasing hormone, insufficient rise of FSH after administration of gonadotrophin-releasing hormone, and/or abnormal parathyroid and thyroid hormone. EKG assesses severity of conduction disturbances. CSF frequently reveals elevated protein (>100 mg/dL) in KSS. Blood studies for mitochondrial DNA deletions or point mutation may be negative.

Kearns–Sayre syndrome is associated on CT scans with cortical and white matter atrophy, hypodensity of the cerebral and cerebellar white matter, and variable hypodensity or calcification of the basal ganglia (Kendall 1992). MRI scans show T_2 prolongation in the deep gray matter nuclei, particularly the thalamus and globus pallidus, and patchy white matter involvement (Demange *et al*. 1989). Proton MR spectroscopic evaluation shows large increase in lactate/creatinine and large decreases in n-acetylaspartate/creatinine in central brain regions (Matthews *et al*. 1993).

Muscle biopsy is particularly useful in establishing diagnosis of KSS or CPEO, demonstrating ragged-red fibers on Gomori-trichrome stain and dissociation in enzyme activity on oxidative stains (i.e. low cytochrome oxidase stain, strong succinic dehydrogenase stain) of the same fibers. Electron microscopy not only confirms the presence of supranumary mitochondria, but also demonstrates that some are enlarged, the cristae of their inner membranes disordered or simplified, with paracrystalline "parking lot" inclusions in their matrix. Biochemical analysis demonstrates partial impairments in a variety of biochemical reactions, all of them related to oxidative phosphorylation metabolism.

Mitochondrial DNA analysis allows detection of mitochondrial deletions or deletions/duplications by Southern blotting. Mitochondrial DNA point mutation analysis should be considered if the Southern blot analysis is normal. In patients with autosomal inheritance and mitochondrial DNA deletions, the ANT1, POLG and Twinkle genes should

FEATURES

Table 12.50 Kearns–Sayre Syndrome

Discriminating features

1. Ragged-red fibers
2. Mitochondrial DNA deletions, duplication, or partial mutation

Consistent features

1. Ophthalmoplegia
2. Ptosis
3. Retinal degeneration
4. Lactic acidosis
5. Onset before age 20 years

Variable features

1. Elevated CSF protein
2. Cerebellar ataxia
3. Cardiac conduction defect
4. Short stature
5. Sensorineural deafness
6. Muscle weakness
7. Mental retardation
8. Endocrinopathy
9. Renal tubulopathy
10. Corneal clouding
11. Neuropathy
12. Pyramidal/extrapyramidal symptoms
13. Pearson syndrome
14. Sporadic, dominant, recessive, or maternally inherited

KEY CLINICAL QUESTIONS

- Is the ophthalmoplegia associated with retinal degeneration? In that case one should suspect Kearns–Sayre syndrome.

FEATURES

Table 12.51 Chronic Progressive External Ophthalmoplegia

Discriminating features

1. Ragged-red fibers
2. Mitochondrial deletions and point mutations

Consistent features

1. Ophthalmoplegia
2. Ptosis

Variable features

1. Myopathy
2. MELAS
3. MERRF
4. MNGIE
5. Features of KSS
6. Sporadic, dominant, recessive or maternally inherited

be sequenced. Patients without mitochondrial DNA deletion or rearrangement should be evaluated for heteroplasmic mitochondrial DNA point mutation in the following tRNA genes: $tRNA^{Lys}$ (MERRF 8344), $tRNA^{Leucine(UUR)}$ (MELAS 3243), $tRNA^{Leucine(CUN)}$ (CPEO 12308, 12311 and 12315), $tRNA^{Tyrosine)}$ (CPEO 5877), $tRNA^{Cysteine)}$ (CPEO 5814), $tRNA^{Asparagine)}$ (CPEO 5692 and 5703) and $tRNA^{Isoleucine}$ (CPEO 4285 and 4298) (Tables 12.50 and 12.51).

Mitochondrial neurogastrointestinal encephalomyopathy

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) (Hirano 1994) is an autosomal recessive disorder with multiple mitochondrial DNA deletions and characterized clinically by progressive ophthalmoparesis including ptosis, mitochondrial myopathy, peripheral neuropathy, gastrointestinal dysmotility and progressive encephalopathy. The disorder has similarities with CPEO and Kearns–Sayre syndrome. The disease locus has been mapped to chromosome 22q13.32-qter. The mutated gene encodes thymidine phosphorylase, an enzyme catabolizing thymidine to thymine and uracil (Nishino *et al.* 1999). MNGIE is the first known disorder of mitochondrial nucleoside metabolism.

Age of onset ranges between 2 and 30 years of age. The initial symptoms are gastrointestinal or ocular. Diarrhea, malabsorption, nausea, vomiting and weight loss with normal pancreatic function are the most frequent gastrointestinal symptoms. The most common ocular feature is progressive external ophthalmoparesis, including ptosis. Limb weakness is frequently associated with areflexia. Most patients have a thin body habitus. Voice may be nasal. Short stature and hearing loss are less common findings. Mental functions are usually preserved in early stages of the illness. Visual acuity may be decreased. Seizures may occur in some patients. Survival into adulthood is common.

MRI of the brain shows signs of leukoencephalopathy. Nerve conduction studies and electromyographic studies are consistent with a diffuse sensorimotor neuropathy. Gastrointestinal tract studies show delayed gastric emptying, decreased duodenal motility and in some patients, gastrointestinal pseudo-obstruction. Electrocardiogram reveals heart block in a third of the patients. Lactic acidosis suggests a mitochondrial impairment in 60% of patients. CSF protein can be elevated. Plasma thymidine level is increased more than 20-fold in MNGIE patients. Spectrophometric assay of thymidine phosphorylase in peripheral leukocytes demonstrates a severely reduced activity of the enzyme in affected patients (Nishino *et al.* 1999). Homozygous or compound-heterozygous thymidine phosphorylase gene mutations are identified in patients from diverse ethnic groups.

Muscle biopsy although useful is not necessary in establishing diagnosis. Gomori trichrome studies show ragged-red fibers in most cases. Succinate dehydrogenase stain shows a moderate number of abnormally intensely stained fibers. Electron microscopy reveals abnormally large mitochondria containing paracrystalline inclusions. Studies of respiratory chain enzymes demonstrate various abnormali-

KEY CLINICAL QUESTIONS

- Is the ophthalmoplegia associated with gastrointestinal symptoms? In that case one should suspect MNGIE instead of CPEO or KSS.

PEARLS & PERILS

- Both Kearns–Sayre syndrome and MNGIE present with external ophthalmoplegia and are associated with multiple mitochondrial DNA deletions. MNGIE can readily be identified by assay of plasma levels of thymidine.
- Some patients with mitochondrial point mutation in mitochondrial tRNA glycine (CIP 10006) and tRNA serine (CIP 12258) genes present clinically with a chronic intestinal pseudo-obstruction associated with a chronic progressive external ophthalmoparesis mimicking MNGIE syndrome.
- CPEO and gastrointestinal dysmotility can also be seen in some patients with multiple mitochondrial DNA deletions (e.g. mutation in POLG gene).

FEATURES

Table 12.52 Mitochondrial Neurogastrointestinal Encephalomyopathy

Discriminating features

1. Decreased thymidine phosphorylase activity
2. Homozygous and compound heterozygous mutations in thymidine phosphorylase gene

Consistent features

1. Progressive external ophthalmoplegia
2. Gastrointestinal symptoms
3. Sensorimotor neuropathy
4. Ragged-red fibers
5. Elevated thymidine plasma levels

Variable features

1. Hearing loss
2. Short stature
3. Hyperreflexia
4. Ataxia
5. Limb weakness and atrophy
6. Retinopathy
7. Heart block
8. Elevated CSF protein
9. Lactic acidosis
10. Multiple mitochondrial DNA deletions

ties (complex I, complex IV, or multiple complex defects). Southern blot analysis reveals multiple mitochondrial DNA deletions in 50% of patients (Table 12.52). Treatment of MNGIE is symptomatic and palliative.

Leber hereditary optic neuropathy

Leber hereditary optic neuropathy (LHON) is a maternally inherited form of central visual loss due to apoptotic death of retinal ganglion cells and optic nerve degeneration. LHON affects predominantly men (80% of cases) and occurs acutely or subacutely in adolescence or early adulthood (Newman *et al*. 1991). While LHON is predominantly an ocular disease, patients can have a detectable deficiency of NADH dehydrogenase (complex I) in muscle (Larsson *et al*. 1991). Maternal inheritance is suggested by detection of mitochondrial DNA point mutations in affected patients and asymptomatic relatives. More than 90% of LHON families have a heteroplasmic mitochondrial DNA point mutation in four genes encoding subunits of the NADH dehydrogenase (complex I): LHON 3460 (ND1 subunit), LHON 11778 (ND4 subunit), and LHON 14484 and 14459 (ND6 subunit). All the pathogenic mutations, including all the rare mutations seen in other maternal pedigrees, encode subunits of respiratory chain complex I.

Clinically, the onset of visual loss is in the second or third decade. The vision loss begins in the central visual field with loss of color vision. Both eyes are usually affected within weeks to months. Tobacco and alcohol may precipitate visual loss. Recovery of vision has been reported in some patients after many months or years. Asymptomatic individuals and acutely affected patients frequently have peripapillary telangiectasia (Nikoskelainen *et al*. 1983). Optic atrophy is a late sequela in patients who fail to recover vision.

In some patients, there is evidence of neurologic involvement. Neurologic symptoms may be the only manifestation in some individuals of a LHON kindred or may precede visual decline. Some individuals may present with pediatric-onset dystonia associated with bilateral striatal necrosis mimicking neurodegeneration with brain iron accumulation (Larsson *et al*. 1991) or Leigh syndrome (Jun *et al*. 1994). Patients present with gait disturbance, pseudobulbar signs and impaired intelligence. Other individuals develop a spinocerebellar syndrome with prominent ataxia, hypotonia, and weakness (Wilson 1963). A multiple sclerosis-like illness has been reported in other patients (Keller-Wood *et al*. 1994).

Autonomic nervous system involvement may manifest by vasomotor lability, excessive perspiration, and constipation (Wilson 1963). A pseudobulbar syndrome with poor voluntary tongue movements, and incoordination of swallowing may be observed in terminal stages of the illness. Intellectual impairment and sensorineural hearing impairment occur. Evidence that the disorder is a multi-system disease includes the findings of short stature, variable myopathic features, and cardiomyopathy (Rose *et al*. 1970). Several mitochondrial DNA point mutations have been shown to be associated with LHON.

Serum lactate and pyruvate are usually normal. Neurophysiologic studies are useful in confirming neurologic phenotype in LHON Plus patients. CT scan of the head may reveal low density in the putamina. T_1-weighted MR scan may show low intensity in pallido nigra system. EKG may

PEARLS & PERILS

- Maternal relatives of LHON patients may present in infancy or childhood with bilateral putaminal necrosis and severe dystonia, corticospinal tract dysfunction and extrapyramidal rigidity. Diagnosis of neurodegeneration with brain iron accumulation (NBIA) or Leigh's syndrome is sometimes made.
- Posterior column dysfunction and peripheral neuropathy are not uncommon in some patients with LHON presenting with ataxia, tremor, amyotrophy, and sensory loss.
- Blood for mitochondrial point mutation is all you need for LHON diagnosis. Muscle biopsy is not necessary.
- A multiple sclerosis-like illness is sometimes seen in LHON.

KEY CLINICAL QUESTIONS

- Does the patient have a bilateral, painless, progressive central visual loss? Funduscopic exam shows nonedematous disk elevation and peripapillary telangiectasia. The diagnosis is unlikely if eye movements are painful or there is papilledema.

show in some families a pre-excitation syndrome with prolonged QT interval.

In affected individuals, analysis of mitochondrial DNA should be performed on blood looking for LHON 11778, LHON 14484 and LHON 3460 in pedigrees without neurologic symptoms and LHON 11696, LHON 14596 and LHON 14459 in pedigrees with pediatric-onset dystonia associated with bilateral strial necrosis. If analysis on blood sample is negative muscle biopsy for oxidative phosphorylation studies and mitochondrial DNA point mutation analysis should be obtained (Table 12.53). Treatment of LHON is symptomatic and palliative. A new therapeutic approach such as the lowering of blood thymidine concentration is suggested by the knowledge of the basic metabolic defect.

Lethal infantile mitochondrial disease

Lethal infantile mitochondrial disease (LIMD) is an autosomal recessive neurodegenerative disease characterized by onset in infancy of a myopathy associated with multi-system involvement and progressive mental deterioration. Affected tissues in all patients show respiratory chain defects involving cytochrome oxidase (complex IV) alone or in connection with NADH dehydrogenase (complex I) or succinate cytochrome c reductase (complex III) or both. LIMD is caused in most cases by tissue-specific depletions of the mitochondrial DNA (Figarella-Branger *et al*. 1992). This disorder is caused by mutations in the deoxyguanosine kinase gene and most likely other genes encoding enzymes of the nucleotide salvage pathway, the mitochondrial deoxyribonucleoside kinases (Elpeleg *et al*. 2002).

LIMD patients appear clinically normal at birth. The mean age of onset of symptoms is 3 weeks. The infants present with feeding difficulties, failure to thrive, profound weakness, and severe hypotonia. Respiratory failure soon occurs. Extraocular muscles are spared. The clinical picture deteriorates progressively. Most children become lethargic and present with myoclonic seizures. Death occurs during infancy from cardiac arrest.

Lactic acidosis is usually severe. Hepatic dysfunction may be prominent (Figarella-Branger *et al*. 1992). Renal dysfunction with proximal tubule abnormalities is suggested by a generalized amino aciduria or the de Toni–Debré–Fanconi syndrome (Zeviani *et al.* 1985). Central nervous system involvement is suggested by elevated CSF protein levels (Heiman-Patterson *et al.* 1982), abnormal EEG with diffuse slow waves (Zeviani *et al.* 1985) and paroxysmal discharges (Fritschler *et al.* 1992) and abnormal neuroimaging studies with delayed myelination (Tritschler *et al.* 1992). A dilated or hypertrophic cardiomyopathy is found late in the course of the illness (Figarella-Branger *et al.* 1992).

Muscle biopsy shows abundant ragged-red fibers with markedly decreased cytochrome oxidase activity by histochemistry. Ultrastructural studies show a massive mitochondrial proliferation with lipid and glycogen accumulation.

FEATURES

Table 12.53 Leber Hereditary Optic Neuropathy

Discriminating feature

1. mtDNA point mutations

Consistent features

1. Male preponderance
2. Peripapillar telangiectasia
3. Visual impairment

Variable features

1. Ataxia (spinocerebellar)
2. Dystonia
3. Amyotrophy
4. Peripheral neuropathy
5. Multiple sclerosis
6. Dementia (rare)
7. Spastic paraparesis
8. Autonomic disturbances
9. Pseudobulbar syndrome
10. Cardiac dysrhythmia
11. Short stature
12. Hearing loss

PEARLS & PERILS

- Lethal infantile mitochondrial disease should be differentiated from benign reversible muscle cytochrome c oxidase deficiency. A mitochondrial DNA depletion and multi-system involvement are characteristic of lethal infantile mitochondrial disease.

KEY CLINICAL QUESTIONS

- How long does it take for your baby to empty his bottle and does your infant act as if out of breath while eating? In a floppy infant, episodic tachypnea associated with feeding difficulties should suggest the diagnosis.

FEATURES

Table 12.54 Lethal Infantile Mitochondrial Disease

Discriminating features

1. Depletion of the mtDNA
2. Mutations in the deoxyguanosine kinase gene

Consistent features

1. Cytochrome oxidase deficiency and other variable defects of respiratory chain
2. Mitochondrial proliferation.
3. Hypotonia and weakness
4. Respiratory failure
5. Lactic acidosis

Variable features

1. Renal dysfunction
2. Liver dysfunction
3. Cardiac dysfunction
4. Progressive encephalopathy

Mitochondria are enormous and abnormally shaped but no paracrystalline inclusions are seen. The presence of DNA depletion has been documented by quantitative Southern blot hybridization analysis, by in situ hybridization of affected muscle sections with mtDNA probes, and by immunohistochemistry of affected muscle sections using anti-DNA antibodies. Knowledge of the mutation responsible for LIMD makes the prenatal diagnosis feasible (Table 12.54). No treatment has improved outcome.

Lafora disease

Lafora disease is an autosomal recessive inherited form of progressive myoclonus epilepsy characterized by onset in the first or second decade of seizures and myoclonus, and, in advanced stages, severe dementia and diffuse neurologic signs and symptoms. Lafora bodies are characteristic endoplasmic reticulum-associated polyglucosan inclusions found in neurons and in a variety of other sites including heart, skeletal muscles, liver, and sweat gland duct cells (Carpenter & Karpati 1981). Polyglucosan is a heavily phosphorylated insoluble glycogen-like polymer. One gene locus of Lafora disease, called EMP2A, maps to chromosome 6q24 (Serratosa *et al*. 1995). Eighty per cent of cases are due to mutations in the EPM2A gene, which encodes for Lafora, a protein tyrosine phosphatase associated with polyribosomes and involved in posttranslational processing of ubiquitin. A second locus, called EMP2B on chromosome 6p22 encodes Malin, a putative E3 ubiquitine ligase (Chan *et al*. 2003). Other gene loci are likely to other proteins colocalizing to the endoplasmic reticulum and resulting in an increased glycogen synthase activity.

There are two forms of Lafora disease. The classic form, first described by Unverricht in 1891 begins between 6 and 19 years of age (mean: 11 years). The first manifestations are decreased scholastic performance, behavior disorders, or seizures (Van Heycop Ten Ham 1974). Generalized seizures are initially nocturnal. Partial simple seizures with visual manifestations may constitute the aura of generalized seizures (Rapin 1986). Absence and drop attacks may also occur. Myoclonic jerks appear insidiously during the following months, characteristically arrhythmic, asymmetrical, segmental or fragmentary, and variable in intensity, becoming almost constant. The face is frequently involved. Myoclonic jerks are spontaneous or stimulus sensitive but are not induced by movements. Oscillatory eye movements contribute to visual deterioration. Swallowing and speech difficulties become severe. In the limbs, flexor muscles are more affected. Within 1 or 2 years of the onset of seizures, dementia develops. Pyramidal, cerebellar, and extrapyramidal manifestation (parkinsonian rigidity, choreoathetosis) appear after a variable delay. Death occurs within 2–10 years as a result of heart failure, liver failure, or aspiration pneumonia.

The more protracted, or Lundborg variety, begins between the ages of 17 and 20 years. Grand mal seizures are the first manifestation. Myoclonic jerks and dementia are slowly progressive and death usually occurs after the age of 40 years.

Early in Lafora disease the EEG has spike-wave activity superimposed on slow background. Generalized myoclonic seizures may be induced by photic stimulation. With progression, all patients develop fast-frequency polyspike waves. In the terminal phase, the EEG is totally disorganized. No enzymatic defect has been identified so far.

KEY CLINICAL QUESTIONS

- Did you notice a rapid cognitive decline and erratic fragmentary myoclonic jerks since the onset of the epilepsy?

PEARLS & PERILS

- Lafora disease, a progressive degenerative disorder associated with epilepsy, dementia and occasional visual impairment, should be differentiated from other progressive myoclonic epilepsies.
- Diagnosis is readily established by axillary skin biopsy.

Ketogenic diet is being investigated in clinical trials. This low carbohydrate diet has the promise of reducing intracellular polyglucosan build-up.

Antemortem diagnosis is accomplished by demonstrating positive, diastases resistant, basophilic, and variably metachromatic inclusion bodies, known as Lafora bodies, in liver, striated muscles, or sweat gland biopsy specimens. In the striated muscles, the fibers may show a stippling pattern by light microscopy (Carpenter & Karpati 1981). In the skin, Lafora bodies are demonstrated in the cytoplasm of both the apocrine myoepithelial cells, and eccrine and apocrine sweat duct cells (Serratosa *et al*. 1995). In the CNS, Lafora bodies are found in the cytoplasm of nerve cells, especially in substantia nigra, basal ganglia, and cerebral cortex (Van Heycop Ten Ham 1974). Ultrastructurally, Lafora's bodies are filamentous and granular nonmembrane-bound inclusions. Lafora bodies contain insoluble aggregates of glucose phosphate polymers (polyglycosans) (Yokoi *et al*. 1968) (Table 12.55).

Cerebrotendinous xanthomatosis

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder of mitochondrial bile acid biosynthesis leading to diffuse tendinous xanthomatosis, juvenile cataracts, and multiple progressive neurological manifestations. Other possible manifestations include recurrent bone fractures, pes cavus, and arteriosclerosis (Beringer *et al.* 1993). The disorder is caused by an almost complete lack of the mitochondrial cytochrome P-450 sterol 27-hydroxylase enzyme which catalyzes the first steps in bile acid biosynthesis. The gene of sterol 27-hydroxylase has been mapped to chromosome 2 (Beringer *et al.* 1993) and mutations identified (Kim *et al.* 1994).

The symptoms may develop during the first and second decades of life and become severe with increasing age, leading to profound disability. The diagnosis of CTX should be suspected in patients with unexplained juvenile cataracts, tendon xanthoma (most commonly Achilles tendon xanthoma), tuberous xanthoma (elbow), or with multiple progressive neurologic symptoms which are variable within each CTX family. The latter include behavioral abnormalities, mental deterioration, cerebellar ataxia, pyramidal dysfunction, and seizures. With advancing age, spasticity, ataxia and parkinsonism become more severe, speech becomes more difficult and signs of peripheral neuropathy with loss of pain and vibratory sensation become noticeable. Death usually results from pseudobulbar paralysis between the fourth and sixth decade.

Laboratory studies show normal serum cholesterol and elevated serum cholestanol levels. Urinary excretion of C26 bile alcohol glucouronides is increased and 5-beta cholestane-pentols are the dominant bile alcohols in the urine. When carriers and noncarriers for the disease are subjected to cholestane treatment (to stimulate bile acid synthesis), the urinary excretion of 5-beta cholesterol pentols is considerably increased in carriers of CTX (Koopman *et al*. 1986). CT scan of the brain may show cerebral atrophy, cerebellar atrophy, and focal low density in the cerebral white matter. Magnetic resonance imaging of the brain and spinal cord may be used to evaluate cerebral, cerebellar, and cord atrophy (Hokezu *et al*. 1992). A definitive identification of the lack of the 27-hydroxylase can be done with fibroblast cultures (Skrede *et al*. 1986). The diagnosis is confirmed through genetic analysis (Table 12.56).

Treatment with chenodeoxycholic acid should normalize blood cholestanol levels and suppress excretion of bile alcohols in urine. When treated early, when neurological disability is mild, a number of patients show reversal of their neurologic symptoms. If treatment is delayed until the appearance of severe neurologic deficits, the deficits are irreversible (Peynet *et al.* 1991).

KEY CLINICAL QUESTIONS

- Is there a family history of cataract, dementia, ataxia or seizures and does anyone have tendon xanthomas? Demonstration of a high cholestanol serum level suggests the diagnosis.

FEATURES

Table 12.55 Lafora Disease

Discriminating feature

1. Lafora bodies in cytoplasm of neurons and sweat gland duct cells

Consistent features

1. Polymyoclonia
2. Generalized epilepsy
3. Neurologic deterioration
4. Onset between 10 and 20 years.

Variable features

1. Dementia
2. Ataxia
3. Choreoathetosis
4. Focal seizures arising from occipital regions.

PEARLS & PERILS

- The slowly progressive nature of the disease and the nonuniformity of the clinical manifestation even within each CTX family may preclude early clinical diagnosis.
- CTX should be suspected if there is no hypercholesterolemia in the presence of tendon xanthoma.
- CTX, although extremely rare, is a treatable neurodegenerative disorder.

FEATURES

Table 12.56 Cerebrotendinous Xanthomatosis

Discriminating features

1. Lack of sterol 27-hydroxylase activity in skin fibroblasts
2. Analysis of genomic DNA

Consistent features

1. Normal serum cholesterol levels
2. Elevated cholestanol level
3. Abnormal bile acids in urine with increased excretion of C-27 bile alcohol glucuronides

Variable features

1. Cataract
2. Tendon xanthoma
3. Tuberous xanthoma
4. Mental retardation
5. Dementia
6. Ataxia
7. Seizures
8. Peripheral neuropathy
9. Motor paresis

CONSIDER CONSULTATION WHEN…

- An apparent cerebral palsy is transmitted to multiple family members following a maternal lineage. PMD and Menkes disease should be suspected if only males are affected. When both sexes are affected mitochondrial encephalopathy is likely.
- An apparent cerebral palsy is associated with intractable seizures and dysmorphic features or cerebral dysgenesis (suggesting a mitochondrial disorder or peroxisomal disorder).
- An infant develops a macrocephaly, startle response to stimuli and ocular symptoms. Etiologic workup and management are demanding.
- A patient develops progressive neurologic signs and symptoms such as psychomotor deterioration, acquired microcephaly, spasticity, seizures, myoclonias, myoclonic epilepsy, complicated migraine, ataxia, movement disorder, ophthalmoplegia, ptosis, dysarthria, stridor, loss of speech, dysphagia, visual impairment, deafness, peripheral neuropathy, muscle weakness, and hypotonia. Such progressive neurologic deterioration may present alone or in association with mental regression, behavior disturbances, stereotyped agitation, personality and mood changes, or psychiatric abnormality. Mental deterioration may precede neurologic decline.
- A patient develops obvious extraneurologic signs and symptoms before neurologic or mental deterioration occurs. Screening the appropriate neurodegenerative disease may allow early diagnosis and appropriate management. For example, if a school-aged child develops a progressive visual failure, screening for Batten disease is achieved by ordering a detailed retinal examination before ordering ultrastructural studies of the lymphocytes. If a male patient develops Addison disease, he should be screened for adrenoleukodystrophy by ordering VLCFAs and a careful neurologic examination may reveal a slight neurologic involvement. If an infant develops chronic diarrhea associated with malabsorption, hypocholesterolemia and osteopenia, vitamin E levels should be monitored.

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CHAPTER 13

Inborn Errors of Metabolism II: Disorders of Purine and Amino Acid Metabolism

William L. Nyhan, MD, PhD

OUTLINE

Lesch–Nyhan syndrome
Purine nucleoside phosphorylase deficiency
Phenylketonuria
Abnormalities in the metabolism of biopterin
Maple syrup urine disease
Propionic acidemia and disorders of propionate metabolism
Isovaleric acidemia
Glutaric aciduria
3-Hydroxy-3-methylglutaric aciduria
4-Hydroxybutyric aciduria
Nonketotic hyperglycinemia
Homocystinuria
Urea cycle disorders
Argininemia

Lesch–Nyhan syndrome

Lesch–Nyhan syndrome is due to an inborn error in the metabolism of purines, leading to substantial interference with central nervous system (CNS) function and bizarre, compulsive, and aggressive behavior (Table 13.1). Affected children appear normal at birth and usually develop normally for the first 6–8 months. They almost always have impressive quantities of urate crystals, which look like orange or yellow sand, in their diapers, and they may have hematuria, urinary tract stones, or infections early in life. However, in most instances the first signs of disease are neurologic. Patients who have been sitting well begin to lose this ability. They develop opisthotonic posturing, which persists intermittently as a regular feature of the disease. Muscle tone gradually increases, and in the established phenotype the child is spastic; deep tendon reflexes are increased, and the plantar response is extensor. Involuntary movements are characteristic; they may be choreic, athetoid, or dystonic. Involuntary movements and spasticity may be evident before the first birthday. Most patients are mentally retarded, but the degree of motor disability is usually greater than the degree of intellectual impairment. For instance none of these patients is able to walk or even to sit unsupported, but virtually all learn to talk, and they all appear to comprehend much of what is said to them.

The most striking feature of the behavior is self-mutilation through biting. Biting usually begins with the arrival of teeth, but age of onset of the abnormal behavior is highly variable. It may begin after years. A hallmark feature is loss of tissue about the lips. There may be partial amputations of the tongue or fingers, and most patients have had some self-induced injury to the fingers. However, the self-mutilating activity is not limited to biting; it is limited only by the patient's disability. Patients also injure others, or try to. There is no abnormality in sensation.

Some children have convulsions. The electroencephalogram (EEG) is usually normal. The computed tomographic (CT) or magnetic resonance imaging (MRI) scan may be normal, or there may be some cerebral atrophy.

Hyperuricemia is a regular feature of the disease. Its clinical consequences of gouty arthritis, urate nephropathy, urinary

FEATURES

Table 13.1 Lesch-Nyhan Syndrome

Discriminating feature

1. Complete deficiency of HPRT

Consistent features

1. Hyperuricemia
2. Uricosuria
3. Mental retardation
4. Spasticity.
5. Choreoathetosis, dystonia
6. Self-mutilation

Variable features

1. Convulsions
2. Hematuria
3. Urinary tract stones
4. Urinary tract infections
5. Tophi
6. Urate nephropathy
7. Vomiting

Lesch-Nyhan Syndrome

PEARLS & PERILS

- If the patient can walk it is not Lesch–Nyhan syndrome.
- Reports on hyperuricemic patients from the routine clinical laboratory may be misleading because the accepted normal ranges given are for populations of adult males in whom hyperuricemia is common. A child with a serum uric acid level of 5 mg/dL is hyperuricemic, but the laboratory will not flag the sample as such. There may also be perils in the assay of urinary urate because it is a favorite food for contaminating microorganisms. Therefore, it is best to conduct this assay on fresh or freshly frozen urine in a local laboratory.
- A small number of efficient excretors displays a normal level of uric acid in the blood.

tract calculi, and tophaceous deposits may be prevented by treatment with allopurinol. Most untreated patients have died of renal failure by 10 years of age.

The concentration of uric acid in the blood is usually from 6 to 10 mg/dL, but lower levels are occasionally encountered. The urinary content of uric acid is usually 2–4 mg/mg creatinine, whereas in normal individuals older than 1 year of age it is less than 1 mg/mg creatinine. The diagnosis depends on the demonstration of virtually absent activity of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT). The assay can be performed on erythrocytes, and the normal enzyme is stable during shipment at ambient temperatures. The blood should not be frozen. The companion enzyme adenine phosphoribosyltransferase (APRT) is often run as a control on conditions of shipment. In patients with Lesch–Nyhan syndrome the activity of this enzyme is increased, usually to 150% of normal.

The gene for Lesch–Nyhan syndrome is on the long arm of the X chromosome and is usually fully recessive. Clinical illness is usually expressed only in the male. However, there have now been six females with the disease, so testing for HGPRT should not ignore a female with the phenotype. Following the random inactivation of an X chromosome specified by the Lyon hypothesis, there appears to be selection against cells expressing the abnormal gene in many tissues. This makes heterozygote detection difficult, because carriers of this gene do not have two demonstrable populations of erythrocytes or of leukocytes. Hair roots are, to a large extent clonal and therefore heterozygosity can be determined by the assay of enzyme activity on a substantial number (30) of individual hair follicles. The enzyme is expressed in cultured amniocytes and chorionic villus samples. Prenatal diagnosis has been accomplished using both materials. The human gene for HGPRT has been cloned, and a considerable number and variety of mutations have been identified. Once the mutation in a family is known mutational analysis is the most convenient method for prenatal diagnosis and carrier detection.

The differential diagnosis includes an enlarging spectrum of disorders caused by variants of the HGPRT enzyme that are deficient in activity but not as deficient as the Lesch–Nyhan enzyme. At one end of the spectrum are patients with hyperuricemia and gout or renal stone disease and no abnormalities of the CNS. There are others, however, in whom the degree of deficiency is so severe that they look neurologically like patients with Lesch–Nyhan syndrome; but these patients have normal, or nearly normal, intelligence, and their behavior is normal. The recognition of this neurologic syndrome of HGPRT deficiency makes it important to screen more broadly among patients diagnosed as having cerebral palsy rather than solely among patients demonstrating self-mutilation. The deficiency can readily be detected by the assay of erythrocytes. On the other hand the reliable distinction of these patients from classic Lesch–Nyhan patients, which may be very important for prognosis in a patient diagnosed sufficiently early that he or she may be either premutilative or nonmutilative, requires the assay of cultured fibroblasts.

Some patients with hyperuricemia and uricosuria and normal HGPRT levels have abnormal phosphoribosylpyrophosphate synthetase levels. One of our patients also had severe deafness, some developmental retardation, and absent lacrimal glands.

Treatment of any of the overproduction hyperuricemias of childhood is with allopurinol. Patients often require larger doses than adults with gout. The goal is to keep the serum uric acid level at less than 3 mg/dL. Thereafter it may be useful to monitor the excretion of xanthine, hypoxanthine, and uric acid in order optimally to avoid urinary tract calculi. Many patients are less stiff, especially in the morning, if treated with diazepam (Valium). Operative or other orthopedic treatment directed at dislocation of the hips is not effective. The only treatments effective for the self-mutilative behavior are physical restraint and the removal of teeth.

Purine nucleoside phosphorylase deficiency

Deficiency of purine nucleoside phosphorylase (PNP), like deficiency of adenosine deaminase, leads to severe combined immunodeficiency. In this disorder T-cell function is always impaired, whereas B-cell function may be normal or somewhat impaired. There is an associated lymphopenia and deficiency of thymic function. Autopsies have revealed hypoplasia of the thymus and cortical depletion. Tonsils and lymph nodes may be hard to find. T-lymphocyte-mediated immunity is markedly deficient. Skin tests for delayed hypersensitivity are negative, and lymphocytes do not respond to phytohemagglutinin. As a

PEARLS & PERILS

Purine Nucleoside Phosphorylase Deficiency

- The importance of early diagnosis cannot be overemphasized; in the presence of a suitable sibling donor, this otherwise fatal disease is curable by bone marrow transplantation.

consequence affected patients have frequent life-threatening infections. Most have died of infection. One patient developed vaccinia gangrenosa following vaccination against smallpox. Malignant neoplasms have also been observed, as has autoimmune hemolytic anemia.

Two of the earliest patients described had mild mental retardation and spastic tetraparesis. Another patient had a mild intention tremor. It has now been recognized that surviving patients with virtually complete deficiency of PNP may have more severe neurologic features. Five siblings from two families had severe developmental retardation and spastic tetraparesis. Spastic diplegia and behavioral abnormalities were reported in another patient. Patients with PNP deficiency may be suspected in the laboratory by the presence of hypouricemia and an associated low level of excretion of uric acid in the urine. Nevertheless, they overproduce purines and excrete large amounts of inosine and guanosine in the urine. Concentrations of deoxyguanosine triphosphate (deoxy GTP) accumulate intracellularly.

The molecular defect in PNP can be demonstrated in erythrocytes and leukocytes, as well as other cells; most severely affected patients have essentially no detectable activity (Table 13.2).

PNP deficiency is inherited in an autosomal recessive fashion. Heterozygotes display activity of PNP that is intermediate between the activities of patients and controls. Prenatal diagnosis should be possible. The human PNP gene has been cloned, and the mutation has been defined in a number of patients.

The disease can be cured by bone marrow transplantation. Improvement has been reported using repeated erythrocyte transfusions.

FEATURES

Table 13.2 Purine Nucleoside Phosphorylase Deficiency

Discriminating feature

1. Deficiency of PNP

Consistent features

1. Immunodeficiencies
2. T-cell depletion
3. Infections
4. Hypouricemia

Variable feature

1. Neurologic abnormalities

Phenylketonuria

Phenylketonuria (PKU) is an inborn error in the metabolism of phenylalanine that causes severe mental retardation. The metabolic defect also interferes with pigment development. Affected individuals are always less deeply pigmented than their relatives, and they are often blonde and blue eyed. However, the only significant effect of the disease is that on the brain. Untreated patients usually have IQ levels of less than 30.

Early symptoms include irritability and vomiting severe enough to have led to surgery for pyloric stenosis. An eczematoid rash may occur on the face, but this is not commonly seen. A characteristic odor, which is that of phenylacetic acid, has been variously described as mousey, wolf-like, musty, or barny.

Neurologic findings in addition to severe mental retardation are found in about two-thirds of patients. About half of these have subtle findings, such as some hypertonicity or an upgoing toe, but some patients may have severe spastic paraplegia. Some are microcephalic. There may be purposeless hand posturing, rhythmic rocking, and tremors of the hands. Hyperkinetic activity, uncontrollable temper, and other behavioral problems are common. Seizures occur in about one fourth of the patients, predominantly in those most severely retarded. EEG abnormalities have been described in approximately 80% of patients. The CT or MRI scan may reveal cortical atrophy.

The neuropathology of PKU consists of a delay in myelination in the CNS. Thus autopsies carried out in childhood have revealed dysmyelination in the subcortical white matter. These findings are absent in patients studied after 21 years of age. The formation of myelin is delayed by the chemical abnormality.

Patients with PKU accumulate large amounts of phenylalanine in body fluids and convert some of this phenylalanine to intermediates, such as phenylpyruvic acid, phenyllactic acid, phenylacetic acid, and phenylacetylglutamine. The disease was first discovered because of the green color that results from the reaction of ferric chloride with phenylpyruvic acid. The optimal method for the detection of PKU is the analysis of the blood for phenylalanine. This technique has been adapted to the assay of spots of dried blood on filter paper and has permitted the development of universal neonatal screening programs that now are the rule in all the developed countries of the world. In this way patients are detected before the development of brain damage and treated with diets restricted in phenylalanine (Table 13.3).

FEATURES

Table 13.3 Phenylketonuria

Discriminating features

1. Deficient hepatic phenylalanine hydrolase
2. Elevated plasma phenylalanine
3. Depressed plasma tyrosine

Consistent features

1. Mental retardation
2. Diminished pigment
3. Phenylpyruvic aciduria
4. Phenyllactic aciduria
5. Phenylacetic aciduria
6. Phenylacetylglutamine

Variable features

1. Vomiting
2. Eczematoid rash
3. Odd odor
4. Restriction fragment length polymorphism

PEARLS & PERILS

Phenylketonuria

- Mental retardation caused by PKU should be preventable in developed countries through programs of routine neonatal screening, definitive diagnosis, and the early institution of dietary therapy.
- Infants now go home from the hospital so soon after birth that patients with PKU may be missed because the patient has not been receiving protein long enough to experience a diagnostic rise in the concentration of phenylalanine.
- Physicians can avoid this problem by the routine determination of phenylalanine in blood at the first office visit after neonatal discharge from the hospital.

The enzymatic defect in PKU is in the enzyme phenylalanine hydroxylase, which catalyzes the conversion of phenylalanine to tyrosine. It is expressed only in liver. Its activity in classic PKU is undetectable, and immunochemical studies have revealed no cross-reacting material. PKU is transmitted as an autosomal recessive characteristic. The messenger RNA coding for phenylalanine hydroxylase has been purified and its cDNA prepared, and the structural gene has been cloned and mapped to chromosome 12. Analysis by means of a panel of restriction enzymes revealed a considerable polymorphism linked tightly to the phenylalanine hydroxylase, and this polymorphism has been employed in informative families* for heterozygote detection and for prenatal diagnosis. A number of different mutations has been identified in the phenylalanine hydroxylase gene. Two mutations that express no enzyme activity or cross-reactive material account for about half of the patients with PKU in the best studied northern European Caucasian population.

Treatment of PKU is accomplished by restriction of dietary intake of phenylalanine. This strategy has been successful in the prevention of the clinical manifestations of the disease when instituted in the neonatal period as a result of case finding in siblings of previous patients or through a program of routine neonatal screening.

The objective is to keep plasma concentrations of phenylalanine under 300 µmol/L. Preparations such as Phenex (Ross) XCAnalog-Maximaid (SHS), Phenylade (Applied Nutrition) and Phenylfree (Mead Johnson) make long-term treatment economically feasible and palatable. Dietary therapy readily lowers levels of phenylalanine in the blood, and phenylpyruvic acid and its metabolic products disappear.

The management of infants on a low-phenylalanine diet is demanding. All infants require a certain amount of phenylalanine, including those with PKU, for whom the minimal requirements are similar to those of normal infants. Patients with PKU often vomit or refuse feedings, and infections may complicate the altered metabolic state. Management should be directed by a clinician with experience with the problem and access to facilities for accurate determination of serum concentrations of phenylalanine. If phenylalanine is restricted below levels required for growth, catabolism results and levels of phenylalanine increase. Hypoglycemic convulsions and death can occur. The optimal time for termination of dietary therapy is unclear. It was once customary to stop the diet at 5 years of age, but recent experience has indicated that discontinuation of dietary treatment at 6 years of age may lead to a reduction in IQ. The rigidity of dietary restriction is relaxed in the teenage years. In a woman with PKU contemplating childbearing it is preferable to begin any diet restriction prior to the onset of pregnancy and to continue with frequent monitoring of levels of phenylalanine throughout gestation.

Abnormalities in the metabolism of biopterin

A group of disorders, which have variously been referred to as malignant hyperphenylalaninemia or atypical phenylketonuria, result from abnormalities in the synthesis of tetrahydrobiopterin, the cofactor for the phenylalanine hydroxylase reaction, or from defective recycling of the cofactor.

* An informative family is one in which the carrier parents are heterozygous for polymorphic bands detectable with the cDNA probe.

PEARLS & PERILS

Abnormalities in the Metabolism of Biopterin

- Everyone with a positive neonatal screen for phenylalanine does not have PKU. Some have benign hyperphenylalaninemia, and a few have defects in biopterin metabolism. In the absence of early recognition and effective therapy, the effects of defective biopterin metabolism on the nervous system are profound.

Initially most children were identified because of progressive neurologic degeneration in those thought to have PKU because of a positive neonatal screening test, and managed with good dietary control of the blood levels of phenylalanine. Now children are being detected earlier by testing for biopterin defects in those with hyperphenylalaninemia detected by screening programs.

In the fully developed phenotype the patient is hypertonic, often severely, and has extensor posturing or episodic opisthotonos. Convulsions may occur as early as 3 months of age. Myoclonic seizures are common. Deep tendon reflexes are exaggerated and Babinski's sign is present. Patients are difficult to feed. They have problems with their secretions and commonly drool. The patient appears expressionless or drowsy and may have tremors or dystonic movements. The intelligence may deteriorate progressively to the range of profound retardation. CT or MRI scan reveals cerebral atrophy, and ultimately the patient is microcephalic. Death usually supervenes in childhood.

Concentrations of phenylalanine in the blood are elevated. The levels are sometimes more like those in atypical hyperphenylalaninemia than in classic PKU. Worrisome is the fact that these disorders can occur, at least in infancy, without elevation of the serum concentration of phenylalanine, as documented in one patient diagnosed early because of an affected sibling.

Ultimately, of course, levels of phenylalanine should rise, because tetrahydrobiopterin is the cofactor required for activity of phenylalanine hydroxylase. Defects have been noted in the synthesis of biopterin at the initial GTP cyclohydrolase step and later in the formation of the reduced biopterin itself. The syndrome also results when there is a deficiency of dihydropteridine reductase, which catalyzes the recycling of tetrahydrobiopterin from the inactive quinonoid oxidation product of the phenylalanine hydroxylase reaction. Tetrahydrobiopterin is also the cofactor for the hydroxylation of tryptophan and tyrosine. Deficiency in this compound interferes with the synthesis of serotonin, dopamine, and norepinephrine.

The diagnosis of these disorders is readily made by analysis of urinary pterins or the administration of tetrahydrobiopterin. The administration of tetrahydrobiopterin leads to a prompt decrease to normal of serum concentrations of phenylalanine in patients with defects in synthesis or the reductase, whereas there is no change in the patient with PKU. The test must be performed while the patient is receiving a normal diet. The usual dose is 2 mg/kg. It has been recommended that the test be given to every infant identified in the screening for PKU. The test may be negative in reductase deficiency.

The definitive diagnosis in dihydropteridine reductase deficiency is made by assay of the enzyme in biopsied liver or cultured fibroblasts or lymphoblasts, or in freshly isolated lymphocytes. It can even be assayed from blood spots on newborn screening cards. Patients with defective biosynthesis of tetrahydrobiopterin can be diagnosed by assay of the pattern of excretion of pterins in the urine or by quantitative assay of tetrahydrobiopterin in plasma, especially after the administration of a phenylalanine load. The cDNA for dihydropteridine reductase has been cloned and localized to chromosome 4p15.3. The GTP-cyclohydrolase deficiency can be documented on assay of lymphocytes and the cDNA has been cloned (Table 13.4). Mutations have been identified in the genes for dihydropteridine reductase, GTP cyclohydrolase, 6-pyruvoyltetrahydropterin synthase, and 4α-carbiholamine dehydratase.

These disorders are all autosomal recessive. Heterozygote detection is possible in dihydropteridine reductase deficiency by assay of the enzyme. Prenatal diagnosis should be possible by enzyme assay. In any of these diseases, mutational analysis provides a method for earlier detection and prenatal diagnosis.

Treatment is by the administration of tetrahydrobiopterin, 5-hydroxytryptophan, and DOPA, the precursors of biogenic amines.

Defects in the GTP cyclohydrolase also cause DOPA-responsive dystonia. This disease can also be caused by deficiency of tyrosine hydroxylase. Those with defects in the GTP cyclohy-

FEATURES

Table 13.4 Abnormalities in the Metabolism of Biopterin

Discriminating features

1. Defective activity of dihydropteridine reductase.
2. Evidence of deficient synthesis of tetrahydrobiopterin

Consistent features

1. Hyperphenylalaninemia
2. Degenerative neurologic disease
3. Convulsions
4. Spasticity

Variable features

1. Rigidity
2. Tremors
3. Dystonic movements

drolase are heterozygotes, and they do not have hyperphenylalaninemia. Penetrance is such that some are asymptomatic, while others have severe dystonia with childhood onset and oculogyric crises. Patients have now been identified with severe DOPA-responsive dystonia who have mutations on both alleles of the cyclohydrolase gene. A striking aspect of this syndrome, in either its autosomal dominant or recessive forms, is a rewarding clinical response to low doses of levodopa.

Maple syrup urine disease

Maple syrup urine disease (MSUD) is an inborn error in the metabolism of the branched-chain amino acids that is fatal in the neonatal period in a majority of patients. Even those diagnosed promptly and treated carefully may die in infancy. The survivors are often retarded in mental development. The metabolic abnormality is very profound. This is a strong argument for programs of neonatal screening, but even in those states in which there are screening programs for MSUD, it is not uncommon to find a patient severely ill by the time the initial positive result becomes known.

In MSUD leucine, isoleucine, and valine are not effectively catabolized because of a defect in their common branched-chain ketoacid decarboxylase. The activity of this enzyme and its deficiency in MSUD are readily demonstrable in leukocytes and in cultured fibroblasts by assay of the conversion of ^{14}C leucine to $^{14}CO_2$.

Infants with MSUD appear well at birth, but symptoms begin within 24 hours to 5 days of life, with feeding difficulty or irregular respirations. There is progressive loss of vigor and the Moro reflex. Symptomatic hypoglycemia may occur. Characteristically these patients develop convulsions, opisthotonos, and generalized muscular rigidity with or without intermittent flaccidity. Coma may be profound. Death usually occurs following the development of decerebrate rigidity. On CT or MRI scan cortical atrophy may be seen, along with hypodense myelin. This finding is consistent with the defective myelinization that has been observed at autopsy (Table 13.5).

FEATURES

Table 13.5 Maple Syrup Urine Disease

Discriminating feature

1. Deficiency of branched-chain ketoacid decarboxylase

Consistent features

1. Elevated concentrations of leucine, isoleucine, and valine
2. Positive dinitrophenylhydrazine test of urine
3. Branched-chain ketoaciduria

Variable features

1. Maple syrup odor of urine
2. Mental retardation
3. Spasticity
4. Opisthotonos
5. Coma
6. Convulsions
7. Hypodense cerebral myelin

PEARLS & PERILS

Maple Syrup Urine Disease

- The characteristic maple syrup, or caramel, odor can be detected in urine, skin, or hair and may be very striking but may not be detected at all, especially in very ill patients who may not have ingested protein for days.
- It has not been possible to detect MSUD prenatally by analysis of the amino acids of amniotic fluid.
- A pitfall was reported in an infant in whom prenatal assay of the enzyme was normal but who went on to develop typical elevations of amino acids in the blood.

The name of the disease derives from the odor of the urine, which is reminiscent of maple syrup. The branched-chain amino acids are present in high concentration in the blood and urine, and so are their ketoacid analogs. Diagnosis is best made by the quantitation of the amino acids of the blood plasma. Ketoacids may be recognized in the urine by the yellow precipitate that forms on the addition of 2,4-dinitrophenylhydrazine.

Milder forms of the disorder occur, representing less complete deficiencies of the decarboxylase enzyme. Patients with some of these enzyme variants have been referred to as having intermittent branched chain ketoaciduria because of the intermittent occurrence of the symptoms. The enzyme abnormality is always present, just as in classic MSUD. Ataxia and repeated episodes of lethargy may progress to coma in patients with or without mental retardation. The episodes may be precipitated by infection, surgery, or anesthesia. A variant form of the disease has been described that is responsive to the administration of thiamine.

All of the forms of branched-chain ketoaciduria are transmitted as autosomal recessive traits. The enzyme has 3 protein components, designated E_1, E_2 and E_3. Mutations have been identified in the E_1 decarboxylase enzyme and in the E_2 protein. In the Mennonite population, in which the abnormal gene is very common, the mutation is a T to A change in the $E_1\alpha$ subunit.

The enzyme is expressed in cultured amniocytes. The disorder has been detected prenatally in a number of affected fetuses. In addition, methods have been developed for rapid, accurate diagnosis in very small numbers of cells on microtiter plates. This methodology should be applicable to chorionic villus samples. Mutational analysis should become more widely available for prenatal diagnosis.

Any patient shown to be responsive to thiamine should be treated accordingly. The mainstay of treatment for the

majority of patients is dietary regulation. The intakes of leucine, isoleucine, and valine are maintained at levels at which the concentrations of the branched-chain amino acids in plasma are kept within normal limits. This therapy may be difficult. However, in patients in whom diagnosis is made very early a normal IQ may be achieved. Commercial products are available that are useful in management.

Propionic acidemia and disorders of propionate metabolism

Propionic acidemia is the protypic organic acidemia. In this disorder and in methylmalonic acidemia and multiple carboxylase deficiency, the patient presents in early infancy with life-threatening acidotic illness, characterized clinically by vomiting and dehydration and progressing to deep coma. It is characterized metabolically by massive ketosis, a low serum concentration of bicarbonate, and a low pH. There may be an elevated blood concentration of ammonia. Concentrations of glycine in blood and urine are elevated.

There are recurrent episodes of metabolic acidosis associated with the ketosis, similar to those observed in diabetic coma. Patients usually have neutropenia and thrombocytopenia, and may be anemic. Osteoporosis may be severe enough to lead to pathologic fractures. Mental retardation may occur, but this usually appears to be a consequence more of the complications of overwhelming illness in a young infant (such as shock and diminished cerebral perfusion) or of complicating hyperammonemia, than of the metabolic defect itself. However, some patients have been reported with an exclusively neurologic presentation. Such patients have had chorea and dystonia. Catastrophic acute infarction of the basal ganglia has also been reported.

Symptoms usually begin with vomiting, and patients have been diagnosed as having pyloric stenosis. Convulsions and EEG abnormalities may be present. The disease is transmitted as an autosomal recessive trait.

The diagnosis of propionicacidemia is most readily made by organic acid analysis of the urine, in which the diagnostic compound is methylcitrate. The diagnosis may be suspected by finding elevated quantities of glycine in the plasma. Other distinctive metabolites found in the urine are hydroxypropionate, tiglate, tiglylglycine, and propionylglycine.

The molecular defect is in the activity of propionyl-CoA carboxylase, an enzyme on the catabolic pathway for isoleucine, valine, threonine, and methionine, which catalyzes the conversion of propionyl CoA to methylmalonyl CoA. The enzyme has two subunits, α and β, and the genes of both have been cloned and localized to chromosomes 13 and 3, respectively. A number of mutations has been found. The enzyme may be assayed in leukocytes or cultured fibroblasts. Prenatal diagnosis has been carried out by assay of this enzyme in cultured amniocytes. However, an index of the difficulties inherent in this approach is the fact that the first pregnancy in which the prenatal diagnosis was reported was already so far advanced that termination was not feasible; a baby with propionicacidemia was born who died in infancy. This type of experience has been a stimulus for the development of more rapid methods of prenatal diagnosis. Among them has been the incorporation of [^{14}C]propionate into macromolecules, a technique that requires only two to four passages to obtain a sufficient number of amniocytes. It can be applied also to the diagnosis of methylmalonicacidemia. Propionyl-CoA carboxylase can also be assayed in chorionic villus samples. The direct chemical prenatal diagnosis of propionicacidemia can be accomplished by the demonstration of methylcitric acid in the amniotic fluid. Stable isotope dilution and selected ion monitoring gas chromatography-mass spectrometry have allowed rapid, highly sensitive prenatal diagnosis of the fetus with propionicacidemia. Patients with methylmalonicacidemia and multiple carboxylase deficiency can also be diagnosed in this way (Table 13.6).

Prenatal diagnosis permits the institution of prenatal treatment. This has been accomplished with excellent results in B_{12} responsive methylmalonicacidemia and in biotin-responsive multiple carboxylase deficiency. Prenatal therapy of a pregnant woman carrying a fetus with methylmalonicacidemia or multiple carboxylase deficiency with pharmacologic doses of cobalamin or biotin has been highly successful. This approach permits the avoidance of the initial catabolic episode, which can occur within hours of birth and can be fatal.

Methylmalonicacidemia and multiple carboxylase deficiency also present with an identical picture of overwhelming illness that is usually fatal in the neonatal period. These infants have episodes of acidosis with massive ketosis, dehydration, and hyperammonemia, which progress to deep coma. Infants with multiple carboxylase deficiency have, in addition, generalized erythematous cutaneous lesions and alopecia totalis. Each has a characteristic pattern of organic acid excretion. The first is characterized by the excretion of large amounts of methylmalonic acid, but 3-hydroxypropionic acid and methylcitric acid are also found in the urine. In multiple carboxylase deficiency 3-hydroxypropionic acid and methylcitric acid are found, along with 3-methylcrotonylglycine and large amounts of 3-hydroxyisovaleric acid and lactic acid.

Patients with methylmalonicacidemia have defective activity of methylmalonyl CoA mutase. The gene for the enzyme has been localized to chromosome 6. A number of mutations has been identified. In a B_{12} responsive subset of patients, the fundamental defect is in the conversion of hydroxycobalamin to deoxyadenosylcobalamin, the cofactor for the mutase enzyme. Similarly patients with multiple carboxylase deficiency have abnormal activity of propionyl

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Table 13.6 Disorders of Propionate Metabolism

Propionicacidemia

Discriminating feature

1. Deficiency of propionyl-CoA carboxylase

Consistent features

1. Methylcitraturia
2. Hydroxypropionaturia
3. Propionicacidemia
4. Recurrent episodes of ketosis and acidosis, leading to coma and potentially fatal illness
5. Osteoporosis
6. Vomiting
7. Hypotonia
8. Anorexia
9. Moniliasis

Variable features

1. Hyperammonemia
2. Anemia
3. Hyperglycinemia, hyperglycinuria
4. Pathologic fractures
5. Mental retardation
6. Immunodeficiency
7. Abnormal MRI of the basal ganglia

Methylmalonicacidemia

Discriminating feature

1. Deficiency of methylmalonyl CoA mutase

Consistent features

As in propionicacidemia, plus
1. Failure to thrive

Variable features

As in propionicacidemia

Multiple carboxylase deficiency

Discriminating features

1. Deficiency of holocarboxylase synthetase
2. Deficiency of biotinidase

Consistent features

As in propionicacidemia, plus
1. Alopecia
2. Dermatosis
3. Lacticacidemia, lacticaciduria
4. Deficient leukocyte carboxylases
5. Convulsions in biotinidase deficiency

Variable features

1. Hyperammonemia
2. Ataxia in biotinidase deficiency
3. Spastic diplegia in biotinidase deficiency

CoA carboxylase, 3-methylcrotonyl-CoA carboxylase, and pyruvate carboxylase, but the fundamental defect in the infantile form is in the enzyme holocarboxylase synthetase. A second form of multiple carboxylase deficiency is due to deficiency of biotinidase.

Therapy in propionicacidemia and methylmalonicacidemia requires profound restriction of the dietary intake of protein. In B_{12} responsive methylmalonicacidemia treated with B_{12}, dietary restriction may be less severe, and in multiple carboxylase deficiency treatment with biotin, usually in doses as small as 10 mg/day, is all that is required for effective therapy.

Dietary therapy in propionicacidemia and methylmalonicacidemia requires the amounts of protein to be individually determined. For most patients the requirements are less than 1.0 g/kg per day. Infants diagnosed early and treated with good dietary management may have normal intelligence. Episodes of intercurrent acidosis must be treated vigorously with large amounts of parenteral fluid and electrolytes containing sodium bicarbonate.

Isovalericacidemia

Isovalericacidemia is a disorder of the catabolism of leucine that is remembered as the "sweaty foot syndrome" because of the characteristic pungent odor of isovaleric acid, which does not smell at all like sweaty feet. Patients usually present with severe illness in early life, much like that of propionicacidemia; onset may occur with vomiting. Neurologic abnormalities include tremors and convulsions. The course is progressive to deep coma. Laboratory assessment reveals prominent acidosis and ketosis. Some patients have hyperammonemia. Patients with isovalericacidemia may also have leukopenia, thrombocytopenia, and anemia. Death may occur within a few days or weeks of birth.

Infants who survive the initial episode of illness are subject to recurrent attacks of vomiting, acidosis, and ataxia, progressive to coma. Such episodes may follow infections or surgery. The odor is more likely to be appreciated during an episode of acute illness, but it may be absent. Mental retardation may be the result. Some patients may have persistent ataxia, tremor, brisk deep tendon reflexes, or extrapyramidal involuntary movements.

The diagnosis is best based on the detection of isovalerylglycine in the urine. This compound is excreted in amounts up to 3 g/day. It is stable, and can also be employed to monitor the success of therapeutic measures, and especially to fine tune dietary management. Isovaleric acid itself may be detected in the serum, but its volatility makes assay more difficult. During acute episodes concentrations in the serum may be as high as 10 mM.

3-Hydroxyisovaleric acid is also found in the urine. Levels of glycine may be elevated. The molecular defect is in the

PEARLS & PERILS

Isovalericacidemia

- The excretion of 3-hydroxyisovalerate may engender confusion because it is a regular concomitant of this disease and of multiple carboxylase deficiency. It also occurs in any infant with ketosis. The diagnosis of isovalericacidemia requires a demonstration of the presence of isovalerylglycine.
- In the acutely hyperammonemic infant whose condition is improved by means of dialysis or exchange, resist the urge to begin protein feedings until levels of ammonia are normal and stable, and then begin with very small quantities.

activity of isovaleryl-CoA dehydrogenase, through which isovaleryl CoA is converted into 3-methylcrotonyl CoA. Enzyme assay is not easy and is not generally available. The gene has been sequenced and localized to chromosome 15; a number of mutations has been defined (Table 13.7).

Treatment of the acute episode requires the vigorous use of parenteral fluids containing glucose and electrolytes, as outlined for the management of propionicacidemia. Hemodialysis, exchange transfusion, or peritoneal dialysis may be useful, especially in the hyperammonemic neonate. Supplemental glycine and its conjugation with isovaleric acid may be useful in acute management. Doses employed have been 250 mg/kg.

Glycine has also been employed in doses of 800 mg/day in chronic management. The mainstay of chronic treatment is restriction of dietary intake of leucine by lowering the intake of protein until the amounts of leucine ingested are those necessary for growth.

FEATURES

Table 13.7 Isovalericacidemia

Discriminating features

1. Isovalerylglycinuria
2. Deficiency of isovaleryl-CoA dehydrogenase

Consistent features

1. Episodes of acute illness
2. Ketoacidosis
3. Neutropenia, thrombocytopenia
4. 3-Hydroxyisovaleric aciduria

Variable features

1. Acrid "sweaty foot" odor
2. Mental retardation
3. Anemia
4. Ataxia
5. Convulsions

Glutaricaciduria

Glutaricaciduria type I is a neurodegenerative disorder initially described in two siblings, one of whom also had a tendency to a compensated metabolic acidosis. There is progressive neurologic deterioration occurring episodically following intercurrent infection. Patients have convulsions, spasticity, and involuntary movements. Among the earliest manifestations is macrocephaly. Bilateral subdural accumulations of fluid have been reported, and patients have been thought to have been victims of child abuse. Neuroimaging studies reveal marked fronto-temporal atrophy (Table 13.8).

The cardinal characteristic is the excretion of glutaric acid. This increases after lysine loading and decreases after the restriction of the dietary intake of protein. 3-Hydroxyglutaric and glutaconic acid are also found in the urine. In fact, the authors have observed patients in whom 3-hydroxyglutaric acid was the only diagnostic feature of organic acid analysis. This pattern distinguishes this disease from glutaricaciduria type II, in which several organic acids are excreted in the urine, along with glutaric acid. These include a number of other dicarboxylic acids and hydroxy acids, especially ethylmalonic, adipic, suberic, and sebacic acids. Lactic acid is also present in massive amounts, and concentrations of the amino acids citrulline, lysine, ornithine, and proline may be elevated in plasma and urine.

In glutaricaciduria type I the molecular defect is in glutaryl-CoA dehydrogenase. Glutaryl-CoA is an intermediate in the catabolism of lysine, tryptophan, and hydroxylysine. α-Ketoadipic acid is a common product of each of these three amino acids, which is decarboxylated to form glutaryl-CoA. Glutaryl-CoA dehydrogenase converts glutaryl-CoA to glutaconyl-CoA. It is a mitochondrial flavin adenine dinucleotide-dependent enzyme found in liver and kidney. The gene is located on the short arm of chromosome 19. A splice

FEATURES

Table 13.8 Glutaricaciduria

Discriminating features

1. Glutaricaciduria
2. 3-Hydroxyglutaric aciduria

Consistent features

1. Spasticity
2. Convulsions
3. Cerebral degeneration
4. Involuntary movements
5. Glutaconic aciduria

Variable feature

1. Metabolic acidosis

PEARLS & PERILS

Glutaricaciduria

- This condition raises the importance of screening for organic aciduria in a sizable population of patients with seizures and neurologic deterioration.
- The discovery of subdural effusions in a patient should suggest a search for this diagnosis in children suspected of being victims of child abuse.

site mutation has been identified in a population of Canadian Indians in whom glutaric aciduria is common.

Treatment of glutaricaciduria type I has been reported to be modestly effective. Treatment with a diet specifically low in tryptophan and lysine was followed by a decrease in the excretion of glutaric acid in the urine to about one-third of the usual level. A low-protein diet and treatment with riboflavin, the coenzyme for glutaryl-CoA dehydrogenase, were also followed by substantial reduction in glutaric-aciduria. Clinical improvement or prevention in patients diagnosed presymptomatically has been reported. Treatment with the gamma-aminobutyric acid (GABA) agonist baclofen has also been recommended.

No successful treatment has been reported for classic glutaricaciduria type II. It has proven uniformly fatal. Exchange transfusion or peritoneal dialysis might be useful in acute management, but subsequent therapy is not available. However, patients with milder forms of multiple acyl-CoA dehydrogenase deficiency, some referred to as having ethylmalonicaciduria, have responded well to restriction in fat intake. A trial of riboflavin is reasonable.

3-Hydroxy-3-methylglutaricaciduria

3-Hydroxy-3-methylglutaricaciduria differs from the other organic acidemias in that it presents as hypoketotic hypoglycemia. Thus it must be considered in the differential diagnosis of disorders of fatty acid oxidation. However, it also presents with metabolic acidosis and hyperammonemia, so that the major problem in diagnosis is its distinction from Reye syndrome. It should always be considered in children with "recurrent" attacks of Reye syndrome. Episodes of the illness are, as usual for Reye syndrome, likely to follow an acute infectious illness.

Acute episodes of life-threatening illness occur in early infancy and may lead to coma. Persistent vomiting may be the first symptom. Apnea and death may ensue unless vigorous measures of resuscitation, including mechanical ventilation, are employed. Some patients have had convulsions. Most have had some hepatomegaly. One patient presented with acute pancreatitis. Chronic features may include mental retardation, neurologic abnormalities, and cerebral atrophy. Death and permanent neurologic disability have been reported.

Serum concentrations of glucose may be very low. Levels less than 10 mg/dL were recorded in the first three patients. The absence of ketonuria distinguishes these patients from all of the others with organic acidemia. Nevertheless, there may be a prominent metabolic acidosis and reduction in the serum bicarbonate. Neonatal hyperammonemia is common. Liver function tests may be abnormal.

The organic aciduria is characteristic. The index feature is the excretion of large quantities of 3-hydroxy-3-methylglutaric acid. In addition, 3-methylglutaconic acid and 3-methylglutaric acid are found in the urine. These compounds represent successive steps in the catabolism of leucine. At times of acute illness the urine also contains large amounts of lactic acid. The molecular defect is in 3-hydroxy-3-methylglutaryl CoA lyase, which catalyzes the conversion of 3-hydroxy-3-methylglutaryl-CoA to acetyl-CoA and acetoacetate. The activity of the lyase can be assayed in fibroblasts, leukocytes, and cultured amniocytes. The disorder is transmitted as an autosomal recessive trait. Heterozygotes may be detected by enzyme assay of leukocytes or fibroblasts (see Table 13.9).

Management of the acute crisis requires large amounts of water, electrolytes, and glucose. Long-term management depends on the avoidance of fasting and attendant hypoglycemia. Parents should bring the patient in early when

FEATURES

Table 13.9 3-Hydroxy-3-methylglutaricaciduria

Discriminating features

1. 3-Hydroxy-3-methylglutaricaciduria
2. 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency

Consistent features

1. 3-Methylglutaconicaciduria
2. 3-Methylglutaricaciduria
3. Hypoketotic hypoglycemia
4. Acute overwhelming illness
5. Metabolic acidosis
6. Lethargy or coma

Variable features

1. Lacticacidura
2. Lacticacidemia
3. Hyperammonemia
4. Hypotonia
5. Hepatomegaly
6. Vomiting
7. Elevated liver function tests
8. Convulsions
9. Cerebral atrophy

3-Hydroxy-3-methylglutaricaciduria

PEARLS & PERILS

- The urine of every patient with Reye syndrome should be subjected to an organic acid analysis. In a patient who has had more than one attack, or in an infant younger than 2 years of age thought to have Reye syndrome, organic acid analysis is mandatory.
- Hypoketotic hypoglycemia is an unusual syndrome. 3-Hydroxy-3-methylglutaricaciduria is a well-defined cause of the syndrome. Look for carnitine deficiency or deficiency of carnitine palmitoyl transferase as another cause.

the oral route is compromised by fasting or anorexia. A high-carbohydrate diet is useful, and the intake of both fat and protein should be limited. Glucose polymers and uncooked cornstarch are useful.

4-Hydroxybutyricaciduria

4-Hydroxybutyricaciduria is an inborn error of GABA metabolism that is unusual in that the compound that accumulates is of known neuropharmacologic activity. 4-Hydroxybutyric acid was once developed by the pharmaceutical industry as an intravenous anesthetic. It was designed as a GABA analog that could cross the blood-brain barrier, but it was abandoned when it was found to produce convulsions in animals. Unfortunately the compound has been popularized as a street drug and implicated in date rape.

Affected patients have had seizures as well as mental retardation and ataxia. Ataxia has been nonprogressive. Marked hypotonia has been observed regularly. Psychomotor delay may be mild. One patient had mild ocular apraxia. Language development has usually been retarded. Speech may be dysarthric. Pyramidal tract signs are not observed, and there is no sensory deficit.

The hallmark feature is the accumulation of 4-hydroxybutyric acid in urine, serum and cerebrospinal fluid (CSF). Acidosis is characteristically absent (Table 13.10).

The molecular defect is in the enzyme succinic semialdehyde dehydrogenase. The succinic semialdehyde that accumulates is reduced to 4-hydroxybutyric acid. The enzyme is not expressed in fibroblasts, but it is active in lymphocytes and cultured lymphoblasts and the molecular diagnosis has been established in these cells. It is also active in chorionic villus samples. Therefore, the disease should be diagnosable prenatally by chorionic villus biopsy. Prenatal diagnosis has been accomplished by GCMS assay of 4-hydroxybutyric acid in amniotic fluid. Heterozygous carriers are detectable by assay of the enzyme in lymphocyte or lymphoblast lysates. An effective treatment regimen has not been developed.

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Table 13.10 4-Hydroxybutyricaciduria

Discriminating features

1. Succinic semialdehyde dehydrogenase deficiency
2. 4-Hydroxybutyricaciduria

Consistent features

1. Convulsions
2. Ataxia
3. Mental retardation

Variable features

1. Hyperactivity
2. Somnolence

4-Hydroxybutyricaciduria

PEARLS & PERILS

- This disorder presents another good reason for screening the urine for organic acids in the presence of rather nonspecific neurologic disease, such as convulsions, mental retardation, and ataxia.
- 4-Hydroxybutyric acid may be missed in some systems of organic acid analysis.

Nonketotic hyperglycinemia

Nonketotic hyperglycinemia is an inborn error of metabolism in which large amounts of glycine are found in body fluids, and there is no detectable accumulation of organic acids.

The accepted diagnostic feature is the elevated concentration of glycine in the CSF The child generally presents with severe illness within a few days of birth. Death usually occurs in the first year. Most patients develop apnea and, if admitted to a neonatal intensive care unit, usually require ventilator support. Children who survive have severe mental retardation in which there is little evidence of functional cortical activity. These infants have severe seizure disorders – many have virtually continuous seizures. Hiccuping and myoclonic seizures including infantile spasms are common.

Nonketotic Hyperglycinemia

PEARLS & PERILS

- In the workup of an infant in metabolic coma, routine clinical laboratory tests are very helpful. First hypoglycemia must be ruled out. Metabolic acidosis and reduction of the serum bicarbonate lead one to the diagnosis of an organic acidemia. Hyperammonemia in the absence of acidosis signifies a urea cycle defect Most other patients have nonketotic hyperglycinemia.

Microcephaly, hypertonicity, and hypotonicity may be found. Deep tendon reflexes are exaggerated. Cerebral atrophy is found on CT or MRI scan. Decreased or absent myelination of the supratentorial white matter is characteristic. The EEG displays a distinctive burst suppression pattern.

Heterogeneity has also been described in this condition, and there are some patients with milder clinical pictures. Such patients may have only a modest developmental delay, but this presentation is rare. Glycine concentrations in plasma are elevated; levels usually approximate 800–1600 μm/L (6–12 mg/dL). Glycine excretion in the urine may be enormous. Concentrations in the CSF of patients with nonketotic hyperglycinemia average at least eight times the control level of 0.1 mg/dL. The ratio of the CSF concentration of glycine to that in the plasma is very useful in delineating the diagnosis. The ratio is substantially higher in patients with nonketotic hyperglycinemia than in hyperglycinemic patients with organic acidemia. Normally the ratio is only 0.02. In nonketotic hyperglycinemia the mean ratio was 0.17 ± 0.09. Patients with milder versions of the disorder than the classic phenotype tend to have lower ratios. The molecular defect is in the glycine cleavage enzyme, which catalyzes the conversion of glycine to CO_2 and hydroxymethyltetrahydrofolic acid. This is a multienzyme system, with four distinct protein components designated P, H, T, and L. Among patients with nonketotic hyperglycinemia studied definitively by assay of the enzyme system in autopsied liver or brain, individual defects have been described in the H protein, the P protein, and the T protein. The enzyme may also be assayed in transformed lymphocytes and in chorionic villus. The cDNA for the P protein has been cloned, and a deletion of a phenylalanine at position 756 has been identified in a Japanese patient. In Finland, where the disease is common, a substitution of leucine for serine at position 564 has been found in the gene for the P protein (Table 13.11).

Treatment is generally unsatisfactory. Heroic measures are probably not justified. Treatment with strychnine has been reported, but it is clear that it is not useful in the classic phenotype. A concerted effort to lower the CSF concentration as much as possible within the limits of the toxicity of benzoate may ameliorate seizures in a surviving patient. Dextromethorphan may aid as a glycine antagonist at the N-methyl-D-aspartate receptor.

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Table 13.11 Nonketotic Hyperglycinemia

Discriminating features

1. Elevated CSF and plasma glycine ratio
2. Defective glycine cleavage enzyme
3. Hyperglycinemia

Consistent features

1. Hyperglycinuria
2. Neonatal coma and apnea
3. Myoclonic seizures (infantile spasms)
4. EEG burst suppression pattern
5. Cerebral atrophy

Variable features

1. Hypertonia
2. Hypotonia
3. Increased deep tendon reflexes
4. Hiccuping

Homocystinuria

Homocystinuria is an inborn error of metabolism in which there is defective activity of the enzyme cystathionine synthetase. This enzyme catalyzes the conversion of homocysteine and serine to cystathionine. Homocystinuria is a disorder of connective tissue with similarities to Marfan syndrome. It is also characterized by thromboembolic disease, and therefore the resultant clinical picture is often a consequence of which vessel or vessels become involved. In homocystinuria clinical manifestations tend to be progressive, because many of its clinical manifestations result from thrombotic complications (Table 13.12).

Patients with homocystinuria generally appear normal at birth. However, typical clinical features have been observed as early as 1 month of age. An early manifestation may be failure to thrive. Death may occur before 1 year of age, but less severely affected patients have been asymptomatic. The most characteristic feature of this disorder is subluxation of the ocular lens. In some patients this is the only manifestation of disease. Iridodonesis may alert one to the presence of the detached lens. Myopia, cataracts, glaucoma, and other ocular manifestations may occur.

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Table 13.12 Homocystinuria

Discriminating features

1. Homocystinuria
2. Homocysteinemia
3. Cystathionine synthase deficiency

Consistent feature

1. Mixed disulfide of cysteine and homocysteine in urine

Variable features

1. Hypermethioninemia
2. Ectopia lentis
3. Mental retardation
4. Thromboembolic phenomena
5. Failure to thrive
6. Genu valgum
7. Osteoporosis

Among the other connective tissue abnormalities are changes in the bones. Genu valgum is the most characteristic, but there may be valgus at the ankle as well as pes cavus, or pectus excavatum or carinatum. The gait may be peculiar or shuffling and "Charlie Chaplin-like." The joints tend to be limited in mobility.

The hair is usually fair, fine, and sparse. The complexion is usually fair, and the eyes are blue. A malar flush is striking, and many patients have had livedo reticularis.

Thromboembolic phenomena are both arterial and venous, and are frequently the cause of death. Pulmonary emboli, renal artery thrombosis, and cerebral thrombosis have been common, as well as carotid or coronary thrombosis. Classic tests of clotting function are normal, but platelets from these patients show unusual adhesiveness. Furthermore, the addition of homocystine to normal blood causes the platelets to become sticky. Mental retardation is a common but by no means invariable feature of the disease. Among retarded patients the IQ has been 30–75. There may be acute signs of a stroke, or the insidious development of hemiplegia. Some patients have spastic paraplegia. Many have seizures, and even more have abnormalities of the EEG.

The most prominent metabolic characteristic is the excretion of homocystine in the urine. Homocysteine is an intermediate in the metabolism of methionine. Free homocysteine condenses with itself to form the disulfide homocystine, as cysteine does to form cystine. The diagnosis is made by the demonstration of homocystine in the urine or by the concentration of total homocysteine in the blood. Levels of methionine in blood and urine are usually elevated. The mixed disulfide of cysteine and homocysteine is also present in the urine.

Homocystine is unstable. Therefore testing should be performed on fresh urine. For the analysis of plasma, it is important to precipitate the protein immediately, or homocysteine will attach to the proteins and be removed before analysis. Screening of urine can be carried out by the cyanide-nitroprusside test. Homozygotes do not have normal homocysteine levels. Instances of apparent normality probably represent laboratory errors related to the above noted instability of homocysteine.

The enzymatic defect in the most usual form of homocystinuria is in cystathionine synthase, which catalyzes the conversion of homocysteine and serine to cystathionine. The enzyme defect can be demonstrated in biopsied liver or in cultured fibroblasts or amniotic fluid cells. The disorder is transmitted as an autosomal recessive trait, and heterozygotes have reduced cystathionine synthase activity. Defects in cobalamin metabolism may cause homocystinuria as well as methylmalonicaciduria, and defective activity of 5,10-methylene tetrahydrofolate reductase is a rare cause of homocystinuria.

The cDNA for human cystathionine β-synthase has been cloned and mapped to chromosome 21q22.3. A number of mutations has been identified. Correlations have begun to emerge between phenotype and genotypes, particularly with the advent of patients uncovered by newborn screening, some of whom appear to be a different population from those uncovered by the development of symptomotology. Some genotypes, such as T353M, have been found exclusively in B6-unresponsive patients, while others, such as I278T have been found exclusively in B6-responsive patients. Some patients respond to the administration of pyridoxine with an impressive reduction in the accumulation of homocystine. The usual doses are 100–500 mg/day, but up to 1000 mg/day may be necessary. Those who respond are effectively managed by treatment with pyridoxine. Folate deficiency is avoided by concomitant administration of 1–15 mg/day of folate.

In patients unresponsive to pyridoxine, betaine has been used successfully to provide a methyl donor, reducing concentrations of homocysteine by converting it to methionine. Dietary therapy has also been recommended: methionine is restricted and supplemental cystine is provided.

Urea cycle disorders

The prototypic disorders of the urea cycle include carbamyl phosphate synthetase (CPS) deficiency, ornithine, transcarbamylase (OTC) deficiency, citrullinemia, and argininosuccinic aciduria. Each presents classically with massive neonatal hyperammonemia. This picture may also be produced by transient hyperammonemia of the newborn. The classic disorder of urea cycle function is uniformly fatal in the first days of life. Transient hyperammonemia of the newborn, on the other hand – although lethal if untreated – resolves within 5 days with proper care, and its long-term prognosis is excellent. Most of the urea cycle disorders are autosomal recessive, but OTC deficiency, the most common single disorder of the urea cycle, is determined by a gene on the X chromosome. The disease is expressed in both males and females. Affected male infants have the classic phenotype, in which the disease is fatal in the first days of life. In affected females there is variable expression, owing probably to the variable inactivation of the X chromosome carrying the normal gene or its counterpart carrying the abnormal one.

The infant with a defect in the urea cycle is normal at birth and may do well for some time, usually until 12–48 hours after feedings begin. Refusal of feedings and lethargy develop, followed by grunting or rapid respirations. There may be hypotonia or hypertonia. Some infants have convulsions. Progression is rapid to apnea and hypothermia. The appearance is that of surgical anesthesia. The patient survives only if intubated and provided with mechanical ventilation. The family history may include siblings who died very early in life.

Children with less complete deficiency of a urea cycle enzyme may present with neurological abnormalities or mental

retardation. Some have had recurrent episodes of vomiting, headaches, or ataxia. Even these patients may be at risk of death in hyperammonemic coma. Children with later onset argininosuccinic aciciduria have also had trichorrhexis nodosa, in which scalp hair is brittle and breaks off, leaving such short hair that the child may appear to be bald.

The hallmark feature in children with disorders of the urea cycle is the presence of hyperammonemia. Plasma concentrations of ammonia may vary with protein intake and the presence of a catabolic stimulus. In neonatal hyperammonemic coma, ammonia concentrations of 600–2600 μg/dL have been observed (Table 13.13).

In hyperammonemic patients, the concentrations of glutamine and alanine, and occasionally aspartate, increase as nonspecific responses to the increased ammonemia levels. Similarly, when carbamylphosphate accumulates, orotic acid excretion is increased. Oroticaciduria is characteristic of OTC deficiency. It also occurs in citrullinemia and argininosuccinicaciduria. The finding of oroticaciduria may be used to distinguish patients with these abnormalities from those with CPS deficiency or transient hyperammonemia of the newborn. Hepatomegaly and increased serum activities of serum glutamic oxaloacetic transaminase and serum glutamic pyruvate transaminase occur at times when ammonia concentration is increased and may cause diagnostic confusion with hepatic coma.

In the workup of a patient with hyperammonemia the first step is the quantitative analysis of the amino acids of the plasma and urine. Citrulline is found in large amounts in both plasma and urine in citrullinemia; argininosuccinic acid is found in the urine in patients with argininosuccinicaciduria. In patients without elevation of an amino acid of the urea cycle, oroticaciduria is used to distinguish those with OTC deficiency from those with deficiency of CPS. To distinguish patients with transient hyperammonemia of the newborn from those with CPS deficiency, one looks carefully for the peaks of citrulline and arginine. They should be absent in a newborn with massive hyperammonemia because of a complete defect in CPS, whereas some of each is usually present in transient hyperammonemia of the newborn.

The molecular defect in CPS deficiency is in the first step of the urea cycle. The enzyme catalyzes the formation of carbamyl phosphate from ammonium and bicarbonate and thus provides a branch point to pyrimidine biosynthesis as well as urea synthesis. Assay of the enzyme requires liver biopsy. Biopsy is ideally postponed until the patient has been shown to be stable and able successfully to survive catabolic states such as infection. A restriction fragment length polymorphism (RFLP) for the CPS enzyme is useful in prenatal diagnosis.

Carbamyl phosphate reacts with ornithine in the presence of OTC to form citrulline. The OTC enzyme is exclusively present in the liver. Prenatal diagnosis has not been possible in the usual ways. It has been attempted by biopsy of the fetal liver and assay of the enzyme in liver tissue, but OTC activity in the liver does not develop until the second trimester. Therefore this rather heroic type of prenatal diagnosis has had to be delayed until 18–20 weeks of gestation.

The cloning of the OTC gene has permitted the early prenatal diagnosis of amniocytes and chorionic villus tissue. It also permits heterozygote detection. In informative families RFLPs linked to the gene permit the diagnosis of the affected fetus. Among 15 affected males studied with the cDNA probe 14 were indistinguishable from normal, while one was found to have a deletion.

PEARLS & PERILS

Urea Cycle Disorders

- Neonatal hyperammonemic coma is harmful to the brain. Most male infants with OTC deficiency rescued with benzoate or phenylacetate treatment are retarded, and they tend to worsen with each subsequent episode. Best results are obtained in infants diagnosed prenatally who are prevented from ever having serious hyperammonemia. This may be done more easily in CPS deficiency or argininosuccinicaciduria, or in the female with OTC deficiency, possibly in citrullinemia.
- Patients undergoing this type of therapy should be followed with repeated MRI scans.
- Hepatic transplantation should be considered.

FEATURES

Table 13.13 Urea Cycle Disorders

Discriminating features

1. OTC deficiency
2. CPS deficiency
3. Argininosuccinic synthase deficiency
4. Argininosuccinase deficiency

Consistent features

1. Oroticaciduria in OTC deficiency, citrullinemia and argininosuccinic aciduria
2. Hyperammonemia
3. Hyperglutaminemia
4. Coma
5. Absence of oroticaciduria in CPS deficiency
6. Citrullinemia and citrullinuria in citrullinemia
7. Increased concentrations of argininosuccinate in urine and CSF in argininosuccinicaciduria

Variable features

1. Hyperalaninemia
2. Hyperaspartic acidemia
3. Convulsions
4. Mental retardation
5. Trichorrhexis nodosa (in argininosuccinicaciduria)

Deletions have been found in about 10% of affected males. A number of point mutations has been identified. In 10%, these involve mutation of a TaqI restriction site. In two pregnancies at risk a hemizygous normal male was detected in one and a heterozygous female in the other.

In citrullinemia the molecular defect is in argininosuccinate synthase, which catalyzes the formation of argininosuccinic acid from citrulline. Argininosuccinic acid synthase has been found to be deficient in liver and in cultured fibroblasts. Heterozygotes may be detected by assay of fibroblasts, and prenatal diagnosis has been accomplished. The gene has been cloned. A number of mutations has been found in the argininosuccinate synthetase (ASS) gene, located on chromosome 9q34.1, most of which yield no immunoreactive enzyme.

Argininosuccinic acid is an intermediate in the urea cycle that is formed from citrulline and aspartic acid. It is not normally found in body fluids. In argininosuccinicaciduria there is very efficient renal clearance of the compound, so that plasma concentrations are low and urinary concentrations very high. High concentrations of argininosuccinic acid are also found in the CSF. Argininosuccinicaciduria represents a failure in the cleavage of this compound to arginine and fumaric acid, which is catalyzed by argininosuccinase. The defective enzyme may be demonstrated in erythrocytes and cultured fibroblasts as well as in liver. The disease has been diagnosed prenatally. A number of mutations has been reported.

The treatment of disorders of the urea cycle has been altered dramatically by the advent of alternative approaches to the elimination of waste nitrogen. Thus benzoate is given in order to tie up glycine as hippurate and phenylacetate or phenylbutyrate are given to tie up glutamine as phenylacetylglutamine. Both compounds are efficiently excreted in the urine. In addition arginine is provided as an essential amino acid in case of a complete block and as a source of ornithine to keep the cycle moving. This approach is especially useful in citrullinemia and argininosuccinicaciduria. In the management of the acute episode of coma, hemodialysis is more efficient than exchange transfusion or peritoneal dialysis.

Argininemia

Argininemia is a disorder of the urea cycle in which the clinical picture is very different from that of the other disorders of the cycle. The picture is that of a spastic tetraplegia first noted in the early months or years of life or convulsions in the neonatal period. Developmental delay may be the first evidence of abnormality. In the established phenotype the patient is very spastic and opisthotonic. Scissoring of the lower extremities is common. Muscle tone is hypertonic and the deep tendon reflexes are accentuated. There may be chorea or athetosis. Some patients have tremors. Drooling and dysphagia are common. Along with convulsions there are abnormalities of the EEG. Psychomotor retardation is usually severe. Ultimately there is microcephaly and cerebral atrophy on CT or MRI scan (Table 13.14).

PEARLS & PERILS

Argininemia

- The diagnosis of argininemia may be missed on the basis of a screening pattern of amino acids in the urine because the pattern may appear to be that of cystinuria. The question is readily resolved by the quantitative analysis of the amino acids of the plasma.

Concentrations of ammonia are elevated only intermittently in argininemia, and hyperammonemia, when it occurs, tends to be moderate. The diagnosis is made by the analysis of the amino acids of the blood or urine.

Plasma concentrations of arginine are 4 to 20 times normal. Concentrations in CSF are also markedly elevated. The concentration of arginine in the urine is elevated, but the urine also contains increased quantities of lysine, cystine, and ornithine because of competition for reabsorption by the large amounts of arginine in tubular urine. Patients with argininemia also have massive oroticaciduria. This feature of the disease is not a consequence of hyperammonemia as it is in other urea cycle defects but rather a consequence of the stimulation by accumulated arginine of N-acetylglutamate synthesis, which leads to increased synthesis of carbamylphosphate. In the presence of limiting quantities of ornithine, this leads preferentially to pyrimidine biosynthesis.

The molecular defect is in the activity of arginase, which is readily measured in erythrocytes. The defect has also been

FEATURES

Table 13.14 Argininemia

Discriminating features

1. Arginase deficiency
2. Argininemia

Consistent features

1. Spastic diplegia
2. Developmental delay
3. Hypertonia
4. Opisthotonus
5. Involuntary movements

Variable features

1. Hyperammonemia
2. Hepatomegaly
3. Abnormal liver function tests
4. Convulsions
5. EEG abnormalities

CONSIDER CONSULTATION WHEN...

- A patient with apparent cerebral palsy has hyperuricemia.
- Organic acidemia, such as propionicacidemia or methylmalonicacidemia is found; management of metabolic crisis is demanding.
- The comatose patient is found to have hyperammonemia.
- A patient presents with maple syrup urine disease.

demonstrated in liver, but the enzyme is not expressed in cultured fibroblasts.

The cDNA for arginase has been cloned and mapped to chromosome 6q23. A number of mutations has been identified.

Heterozygosity may be demonstrated by assay of arginase in erythrocytes. Prenatal diagnosis by enzyme assay has not been possible because the enzyme is not expressed in amniocytes. Mutational analysis is the preferred method.

Nutritional therapy designed to keep levels of arginine within normal limits has been known to lead to normal neurologic development. Sodium benzoate may be employed in those patients who develop hyperammonemia and benzoate/phenyl acetate (phenylbutyrate).

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CHAPTER 14

Neoplastic Diseases

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OUTLINE

Epidemiology
Clinical presentation
Staging/risk stratification
Neuroimaging
Neuropathology
Molecular genetics
General aspects of therapy
Specific tumor types
Common long-term sequelae of tumor/treatment

Tumors of the central nervous system represent 16% of all malignancies that arise during childhood and adolescence. Although relatively infrequent, diagnosed in approximately 2200 children in the United States every year, they are the leading cause of morbidity and mortality from cancer in childhood. The majority of brain tumors occurring in children will be primary central nervous system lesions, as metastatic tumors are considerably less frequent than in adulthood. Tumors of varying histologies occur throughout the central nervous system in childhood with a relative prediliction for the posterior fossa.

Although progress has been slow in the management of childhood brain tumors, for many patients long-term survival and cure is possible. Diagnosis has been simplified by the increased availability of sensitive neuroimaging techniques, especially magnetic resonance imaging (MRI). It is unclear whether earlier diagnosis has actually improved long-term survival, but MRI has undoubtedly diagnosed some forms of tumors earlier with more precision; especially as regards extent of the neoplasm at the time of diagnosis. Therapeutic interventions are primarily surgery, radiation therapy, and chemotherapy. The latter has been increasingly employed, especially in young children with aggressive or malignant tumors. With current means of treatment, tumor- and therapy-related long-term sequelae are frequent, and "quality-of-life" for many survivors is significantly impaired.

Epidemiology

Primary central nervous system tumors are the second most common form of cancer in childhood and the most common form of solid tumor. The overall incidence of childhood brain tumors, in patients between 0 and 19 years of age, inclusive, is estimated to be 2.5–3.5 per 100 000 person-years (CBTRUS 2002). Rates are highest for neuroepithelial tumors (3.0 per 100 000 person-years); with pilocytic astrocytomas and medulloblastomas being the most common individual histologies (Fig. 14.1). The incidence of pediatric brain tumors is higher among children between 0 and 4 years of age and remains relatively steady until age 7, when there is a 40% drop in incidence. The lowest incidence occurs among children between 10 and 14. The incidence of central nervous system tumors varies based on histology, as ependymomas and medulloblastomas in children decrease with age and pilocytic astrocytomas peak among children between 5 and 9 years of age, and then decrease over time.

Initial analysis of data collected in the late 1980s and early 1990s documented a statistically significant increase in brain tumor rates; however, more recent data have demonstrated a leveling off in incidence. This suggests that improvements in diagnostic technology and case ascertainment may have been responsible for the increase (Smith *et al.* 1998).

The reported incidence of childhood brain tumors is slightly more common in white people than in black people. Males have a slightly higher incidence than females, with a clear male predominance for both primitive neuroectodermal tumors and ependymomas.

For the majority of childhood brain tumors, there are no specific etiological factors. Patients with neurofibromatosis type I have a higher incidence of visual pathway gliomas, other glial tumors, and, to a lesser extent, other types of central nervous system malignancies. Patients with von Hippel Lindau syndrome are much more likely to develop cerebellar hemangioblastomas. The Li-Fraumeni syndrome is an increasingly recognized genetic predisposition to a variety of different tumors, including gliomas. Medulloblastomas are primarily sporadic but have been linked with a variety of different genetic conditions including the autosomal

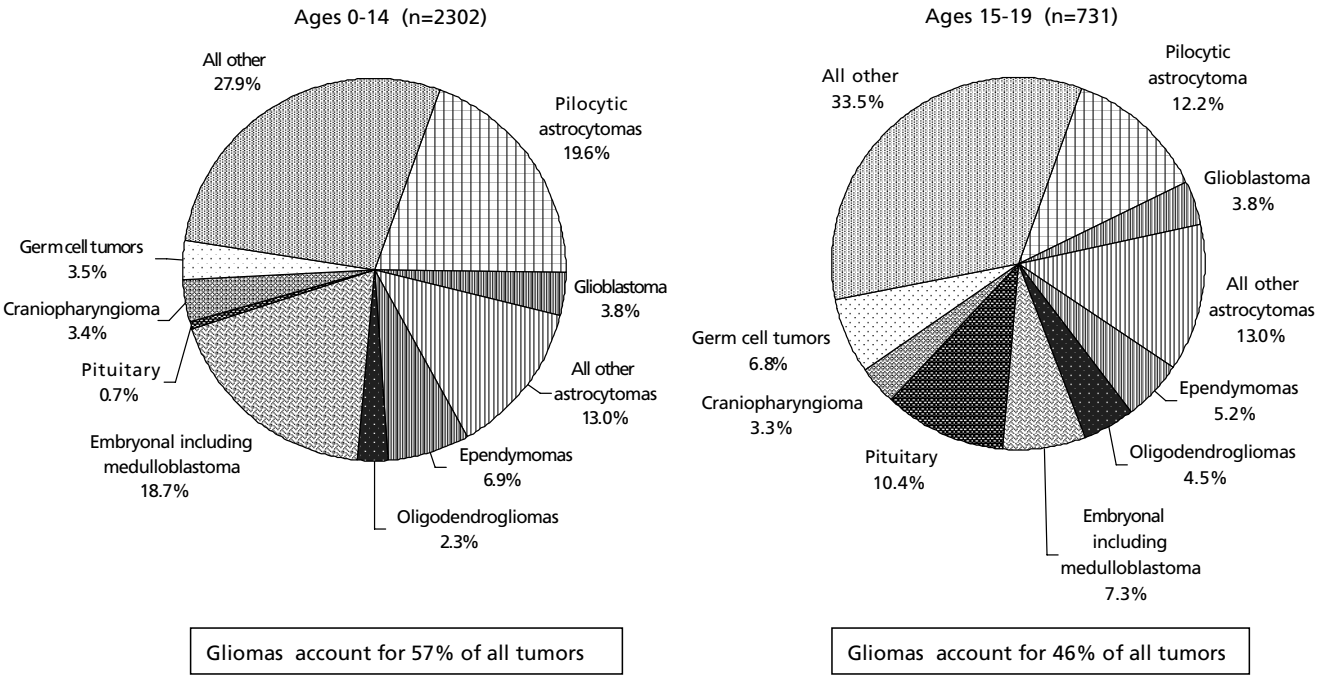

Fig. 14.1 Distribution of pediatric primary brain and CNS tumors by histology. From the Central Brain Tumor Registry of the United States.

dominant nevoid basal cell carcinoma syndrome (Gorlin's syndrome), as well as the recessively inherited Turcott's syndrome.

As regards environmental risk factors, therapeutic doses of ionizing radiation have been definitely linked to an increased risk of brain tumors in children (CBTRUS 2002). There have been inconsistent relationships found between the development of childhood brain tumors and other factors such as maternal food consumption, electromagnetic waves, exposures to products containing n-nitroso compounds, pesticides and father's occupation.

Clinical presentation

Nonspecific signs/symptoms

The signs and symptoms associated with childhood brain tumors are dependent on the location of the tumor and the age of the patient. Since brain tumors in children have a relative prediliction for the posterior fossa, cerebellar or brainstem symptoms are common. Similarly, because of the prediliction for the posterior fossa and other midline sites, obstruction of cerebrospinal fluid flow occurs relatively early in many types of childhood brain tumor resulting in nonspecific signs and symptoms of increased intracranial pressure. In some cases, the symptoms occur quite early in the disease, making diagnosis easier. However, in infiltrating midline lesions, symptoms may be insidious, nonspecific, and often nonlocalizing early in the course of illness, resulting in relatively late diagnosis. Some childhood brain tumors have a proclivity to disseminate the nervous system early in the course of illness. This is especially true for medulloblastomas, pineoblastomas, malignant tumors in infants, and germinomas. Despite this prediliction, dissemination is usually asymptomatic and overshadowed by neurologic dysfunction referable to the primary tumor site. The greatest delay in diagnosis usually occurs in infants and young children because of the relative rarity of childhood brain tumors and the tendency of such lesions to initially present with developmental delay or, later in the course of illness, regression of developmental milestones. Such subtle findings are often overlooked until focal neurologic deficits become apparent.

Obstruction of cerebrospinal fluid results in increased intracranial pressure and some of the more classic symptoms of central nervous system tumors including the triad of increased intracranial pressure: morning headaches, vomiting, and lethargy (Table 14.1). Headaches are an extremely problematic issue in the diagnosis of childhood brain tumors. Although the majority of children with brain tumors will have some type of headaches by the time of diagnosis, the classical headache of increased intracranial pressure may not be apparent early in the course of illness. Headaches early in illness are often nonlocalized and later in illness there may be significant overlap between the types of headaches seen in childhood migraine and those caused by a central nervous system tumor. Headaches that wake a child from sleep or occur early in the morning suggest the

TABLE 14.1

Increased Intracranial Pressure: Brain Tumors Etiology

Etiology
Obstruction of cerebrospinal fluid flow
Focal mass effect (tumor and edema)
Overproduction of cerebrospinal fluid
Signs/symptoms
Headache (especially morning)
Nausea
Vomiting
Lethargy, obtundation
Isolated sixth nerve palsy
Developmental delay; regression (infants)
Setting sun sign (infants)

possibility of increased intracranial pressure. In very young children, headache may be quite difficult to discern and may be intermittent, possibly due to the presence of open fontanels and sutures. Increased intracranial pressure may also cause other nonspecific and nonlocalizing problems such as declining academic performance, fatigue, and personality change. Headaches associated with the primary central nervous system tumors are usually less than 4–6 months in duration, although chronic headaches do not rule out the presence of a tumor and still require clinical evaluation for focal neurologic deficits.

In patients with headaches, especially those with morning headaches associated with vomiting, funduscopic examination is critical. Although papilledema is frequently present at the time of diagnosis, it can be absent very early (in the first 1 or 2 days) of increased intracranial pressure. In long-standing increased intracranial pressure, especially due to slow growing lesions in the suprasellar region, optic pallor, rather than papilledema, may be present by the time diagnosis is made. In infants, the "setting sun" sign, manifest by impaired upgaze and a seemingly forced downward deviation of the eyes, strongly suggests either increased intracranial pressure due to cerebrospinal fluid obstruction with third ventricular dilatation, or, direct compression by the tumor of the tectal region of the midbrain.

Localizing signs/symptoms: infratentorial masses

The other classical signs and symptoms of infratentorial brain tumors include deficits of balance, such as truncal unsteadiness, upper extremity coordination difficulties, and gait difficulties, with or without cranial nerve dysfunction (Table 14.2). Their presence and timing is partially dependent on tumor type. Early in the course of illness, tumors that fill the posterior fossa but do not invade the brainstem (such as medulloblastomas) may result predominantly in truncal unsteadiness. In contrast, tumors arising in the cerebellar hemisphere, such as cerebellar astrocytomas, are more likely to cause lateralizing signs early in illness, with signs and symptoms of increased intracranial pressure occurring later.

Inability to abduct one or both eyes (representing paresis of the sixth cranial nerve), may be a false localizing sign related to increased intracranial pressure rather than due to direct brainstem dysfunction. However, inability to deviate both eyes conjugally (a gaze palsy) or the inability to adduct an eye properly on attempted lateral gaze with jerk nystagmus of the abducting other eye implies an intrinsic brainstem disorder, the latter representing an intranuclear ophthalmoplegia. Such findings, especially when associated with other cranial nerve deficits, strongly suggest direct invasion of the brainstem and, in pediatrics, most likely the presence of a diffuse infiltrating brainstem glioma. Masses that involve the cerebellopontine angle will result in sixth, seventh and eighth nerve dysfunction, often with associated unilateral cerebellar deficits; in children this is most commonly due to an ependymoma. Weakness of the upper and lower portions of the face, consistent with a peripheral or nuclear seventh nerve palsy, suggests an intrinsic brainstem lesion. Horner's syndrome, consisting of ipsilateral ptosis and miosis is often overlooked and occurs in patients with hypothalamic lesions, as well as patients with brainstem or upper cervical cord compromise.

Localizing signs/symptoms: supratentorial tumors

Symptoms and signs of supratentorial lesions in children are not particularly different than those in adults, with the exception that infants and young children with infiltrating lesions can present with delay or arrest in development (Table 14.3). After headaches, seizures are second in frequency as a presenting complaint of patients with supratentorial tumors. Approximately one-quarter of children with supratentorial tumors have seizures as their initial symptom, especially patients with tumors of the temporal or frontal region. The likelihood of an infiltrating tumor causing seizures is dependent on its histological type, rate of growth and location. Slow growing cortical gliomas are most likely to result in convulsions; as many as 50% of patients with low-grade glial lesions will have such an event, in contrast to 20% of those with more aggressive lesions. With the increasing utilization of surgery to manage patients with intractable epilepsy, a significant number of children have been diagnosed with low-grade or indolent mixed neuronal glial lesions (gangliogliomas) as the cause of their uncontrollable seizures. Many of these patients have presented with complex partial seizures. In patients with epilepsy, features associated with an increased risk of a neoplasm include a change in the character of the seizure type in patients with

TABLE 14.2

Posterior Fossa Tumors of Childhood: Signs and Symptoms

Tumor type	Peak age at diagnosis	Duration of symptoms prior to diagnosis	Common signs and symptoms
Medulloblastoma	3–5 years, with a second at 8–12 years	1–3 months	Headaches Nausea and vomiting Truncal/gait Unsteadiness
Cerebellar astrocytoma	Late first decade	2–5 months	Lateralizing cerebellar deficits Headache and vomiting (late)
Ependymoma	Mean age 5–6 years; 50% <5 years of age	2–4 months	Ataxia Cranial nerve deficits Headaches Nausea and vomiting
Brainstem glioma (diffuse, pontine)	5–15 years of age	1–6 months	Multiple cranial nerve palsies Ataxia Long tract signs Sensory loss Headaches Vomiting (late)
Brainstem glioma (focal)	Unclear	Variable, dependent on location	Sixth and seventh nerve palsies (focal pontine); nausea, vomiting, head tilt, unsteadiness (cervicomedullary); hydrocephalus, increased intracranial pressure (tectal)
Atypical teratoid/ rhabdoid	Less than 2 years in majority	1–3 months	Vomiting Failure to thrive Development arrest-delays Unsteadiness

pre-existing seizures, status epilepticus at onset of seizures, prolonged postictal paralysis, resistance to medical control, focal symptoms, and associated focal deficits.

Focal neurologic findings, such as hemiparesis, hyperreflexia, and somewhat less frequently sensory abnormalities, may also be present in the child with an underlying supratentorial malignancy. Such symptoms suggest a more aggressive tumor, but may also be found in children with lower grade neoplasms. In neoplasms involving the so-called "silent" areas of the cortex (the frontal or parietal lobes), focal neurologic deficits may occur late in the course of illness, and may be overshadowed by symptoms/signs of increased intracranial pressure. Frontal lobe lesions may also present with a long history of behavioral difficulties.

Suprasellar lesions notoriously result in delayed diagnosis, especially in very young children with brain tumors. Two major tumor types, the diencephalic glioma and the craniopharyngioma, are both relatively slow growing tumors, and may result in a slowly evolving clinical course and a delay in diagnosis. Chiasmatic gliomas and gliomas of other portions of the visual pathway may present with visual field loss or an insidious loss of visual acuity in one or both eyes, which may be difficult to diagnose in a young child. Chiasmatic tumors may also result in bitemporal hemianopsia, but more frequently result in more complex visual field loss. Chiasmatic gliomas also tend to result in unilateral or bilateral nystagmus with a head tilt and a constellation of findings that may be difficult to distinguish from more benign conditions such as strabismus, amblyopia, or spasm nutans. A relative afferent pupillary defect, the Marcus Gunn pupil, is often an important clue in the early diagnosis of a visual pathway tumor. Craniopharyngiomas, while tending to occur in somewhat older patients than those with chiasmatic tumors, may also cause complex visual field deficits, but more classically result in a bitemporal visual field abnormality. Early signs and symptoms of craniopharyngiomas may be difficult to interpret in the presence of associated behavioral difficulties. Another syndrome of diencephalic lesions which often results in delayed diagnosis is a constellation of failure to thrive and emaciation in an otherwise seemingly "normal" child, with adequate appetite and gastrointestinal function, the "diencephalic syndrome." In retrospect, often these children are not euphoric but are rather irritable, have some component of developmental delay, and on careful testing may have ophthalmologic dysfunction, especially nystagmus.

Another syndrome that may become apparent in pediatrics is the Parinaud's syndrome, caused by compression of the midbrain. This is primarily due to pineal region tumors, although a similar syndrome can be caused by dilatation of

TABLE 14.3

Supratentorial Tumors of Childhood: Signs and Symptoms

Tumor type	Peak age at diagnosis	Duration of symptoms prior to diagnosis	Common signs and symptoms
Cortical low-grade gliomas	Variable	Month to years	Seizures Nonspecific headaches Focal deficits later
Diencephalic gliomas	More common first decade of life, peak under age 3	Variable, often months	Visualize loss Visual field loss Diencephalic syndrome Nystagmus Hemiparesis (thalamic)
Germ cell tumors	Second decade of life; peak 10–14 years of age	2–4 months pineal; ? longer suprasellar	Headaches Vomiting Parinaud's syndrome (pineal) Precocious puberty or delayed puberty (suprasellar)
Ependymoma	Peak in infancy	Variable; usually brief	Seizures Focal deficits Headache
Craniopharyngioma	Any time, median age 8 years	Often prolonged, >6 months	Headache Visual field loss Change in personality Falling school performance

the third ventricle. It is manifest by poor saccadic upward gaze (with relatively preserved pursuit), slightly dilated pupils that react on accommodation but not to light, retraction or convergence nystagmus and lid retraction.

Staging/risk stratification

Staging is a major component of the management of many forms of childhood brain tumors. The classical TMN (tumor, metastasis, nodes) staging system is generally not appropriate for childhood brain tumors, since extra-central nervous system spread at the time of diagnosis is very unusual and nodal involvement is not a clinical issue. However, for some tumor types which readily disseminate the central nervous system at the time of diagnosis, evaluation of extent of disease at time of diagnosis is a critical part of disease planning. Tumors which have a high prediliction for spread at diagnosis include medulloblastoma, pineoblastoma, germ cell tumors, and atypical teratoid tumors. Other lesions, such as cortical primitive neuroectodermal tumors, ependymomas, and both high- and low-grade gliomas, may be spread at time of diagnosis, but in the majority, are localized to the primary site until later in disease.

Evaluation for extent of disease usually requires both magnetic resonance imaging and evaluation of cerebrospinal fluid. To overcome the issue of postoperative artifact, magnetic resonance imaging of the entire neuroaxis is best performed prior to surgery, if there is likelihood that the tumor is of the histological type that may disseminate early in illness. The m-staging system is usually graded on a 0 to 4 basis, with m0 disease representing no evidence of metastatic spread, m1 disease denoting positive cerebrospinal fluid cytology, and m2-m3 disease denoting spread of disease visible on neuroimaging to the spinal leptomeninges or other regions of brain. Spread outside the central nervous system at the time of diagnosis (m4 disease) is quite infrequent and occurs primarily in young infants.

When staging was initially introduced into the management of childhood brain tumors, the t-stage, or tumor size, was often assessed on the combination of preoperative imaging and the impressions of the surgeon at the time of surgery. This type of t-staging has essentially been supplanted by postoperative imaging. In an attempt to avoid confusion between residual tumor and postsurgical changes, such postoperative imaging is usually performed within 48 hours after surgery.

Age at the time of diagnosis, although not a true staging parameter, is also utilized to stratify patients, as a very young age at the time of diagnosis (less than 3 years of age for children with medulloblastoma) has been related to a poorer outcome for children with medulloblastoma. It is unclear whether this is related to an age-dependent biologic difference between tumors and/or because treatment utilized for younger children differs from that given to older patients.

The results of staging studies are utilized for treatment planning and stratification of tumors into risk groups. It is

likely that current disease stratification schemas will dramatically change with the incorporation of molecular genetic tumor findings.

Neuroimaging

Magnetic resonance imaging is clearly the imaging modality of choice for assessment of brain tumors, offering improved sensitivity over computed tomography (CT). The speed and availability of CT, however, often results in it being used as first line imaging for children with suspected intracranial pathology. CT can also provide complementary information to MRI. Intratumoral calcifications, for example in craniopharyngioma, and bony erosion or remodeling, are better detected by CT. Further, CT can provide useful information on both hemorrhage and tumor cellularity.

The superior image contrast of MR imaging allows early detection of changes in tissue composition, while its multiplanar capabilities offers improved tumor localization. MR imaging makes it possible for a tumor to be accurately located within either the intra- or extra-axial space or the ventricular system, an important distinction for subsequent differential diagnosis. High-resolution 3D imaging provides even more detailed anatomy, an important adjunct for surgical or radiotherapy planning. Functional MRI can prove to be a useful adjunct to surgical planning of brain tumors, providing valuable data on the tumor location with respect to important structures, such as the sensorimotor cortex.

MR imaging offers more than simple detection and localization of a tumor, it also provides the means to assess tumor composition and thus help determine pathologic type. There are now a multitude of MR sequences, which offer improved tissue characterization.

Postgadolinium T1-weighted sequences also provide a sensitive means for detecting leptomeningeal or subependymal metastases, although there is some indication that postgadolinium FLAIR images may be even more sensitive in some tumors. In tumors where metastatic involvement of the spine is common, it is preferable to undertake full staging prior to surgery, as postoperative findings can cause false positive findings.

MR spectroscopy (MRS) offers a further means of improving imaging specificity, by supplementing anatomic findings with biochemical data. Proton spectroscopy is the most common spectroscopic technique in use, providing data on a valuable range of metabolites. Choline, a marker of cell proliferation, commonly increases within brain tumors while N-acetyl aspartate, a neuronal marker, decreases. Some tumors show specific patterns of metabolites, which can improve diagnostic accuracy.

Diffusion and perfusion-weighted imaging may provide a further means of physiologically characterizing pediatric brain tumors. Early data suggest that diffusion-weighted imaging may prove helpful in grading gliomas, with more restricted water diffusion seen in higher grade tumors, likely due to an increase in cellularity

Neuropathology

Primary brain tumors constitute a remarkably diverse group of lesions, derived from any of the many normal cellular constituents, with all possible degrees of differentiation. They have a wide variety of macroscopic and histological appearances, therefore it is not surprising that many attempts have been made to produce a classification that should be universally accepted. The first attempt is nearly 150 years old and the last one, only a few years old, has become the official WHO classification.

The revised 2000 WHO classification has adopted the basic principle of histological typing where tumors are defined primarily by morphological appearances, including constituent cell type and tissue pattern. The overall aim is to classify the neoplasms, whenever possible, according to their histogenesis and from this point of view modern investigative techniques such as those of genetics and immunohistochemistry are of great help. The diagnosis is therefore formulated considering gross and microscopic appearances, results of immunostains and, when possible, distinctive molecular features.

Immunostains are of great help in identifying the histogenesis of the tumor. For example, neoplasms positive for glial fibrillary acidic protein (GFAP) are classified as derived from a glial element such as astrocytomas. Tumors positive for synaptophysin and/or neurofilament proteins are classified as neuronal tumors. The embryonal tumors, including medulloblastoma and supratentorial PNETs are considered tumors derived from primitive cells and may show variable immunohistochemical staining.

Molecular genetics

To date, only a small number of genetic alterations have been identified for childhood brain tumors. Most of these associations have been described in medulloblastoma. However, with the advent of technology that allows for high-throughput genetic screening, a broader range of gene expression patterns in childhood brain tumors is beginning to emerge and the molecular pathogenesis of these tumors is becoming more clearly defined. These newly discovered "genetic fingerprints" have started to unveil the vast molecular diversity that exists between the different brain tumor classes, as well as between the histologic subtypes and clinical behaviors within the same tumor class.

Medulloblastoma and supratentorial PNET

Isochromosome 17q is the most common cytogenetic alteration in medulloblastoma, occurring in up to 50% of tumors. Despite intense investigation, a clear association between

17p loss and clinical outcome has not been found. Likewise, a putative tumor suppressor gene mapping to the deleted chromosome 17p region has not been discovered. Supratentorial PNETs, which have an identical histologic appearance, do not have isochromosome 17q, suggesting that these tumors are molecularly distinct.

The neurotrophin-3 receptor, TRKC, was the first molecular alteration that was shown to be an independent predictor of medulloblastoma outcome (Grotzer *et al.* 2002). Tumor expression of TRKC directly correlates with good outcome, presumably by acting to promote the differentiation of primitive medulloblastoma cells. Expression of ErbB2, a member of the epidermal growth factor receptor (EGFR) family, and the MYCC oncogene independently correlates with adverse outcome in medulloblastoma. ErbB2 protein has been detected in up to 85% of medulloblastomas. MYCC amplification is seen in only 5% of medulloblastomas, but its presence is associated with the aggressive large cell anaplastic medulloblastoma variant, which is uniformly fatal.

Medulloblastomas arise in patients with nevoid basal cell carcinoma syndrome (Gorlin syndrome), a condition caused by a somatic mutation of the patched (PTCH) gene on chromosome 9q22. PTCH is an important regulator of the sonic hedgehog (Shh) pro-mitogenic signaling pathway. Gorlin syndrome accounts for 1–2% of all medulloblastomas, most commonly of the desmoplastic subtype. Mutations in this pathway have also been identified in 2–10% of sporadic occurring medulloblastomas. Metastatic medulloblastoma, in comparison to nonmetastatic medulloblastoma, is associated with significant overexpression of the platelet-derived growth factor receptor and the downstream RAS oncogenic pathway (MacDonald *et al.* 2001).

Glioma

In comparison to adult gliomas, the molecular changes associated with childhood gliomas are less well defined. It is known that low-grade gliomas, usually of the optic nerves and chiasm, occur in about 15% of children with neurofibromatosis type-1 (NF-1) and that more than half of all patients diagnosed with optic pathway gliomas will have underlying NF-1. It has also been shown that chromosome 17p deletions occur in up to 75% of high-grade gliomas, but are seen in only 10% of low-grade gliomas.

More recent evidence interestingly shows that childhood and adult gliomas differ in the incidence of EGFR gene amplification and mutations of the TP53 and PTEN tumor suppressor genes. Overexpression of EGFR is seen in 60–80% of high-grade gliomas in children and adults, but amplification of the EGFR gene, found in 40% of adult high-grade tumors, is rarely seen in childhood gliomas. PTEN mutations occur in only 8% of high-grade lesions in children, compared to 30% of adult high-grade tumors; however, PTEN mutations are associated with decreased survival among children with high-grade gliomas. Molecular genetic findings suggest that infant high-grade gliomas are molecularly and clinically distinct from high-grade gliomas seen in older children and adults.

Atypical teratoid/rhabdoid tumors

One of the most important molecular genetic alterations in childhood brain tumors is the discovery of hSNF5/INI1 gene mutations in association with atypical teratoid/rhabdoid tumors (AT/RT). AT/RT has sometimes been confused with medulloblastoma and PNET, but now screening for hSNF5/INI1 mutations can confirm the molecular diagnosis of AT/RT, which has important prognostic and therapeutic implications.

General aspects of therapy

Surgery

Considerable changes have occurred over the past decade that have promoted increased success in obtaining meaningful tumor resections while concomitantly decreasing perioperative surgical morbidity, as well as mortality. A number of studies have demonstrated the effectiveness of total or "near-total" resections in improving long-term survival of children with malignant brain tumors. As a result of this, the surgeon is now being asked to deliver more than a simple diagnosis via stereotactic biopsy. Consequently, preoperative evaluation has become increasingly sophisticated with an array of radiological, electrodiagnostic and laboratory studies permitting an earlier approach to surgical intervention, which, in turn, has resulted in better postsurgical outcomes due to healthier pre-existing neurological conditions. Surgical techniques have also improved secondary to better preoperative planning, minimal exposure, safer intraoperative methods of tumor resection and the increasing utilization of real-time visualization of tumor localization. Postoperative considerations have also contributed to improved outcomes due to an enhanced understanding of neurophysiology, especially for individuals with intracranial hypertension and marginal intracerebral perfusion

In the operating room, current technology permits real-time localization of tumor and surrounding brain when coupled with preoperative CT, MRI, angiographic studies. This has been a critical component of the push for minimalization in the surgical arena, which allows localization of tumors with a 1–2 mm degree of accuracy, and offers the surgeon the opportunity to plan surgical trajectories while avoiding adjacent critical structures. Current systems utilizing a fixed-pin rigid immobilization of the patient's head are being improved to permit surface mapping of the patient's head and face, which will bring this advance to the previously excluded group of infants. In the push for minimizing surgical exposure and risk to surrounding brain, endoscopic

techniques continue to evolve. Intraventricular tumors are particularly amenable to this approach, and may be successfully biopsied through a burr hole and removed by the endoscope. This is particularly valuable for pineal tumors with extension into the third ventricle, colloid cysts and other intraventricular lesions. Tumor resection techniques have also improved and now offer the surgeon a number of different methods for safer removal. Laser (Yag, CO_2), ultrasonic aspiration, and electromechanical disruption now offer the surgeon the ability to safely remove lesions in previously inaccessible locations while minimizing direct trauma to surrounding tissues. Improved anesthetic techniques have also contributed significantly to reducing intraoperative difficulties with cerebral perfusion as well as blood loss, even in the youngest patients.

Radiotherapy

Radiotherapy is a component of management of all malignant and many benign brain tumors of childhood. Children are a special challenge to radiation oncologists and sedation or anesthesia is usually necessary for younger patients to allow for the precision required. Pre- and post-treatment MRI and CT are often co-registered to most exactly define the target volume. A variety of newer treatment planning systems allow optimization of dose distribution in three dimensions. These techniques have different names, but all are a variation of conformal therapy utilizing multiple beams, with individual beam shaping the radiation portal. The primary form of radiotherapy used is photons. Electrons have also been used to treat the spinal axis, and more recently proton beam irradiation has been utilized in attempts to treat deeper-seated areas with less toxicity to the surrounding brain.

The choice of the total dose and volume of radiotherapy is not only dependent on the type of tumor present and, in great part, on the tolerance of the normal surrounding brain. The latter is related to the age of the child, the volume of radiotherapy needed, and other poorly understood host factors. Conventionally, daily fractions of 1.8 cGy of radiation therapy are utilized. Total doses of local radiotherapy range between 4500 and 5580 cGy, with children harboring aggressive lesions requiring the higher doses of radiotherapy. For many pediatric tumors, including medulloblastoma, pineoblastoma, and germ cell tumors, treatment is initiated with craniospinal radiotherapy because of the high likelihood of spread or disease recurrence outside the primary site, with additional local boost radiotherapy given to control primary site disease. Doses of craniospinal radiotherapy are also, in part, age-dependent. 3600 cGy of craniospinal radiation therapy has been conventionally utilized for aggressive central nervous system tumors. The neurocognitive and endocrinologic sequelae associated with such treatment there have led to recent attempts to reduce the dose of craniospinal radiation therapy by one-third or greater to decrease long-term sequelae. Similarly, for younger children, craniospinal radiation therapy is often reduced or delayed, to attempt to diminish permanent damage.

Alterations in the dose fractionation schedule of radiotherapy, such as utilizing radiotherapy in smaller doses multiple times per day instead of larger doses once per day, have theoretical advantages; however, such approaches have yet to be shown to improve survival or decrease sequelae.

Local treatment failure remains the predominant form of disease relapse; thus, there has been significant interest in using other types of radiotherapy to improve local disease control. These include techniques such as brachytherapy, stereotactic irradiation (including boost radiotherapy), and the use of radioactive colloidal solutions. Stereotactic radiation therapy includes an increasing array of options such as the cobalt-60 beam system (the gamma knife) or other focused radiotherapy techniques. Because of the types of tumors occurring in children and the risk of at least transient increased swelling with the techniques, they are appropriate for only a minority of patients. Stereotactic radiation may also be utilized to deliver fractionated treatment which may result in a reduced exposure of the surrounding brain, with less short-term sequelae. Radiocolloid solutions have been predominantly utilized to treat cysts, especially in patients with craniopharyngiomas. Brachytherapy, although having significant theoretical advantages, has not been widely utilized in pediatrics. Attempts are being made to increase cellular radiosensitivity using specific hypoxic cell sensitizers and chemotherapeutic agents that possess radiosensitizing properties (such as the platinum derivatives).

Chemotherapy

Within the last decade, chemotherapy has had an expanded role in the treatment of childhood brain tumors, largely because of efforts to avoid or delay the need for radiotherapy, particularly in infants and young children in whom the risk of radiation-induced neurotoxicity is greatest. Yet, the success of chemotherapy has remained somewhat limited. Two major reasons for this limitation are impediment to drug delivery across the blood-brain barrier (BBB) and chemotherapy resistance. Newer therapeutic strategies have thus been designed to (1) overcome the BBB, (2) decrease resistance to chemotherapy or (3) utilize drugs that specifically target tumor biology.

High-dose systemic chemotherapy

The goal of high-dose chemotherapy (HDCT) is to effectively increase the delivery of cytotoxic agents to the tumor by overcoming the limited permeability of the BBB. Several trials have been conducted in children with primary and refractory malignant brain tumors utilizing myeloablative or myelosuppressive HDCT, with either autologous bone marrow transplant (ABMT) or peripheral blood stem cell (PBSC) support. Classic lipid-soluble alkylating agents, which have

nonoverlapping hematologic toxicities and show little cross-resistance have been predominantly investigated. The most impressive responses have been noted in medulloblastoma. Despite the promising responses observed, the toxicity associated with these regimens has been high (5–15% death rate). In an effort to reduce this toxicity, more recent investigations have used multiple cycles of somewhat lower doses of chemotherapy followed by PBSC support. To a great extent this has decreased transplant-related complications; however, the data regarding treatment efficacy are still preliminary.

Regional chemotherapy

Intrathecal or intraventricular administration of cytotoxic agents is an alternative method to increase tumor exposure to chemotherapy as well as control leptomeningeal tumor dissemination. To date, these methods have been limited by the lack of available active agents that can be given by this route of administration. Convection-enhanced intracavitary and intratumoral delivery of radionuclide- and immunotoxin-conjugated antibodies is the most recent regional strategy that has the added advantage of directed tumor targeting.

Disruption of the blood-brain barrier

The BBB is disrupted and leaky at various sites within the tumor vasculature and is one reason why water-soluble alkylators and platinum compounds have shown activity against pediatric brain tumors. For these reasons, agents that further disrupt the BBB, such as synthetic bradykinin agonists, have been developed to take advantage of the physiologic response to active hydrophilic compounds.

Inhibition of chemotherapy resistance

Strategies to overcome tumor resistance to drug therapy have been employed with some success. A key example of this has been with the alkylator, temozolomide, which has shown activity against malignant gliomas in adults. A major resistance mechanism against this drug is DNA alkylation repair via the enzyme AGT. The drug, 0–6-benzylguanine depletes tumor AGT levels thus rendering the tumor more sensitive to temozolomide.

Biologic therapy

Therapy that specifically targets tumor biology has gained recent attention. In contrast to traditional chemotherapy, biologic therapy can be cytostatic rather than cytotoxic. Examples of this include differentiation therapy with retinoid derivatives, gene therapy with thymidine kinase and ganciclovir treatment, angiogenesis inhibitors, receptor tyrosine kinase inhibitors such as anti-EGFR small molecules, and farnesyl transferase inhibitors that block Ras oncogene activation.

Specific tumor types

Medulloblastoma

Medulloblastoma is the most common malignant primary central nervous system tumor of childhood, accounting for 40% of all posterior fossa tumors and 15–20% of all brain tumors (Packer *et al.* 1994). The tumor has a bimodal peak in incidence, arising most commonly in children between 3 and 5 years of age and then again peaking at the end of the first decade of life. Medulloblastomas are more common in males, with a 2:1 male to female ratio.

In children, medulloblastomas most commonly arise in the midline, seeming to arise from the cerebellum in region of the roof of the fourth ventricle, causing early symptoms and signs of increased intracranial pressure, as the tumor fills the fourth ventricle and causes obstruction of cerebrospinal fluid flow. The resultant most common presentation of medulloblastoma includes headache, vomiting (especially morning vomiting), lethargy and unsteadiness. The duration of symptoms before diagnosis is usually relatively brief, ranging from 1 to 3 months, and by the time of diagnosis hydrocephalus is present in the majority of patients. On examination patients demonstrate gait ataxia, truncal unsteadiness and associated papilledema.

Due to increased intracranial pressure and associated hydrocephalus, children often have sixth nerve paresis; other cranial nerve deficits are less common despite apparent infiltration or attachment to the back of the brainstem in up to one-third of patients at the time of diagnosis. Later in the course of illness, there may be associated hypo- or hyperreflexia, hypotonia and long tract signs (especially due to the hydrocephalus). Stiff neck and head tilt may represent herniation of the cerebellar tonsils, which is an ominous sign. Although up to one-third of patients with medulloblastoma will have disseminated disease at the time of diagnosis, usually this dissemination is subclinical and back pain and leg weakness secondary to spinal cord involvement are uncommon at presentation.

In young children, clinical presentation may be subtle, as cerebellar deficits are often overlooked early in the course of illness and there may be macrocephaly, intermittent lethargy, a bulging fontanel, and the setting-sun sign. Patients with medulloblastoma may also present in extremis with the abrupt onset or change in mental status, severe headaches, and obtundation. Although this may be due to acute obstruction of cerebrospinal fluid flow, it may also be due to hemorrhage within the tumor with sudden expansion of the lesion.

Neuroimaging

In children, medulloblastoma commonly occurs as a midline posterior fossa mass, originating in the inferior medullary velum and expanding to fill the fourth ventricle (Fig. 14.2).

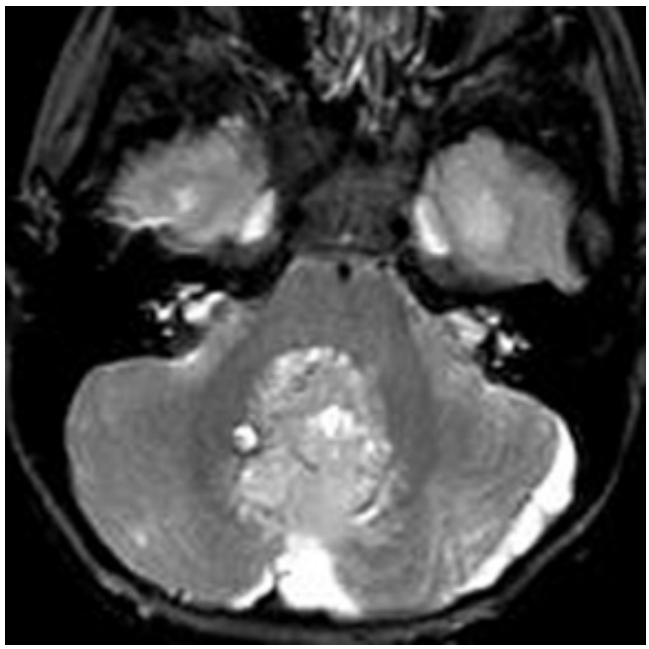

Fig. 14.2 Medulloblastoma. This axial T2-weighted image of the posterior fossa shows a characteristically isointense medulloblastoma filling the fourth ventricle.

In approximately a third of cases, medulloblastoma invades the posterior aspect of the brainstem and occasionally it may spread to surrounding cisterns. Mild to moderate surrounding edema surrounds the tumor and obstructive hydrocephalus commonly occurs. The tumor's hyperdensity on CT and T2 isointensity on MRI result from dense cellularity, and may be useful characteristics in distinguishing medulloblastoma from other posterior fossa tumors. Following contrast, the tumor often shows dense enhancement; however, the presence of foci of calcification or necrosis may cause a more heterogeneous enhancement pattern. Metastatic disease, when present, is usually seen in the posterior fossa cisterns, sylvian fissures and spinal subarachnoid space, but it may also occur to the ventricular system or brain parenchyma.

Microscopy

The classic medulloblastoma is composed of densely packed cells with hyperchromatic, round to oval or carrot-shaped nuclei and indiscernible cytoplasm (Fig. 14.3). Homer Wright rosettes, which consist of tumor cell nuclei disposed in a circular fashion around tangled cytoplasm processes, are a histological hallmark of medulloblastomas but are observed in only 40% of cases. Mitoses are usually numerous and the growth fraction, as determined by the antibodies Ki-67/MIB-1, has been reported to vary greatly with value up to 40%. These tumors may be strongly immunoreactive for vimentin and at least focally for synaptophysin. The desmoplastic variant is characterized by a dense intercellular network of reticulin fibers with lucent, reticulin-free nodular zone or "pale island". The large cell/anaplastic medulloblastoma is an uncommon, highly malignant variant, histologically characterized by monotonously large cells with vesicular nuclei, prominent nucleoli and more abundant cytoplasm.

Management and outcome

Of all primary central nervous system tumors of childhood, staging is most integral to the management of medulloblas-

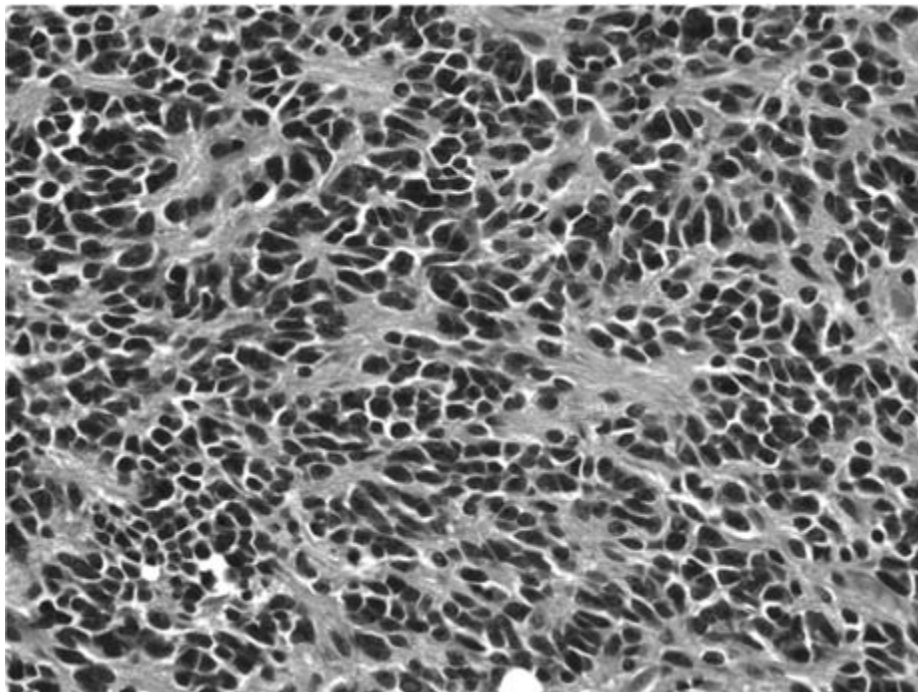

Fig. 14.3 Medulloblastoma. Classical medulloblastoma is characterized by Homer–Wright rosettes, histologic expression of neuroblastic differentiation (H&E).

TABLE 14.4 Stratification: Medulloblastoma

	High risk (any factor)	Average risk
Age	<3 years	≥3 years
Resection	Subtotal; biopsy	Total; near-total
Extent	Disseminated	Localized

TABLE 14.5 Posterior Fossa Mutism Syndrome

Can occur postoperativley in any posterior-fossa tumor; primarily medulloblastoma
Delayed onset (? 24 hours) mutism

Other symptoms

Hypotonia
Ataxia
Supranuclear cranial nerve palsies
Agitation
Emotional liability
? Visual loss

toma (Table 14.4). Dependent on age 10–30% of children with medulloblastoma will have evidence of dissemination, as confirmed by pre- or post-MRI of the entire neuroaxis and lumbar cerebrospinal fluid cytological examination. Dissemination within the neuroaxis is most common in infants and occurs in approximately 10% of adolescents and teenagers. Based on the amount of disease left after surgery, the extent of neuroaxis spread at the time of diagnosis and the age of the patients, children with medulloblastoma have been separated into so-called "average-risk" or "high-risk" disease.

Extraneural spread can occur in patients with medulloblastoma, but probably is present at the time of diagnosis in less than 1% of patients. Infants are at somewhat higher risk of having extraneural spread, but staging for disease outside the nervous system, with techniques such as bone scans and bone marrows, are infrequently informative. Many investigators are still, however, performing such tests at diagnosis in children less than 1 year of age. Molecular genetic findings are likely to significantly alter the way medulloblastoma patients are stratified. Tumor over-expression or upregulation of a variety of different genes have been related to prognosis, but these molecular markers have not yet been fully incorporated into stratification schemas (Pomeroy *et al.* 2002).

Multiple studies have demonstrated that the extent of resection has been related to outcome as patients who undergo a "complete" resection have a better prognosis. Extent of surgical resection has never been shown to be predictive of outcome in patients with disseminated disease at the time of diagnosis. Furthermore, there is no clear evidence that patients who undergo a significant tumor resection (a near-total resection) have a different prognosis than patients who have had a "total" resection. Surgical resection has been associated with morbidity. Between 10 and 20% of patients with medulloblastoma will develop the "posterior-fossa mutism syndrome" following surgery (Pollack *et al.* 1995). This is an ill-defined constellation of findings, which includes the delayed onset mutism, cranial nerve dysfunction (suprabulbar dysfunction), hypotonia, cerebellar deficits, and severe emotional lability (Table 14.5). This syndrome results in significant long-term sequelae in nearly 50% of affected patients. The etiology of the posterior fossa mutism syndrome is unknown and it has not been clearly related to surgical technique or direct damage to the brainstem.

Standard postoperative treatment for children with medulloblastoma over 3 years of age includes the use of craniospinal radiotherapy coupled with adjuvant chemotherapy. Although chemotherapy has never been demonstrated in a prospective randomized trial to improve survival over treatment with radiotherapy alone, it has become a basic component of treatment for all children with medulloblastoma based primarily on the results of single-armed studies. To date, there is no clear evidence that chemotherapy given prior to radiotherapy improves survival for children with medulloblastoma. Radiotherapy has conventionally been given to the entire neuroaxis at the time of diagnosis, as treatment with local radiotherapy alone results in long-term disease control in probably less than 10% of patients. The conventional dose of craniospinal radiation therapy has been 3600 cGy with a local boost to the primary site of approximately 1800 cGy (total dose 5400 cGy). Recent studies have suggested that the dose of craniospinal radiation therapy can safely be reduced to 2400 cGy in patients with localized disease at the time of diagnosis. The dose to the primary site has remained at 5400 cGy to 5580 cGy, although studies are presently underway to determine if the volume of local site irradiation can be safely decreased, with conformal techniques, to the tumor site alone, instead of the entire posterior fossa. This is being performed primarily in attempts to avoid cochlear irradiation and decreased ototoxicity. The predominant reason to reduce the dose of craniospinal radiation therapy is to lessen the likelihood of severe neurocognitive sequelae.

For patients with poor-risk disease (Table 14.6), treatment with radiotherapy alone usually results in a 40% or less likelihood of long-term survival. The addition of chemotherapy probably increases the likelihood of disease control by another 20% (Evans *et al.* 1990). Attempts are presently under way to improve survival by altering the timing or type of chemotherapy utilized. High-dose chemotherapy, supported by peripheral stem cell rescue, is one approach under evaluation. Another therapeutic intervention being explored is the use of chemotherapy or other agents dur-

TABLE 14.6

Cortical Childhood Rarer Glial, Neuronal and Mixed Neuronal/Glial Tumors

Neuronal/mixed
Gangliogliomas/gangliocytomas
Desmoplastic infantile astrocytoma and ganglioglioma
Dysembryoplastic neuroepithelial tumor
Central neurocytoma
? Giant cell
Astrocytic
Pleomorphic xanthoastrocytoma
Oligodendroglioma
Oligoastrocytoma

ing radiotherapy in attempts to enhance the efficacy of the radiotherapy delivered.

The management of infants with medulloblastoma remains problematic. Chemotherapy, including high-dose chemotherapy, results in long-term disease control in less than 30% of patients (Duffner *et al.* 1993). The use of radiotherapy in infants and very young children carries with it a high risk of severe long-term neurocognitive and endocrinologic sequelae. Present management of infants and young children includes the use of chemotherapy with agents such as cisplatinum, cyclophosphamide, vincristine, and VP-16. Investigations are underway attempting to intensify the use of chemotherapy, especially with the use of peripheral stem cell support, as well as the incorporation of newer chemotherapeutic agents or chemotherapy delivered intrathecally, in an attempt to prevent leptomeningeal disease progression or relapse. There is also the consideration of utilizing local radiotherapy after chemotherapy in those children with localized disease, although this approach carries with it the likely possibility of increased neurologic sequelae.

Ependymoma

Ependymomas most frequently occur in young children, with more than half of the cases diagnosed before 5 years of age (Horn *et al.* 1999). These tumors typically present with nonspecific and nonlocalizing signs and symptoms related to increased intracranial pressure. Infratentorial tumors often display cerebellar dysfunction and multiple lower cranial nerve findings, especially VI, VII, VIII, IX, and X. Supratentorial tumors may present with seizures and focal cerebral deficits.

Neuroimaging

The majority of ependymomas are in midline posterior fossa masses; however, occasionally they may arise from ependymal rests located within the cerebral hemispheres (Fig. 14.4).

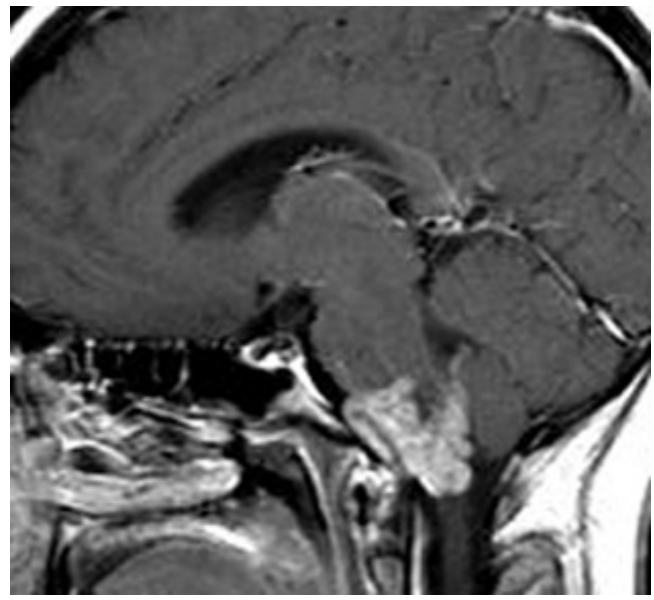

Fig. 14.4 Ependymoma. Sagittal postgadolinium T1-weighted image of the brain shows an enhancing ependymoma extending from the inferior fourth ventricle through the left foramen of Luschka and into the foramen magnum.

Insinuation of a fourth ventricular tumor inferiorly into the foramen of Magendie, or laterally in the foramen of Luschka provides supportive evidence for an ependymoma, over other posterior fossa tumors. Tumors commonly cause obstructive hydrocephalus. Supratentorial tumors are commonly large at presentation, most often presenting as a frontal lobe mass, with significant surrounding mass effect.

Ependymoma often shows calcification, sometimes cysts and occasionally hemorrhage, and thus has a more heterogeneous imaging appearance than medulloblastoma. Imaging characteristics are therefore variable, however solid tumor components are often iso- or hyperdense on CT and isointense to gray matter on T2-weighted imaging. As would be expected, contrast enhancement is heterogeneous. Subarachnoid spread is far less common than with medulloblastoma and occurs primarily with intraventricular tumors. It is suspicious for a higher-grade tumor such as anaplastic ependymoma or ependymoblastoma.

Microscopy

The classical variant of this tumor is characterized by a peculiar cellular pattern. The WHO classification distinguishes four subtypes: cellular, papillary, clear cells and tanycytic. The cellular type is composed of densely packed cells with little tendency to form pseudorosettes and rosettes. Papillary ependymoma resembles choroid plexus papilloma without assuming the frond-like, overtly papillary characteristics of the latter. The clear cell tumors are composed of cells with well-demarcated, clear cytoplasm and need to be distinguished from oligodendrogliomas. Finally the tany-

cytic variant is characterized by markedly elongated cells with highly fibrillary processes.

Management and outcome

Therapeutic intervention begins with an accurate histological diagnosis as well as reasonable attempt at total tumor resection. The single greatest factor in determining long-term survival is the degree of tumor resection for both supratentorial and infratentorial tumors (Horn *et al.* 1999). While a number of studies demonstrate only 50% of infratentorial and supratentorial lesions being completely resected, these patients often enjoy long-term disease-free survival without adjuvant therapy in the setting of benign disease. Surgical considerations will vary by tumor location. Lesions in the posterior fossa typically present with hydrocephalus and often require the placement of a ventricular drain preoperatively. Long-term CSF diversion may be eventually needed and may be accomplished via an endoscopic third ventriculostomy or standard ventriculoperitoneal shunt. Resection of midline posterior fossa ependymomas often involve dissection of the floor of the fourth ventricle with an expected high level of morbidity, whereas more lateral lesions originating in the cerebellopontine angle often manifest complications related to cranial nerve manipulation or ischemic changes due to vascular insufficiency after spasm or direct vessel injury. Nevertheless, the advent of standard microsurgical approaches coupled with perioperative steroids, frameless sterotaxy, intraoperative electrophysiological monitoring, laser/ultrasonic tumor removal and improved postoperative care have all led to significant reductions in morbidity and mortality for lesions in both the posterior fossa as well as the supratentorial compartment.

Due to the tumor or its resection, multiple lower cranial nerve palsies and long-term neurologic impairment may occur. In addition, the 20–40% progression rate for patients without residual disease on postoperative imaging suggests that a significant number of tumors have extensive microscopic residual disease. Progression in almost all cases is local, with distant relapse occurring in less than 10% of cases. The positive role of complete resection and the predominance for local recurrence has led to the concept of second-look surgery for tumors that have been incompletely resected.

Local radiotherapy to 50–55 Gy for supratentorial tumors and 55–59 Gy for infratentorial tumors remains the standard postoperative treatment of nondisseminated ependymomas. Postoperative radiotherapy has been practiced since the 1950s and has become standard therapy due to the substantial improvement in survival that it provides. In a comparison of patients treated with surgery alone or surgery plus radiation therapy, the survival rates were 17% and 40%, respectively. Five-year survival is best for patients who have been totally resected and receive postoperative local radiotherapy, ranging in the 60–70% rate in some series. Studies are presently underway assessing the feasibility of delaying radiation, until the time of progression, for patients with "totally" resected tumors, especially those that are supratentorial and are histologically "benign."

Despite several trials demonstrating measurable disease responses, the role of chemotherapy in the treatment of ependymoma has not been established (Robertson *et al.* 1998). In single-agent trials, platinum compounds have been the most active.

Preliminary studies do support the potential use of chemotherapy in infants in an effort to delay radiation therapy or in children with incompletely resected tumors as an adjunct to second-look surgery prior to radiation therapy. Objective response rates up to 48% and 2-year progression-free survival of 42% have been demonstrated with cyclophosphamide, cisplatin, etoposide, vincristine, and deferred irradiation in the infant population.

Cerebellar astrocytoma

Infratentorial astrocytomas account for 12–18% of all pediatric brain tumors. The majority of childhood cerebellar astrocytomas are low-grade, primarily pilocytic astrocytomas.

As seen for other types of posterior fossa tumors, patients with cerebellar astrocytomas may present with increased intracranial pressure or with focal findings secondary to direct compression of adjacent neural structures (e.g. tectum, cranial nerves, etc.). Compression of the aqueduct of Sylvius or the fourth ventricular outflow by the either solid or cystic component of the astrocytoma may lead to the development of hydrocephalus and ensuing pressure-related symptoms of headache, nausea and vomiting, lethargy, ataxia and occasional precocious puberty. More direct involvement of cranial nerves and cerebellar nuclei may manifest with variable cranial neuropathies, dysconjugate gaze, tinnitus, vertigo as well as dysmetria.

Neuroimaging

The cerebellar astrocytoma is most commonly located in the midline, although in around one-third of cases it extends into one hemisphere. Rarely, it may arise solely within a cerebellar hemisphere (Fig. 14.5). Surrounding mass effect is common, leading to obstructive hydrocephalus at the fourth ventricle.

While the classic description of a cerebellar astrocytoma is that of a cyst with mural nodule, only half of all tumors follow this pattern, with the remainder comprising a solid tumor, commonly with necrosis. Tumors are commonly iso- to hypodense on CT, hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging, however appearances do depend on the extent of cystic or necrotic change. Calcification can occasionally be seen. At least some part of the tumor shows evidence of strong enhancement, commonly the mural nodule, or the more solid part of a necrotic tumor.

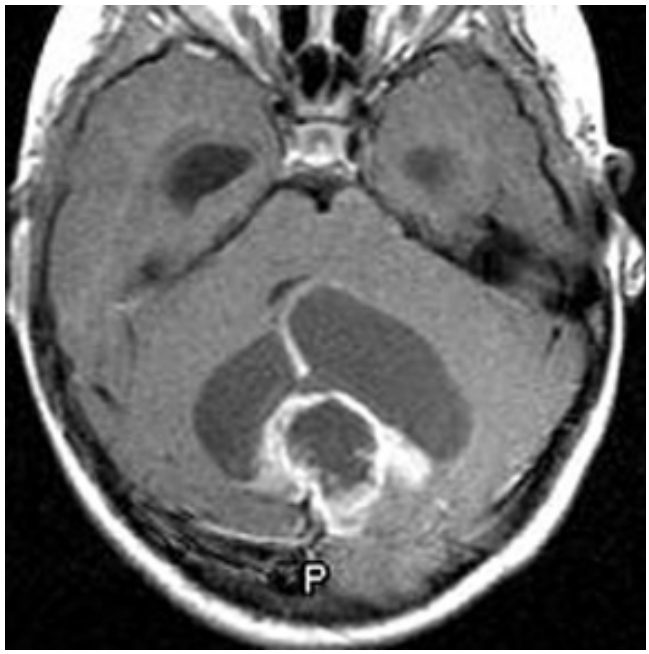

Fig. 14.5 Cerebellar astrocytoma. Axial postgadolinium T1-weighted image of the posterior fossa reveals a cystic mass with a necrotic rim-enhancing tumor within the cerebellar vermis. The fourth ventricle is compressed, indicating a tumor originating outside the ventricular system.

Microscopy

The typical tumor demonstrates a biphasic pattern in which highly fibrillated, pilocytic areas are intermingled with loosely structured, microcystic tumor tissue in a mucinous background. In areas of mucoid degeneration and microcysts formation the cells become round or stellate with plump or not discernible processes. Rosenthal fibers are characteristic of pilocytic, fibrillated areas. They represent regressive products of highly fibrillated tumor cells, appear as bright eosinophil bodies with a shape resembling a sausage, corkscrew or carrot and their numbers vary considerably from many to occasional, rare or absent.

Pilocytic astrocytomas are slowly growing neoplasms with absent or rare mitoses but show focal proliferative activity with a Ki-67/MIB-1 labeling index up to 4%. Necrosis is rare, without pseudopalisading, but vascular proliferation may be extensive, especially along the walls of the tumor cysts.

Management and outcome

Management of infratentorial gliomas relies predominantly upon surgical excision. In addition to obtaining tissue for pathological confirmation, the overwhelming objective in these patients rests upon an attempt at total resection of the tumor (Schneider *et al.* 1992). Patients are treated for pre-existing hydrocephalus with placement of a ventricular drain prior to or at the start of surgery. Whereas more than 90% of astrocytomas are completely resectable, an attempt to defer shunt placement is often made in the postoperative patient. In the patient eventually requiring CSF diversion, placing an endoscopic third ventriculostomy may avoid the need for long-term hardware. It is imperative to remove the solid tumor nodule whereas removal of the gliotic cyst wall is not required. Postoperative care requires close observation for the development or progression of hydrocephalus as well as supportive care for any postresection morbidity involving brainstem or cranial nerves. Cerebellar mutism (posterior-fossa mutism syndrome) has been reported in some patients following surgery, but is less common than after surgery for medulloblastoma.

While the majority of gliomas in the posterior fossa behave in a benign fashion, more aggressive tumors may be characterized by increased MIB-1 labeling and often have mean survival times of less than 12 months despite adjuvant therapy. Nevertheless, it has been demonstrated that low-grade tumors (juvenile pilocytic astrocytomas) can have a 25-year cumulative survival of 94% and recent studies have shown 100% survival at 20 years with gross total resections.

Brainstem gliomas

Brainstem gliomas comprise in between 10% and 15% of all childhood primary central nervous system tumors. They arise at a median age of 5–9 years and occur equally in males and females. The majority of brainstem gliomas are diffuse infiltrating lesions, which usually involve the pons and may also involve the midbrain and medulla and other contiguous sites at the time of diagnosis. Such diffuse infiltrating lesions present with multiple cranial nerve palsies, the most common being sixth and seventh nerve palsies, associated with long tract signs and cerebellar deficits. Prior to the advent of MRI scan, diagnosis was notoriously delayed in children with brainstem gliomas due to the insidious nature of such lesions. However, with present means of neuroimaging, the majority of patients will be diagnosed within 3 months of onset of symptoms. Increased intracranial pressure is present in approximately one-third of patients at the time of diagnosis.

Twenty per cent of brainstem gliomas will be more focal. Tectal tumors present with hydrocephalus and usually little in the way of other localizing deficits. Patients may have indolent courses and develop hydrocephalus early in life and then have no further progression for years following diversion of cerebrospinal fluid. Cervicomedullary brainstem gliomas tend to be dorsally exophytic. Such lesions may present with headache and unsteadiness, but may also cause intermittent nausea and vomiting for weeks to months before causing any other symptoms. Rarely, pontine lesions will be focal and cause isolated cranial nerve palsies, especially sixth and seventh nerve weakness.

Neuroimaging

Brainstem gliomas located in the pons cause diffuse expansion. Anteriorly, the tumor commonly engulfs the basilar artery while posteriorly, it may extend into the cerebellar

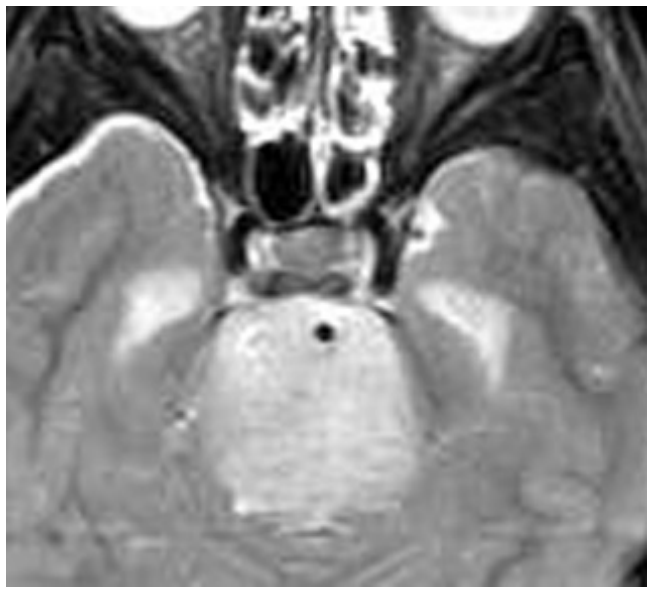

Fig. 14.6 Brainstem glioma. Axial T2-weighted image demonstrates the diffuse homogeneous T2 hyperintense tumor, which engulfs the basilar artery anteriorly. The temporal horns of the lateral ventricles are dilated bilaterally, in keeping with hydrocephalus.

peduncles (Fig. 14.6). Exophytic nodules can occur and tend to project into surrounding CSF spaces. Although gliomas may cause posterior displacement of the fourth ventricle, hydrocephalus is relatively uncommon. This tumor shows hypodensity on CT and homogeneous signal increase on T2-weighted imaging. Enhancement is rare at presentation, although may occur following radiation.

By comparison, focal brainstem gliomas are more common in the midbrain or medulla. Focal dorsally exophytic medullary tumors can be difficult to distinguish from posterior fossa tumors, such as astrocytoma or ependymoma, unless close evaluation is made of anatomical origin. While most focal gliomas show similar signal characteristics to the diffuse tumors, occasionally they can show hemorrhage or cystic change, giving a more heterogeneous appearance. Contrast enhancement is common.

Management and outcome

Treatment of diffuse intrinsic brain stem gliomas has not been effectively altered over the past decades (Packer *et al.* 1990). Although biopsy and partial resections can be undertaken, they have not been shown to affect the natural history of the disease and the information obtained at the time of biopsy usually does not change management. Radiotherapy remains the only proven treatment for brainstem gliomas, resulting in disease stabilization or clinical improvement in approximately 90% of patients. Doses of local radiotherapy, ranging between 5400 cGy and 6000 cGy, will result in tumor shrinkage in approximately one-half of patients, but 90% of patients will progress and die of disease within 18 months of diagnosis.

Alterations in radiation schedule and dose, as well as the addition of chemotherapy, either prior to or after radiotherapy, have not improved survival. Studies are presently under way attempting to improve the efficacy of radiation therapy by the use of radiosensitizers. Due to the severe neurologic compromise patients with brainstem gliomas have at the time of diagnosis and during their disease, corticosteroids are often utilized in an attempt to improve neurologic function. Although corticosteroids may improve neurologic function temporarily, they have no long-term benefit and their chronic use is associated with significant side effects including obesity, hypertension, hyperglycemia, gastrointestinal upset and bloating, cushinoid appearance, and uncontrollable appetite. These symptoms result in increased morbidity and corticosteroids should be tapered and, if possible, discontinued early in the course of treatment.

The management of more focal lesions within the pons remains relatively empiric. Focal lesions within the pons, especially cystic ones presenting with isolated cranial nerve palsies, are often pilocytic astrocytomas. Biopsy and cyst drainage followed by focal radiotherapy can result in prolonged disease control for many patients. Patients with tectal tumors may require no treatment other than cerebrospinal fluid diversion for many years after diagnosis. Biopsy is usually not required for diagnosis in these patients, and if there is progression, treatment with either chemotherapy (in very young children) or focal radiotherapy is usually effective. For patients with cervicomedullary lesions, especially those that are dorsally exophytic, usually the first treatment modality utilized is surgery. Although such lesions are often amenable to extensive resections as they are commonly pilocytic astrocytomas, such resections may cause significant neurologic morbidity. Alternatively, patients with cervicomedullary pilocytic astrocytomas have been treated successfully with partial surgical resection followed by either local radiotherapy or chemotherapy.

Diencephalic gliomas/visual pathway gliomas

Gliomas of the visual pathway, including the optic nerves, chiasm and optic tracts, constitute approximately 5% of all primary central nervous system tumors. More than 75% of isolated optic nerve gliomas occur in the first decade of life. Neurofibromatosis type I is present in 50–80% of patients with isolated optic nerve tumors, and in approximately 15–20% of those with chiasmatic or tumors which diffusely infiltrate the visual pathway. Tumors of the visual pathway have been classified in various ways. Lesions have been said to be either anterior or posterior, dependent on the degree of chiasmatic involvement or spread into other areas of the visual pathway or surrounding brain. Isolated optic nerve gliomas carry a different prognosis and should probably be conceptualized as being different tumors, at least as regards

management, than those lesions that more extensively infiltrate the visual pathway.

The signs and symptoms of visual pathway gliomas depend on their location and the age of the patient. Children less than 3 years of age are often brought to medical attention because of strabismus, proptosis, or nystagmus. Infants may display the triad of head tilt, head bobbing and monocular or disassociated asymmetric nystagmus. Similar symptoms can be found in children with spasms nutans and clinical differentiation is difficult.

At the time of diagnosis, patients with isolated optic nerve tumors usually have some decreased visual acuity in the involved eye. However, vision may be remarkably maintained in the involved eye, especially in patients with neurofibromatosis type I. Funduscopic examination usually discloses optic pallor and atrophy in the involved eye, rather than papiledema. In patients with chiasmatic involvement, decreased visual acuity is usually associated with some type of visual field abnormality. The visual field deficits are often complex and are difficult to delineate in a very young child. Patients may have fine, rapid unilateral or bilateral nystagmus, which may or may not be associated with decreased visual acuity. Growth and endocrine disturbance may be present, especially in patients with extensive hypothalamic involvement. The diencephalic syndrome is a classical presentation for patients with hypothalamic gliomas.

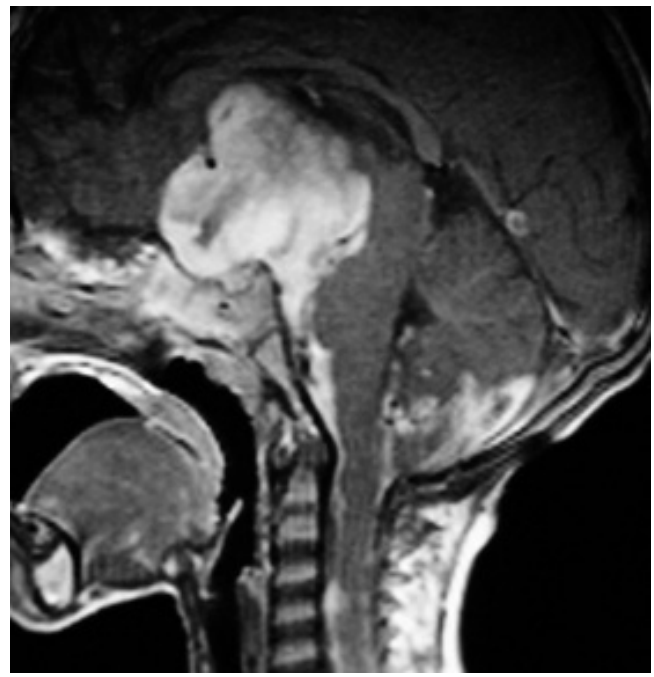

Fig. 14.7 Chiasmatic glioma. Sagittal postgadolinium T1-weighted image of the brain reveals a very large suprasellar tumor extending superiorly into the hypothalamus and anterior third ventricle and posteriorly resulting in mass effect on the brainstem. There is diffuse enhancement within the subarachnoid spaces surrounding the brainstem and upper cervical cord, as well as in the cisterna magna.

Neuroimaging

Diencephalic gliomas present as a lobulated suprasellar mass, which, when large, may be inseparable from the hypothalamus and the anterior third ventricle (Fig. 14.7). The tumor may also involve the optic nerves, or spread posteriorly along the optic tracts to the lateral geniculate nuclei. Tumors extending into the third ventricle may cause obstructive hydrocephalus at the foramen of Monro. While small tumors are generally homogeneously hypodense on CT, isointense on T1-weighted imaging and hyperintense on T2-weighted imaging, larger tumors may contain cystic elements, giving a more heterogeneous appearance. Solid tumor components commonly enhance.

Management and outcome

For patients with isolated optic nerve gliomas, management is dependent on the degree of proptosis and associated cosmetic abnormalities and visual acuity. In patients with significant proptosis and a blind eye, resection is usually undertaken to remove as much of the optic nerve as possible. Often a globe-sparing procedure is possible. However, there remains little evidence that the majority of patients with isolated optic nerve tumors will develop tumor deeper into the visual pathway, even if the tumor is left alone.

In patients with maintained vision, management is more problematic. In such patients, radiotherapy may result in shrinkage of the optic nerve and maintenance of vision. However such radiotherapy may also have long-term cosmetic sequelae because of involvement of the overlying bone. The issue of secondary mutagenesis is an important one, especially in children with neurofibromatosis type I.

For patients with chiasmatic, hypothalamic, or more extensive visual pathway infiltration, the role of surgery is more limited. Patients with neurofibromatosis type I do not require surgical intervention of any type to confirm the presence of a glioma. The need for surgery is more controversial in patients with chiasmatic or hypothalamic disease who do not have a stigmata of neurofibromatosis type I. In these patients, biopsy may distinguish the rare patients with a higher grade infiltrating glioma, although sampling error is an obvious limitation. Patients with extensive visual pathway gliomas are not amenable to gross total resection. Partial resection may relieve obstructive hydrocephalus and, in selected patients, may result in disease stabilization and delay the need for more definitive therapy. However, extensive resections are also associated with significant morbidity, especially in the youngest patients.

Radiotherapy results in visual stabilization in the majority of patients with visual pathway gliomas. Visual improvement has been reported after radiotherapy in a variable proportion of patients ranging between 9% and 44%. Irradiation of large chiasmatic/hypothalamic lesions does result in disease stabilization in the majority of patients and 5- and

10-year progression-free survival rates ranging between 70% and 90%. The doses of radiotherapy required (4500–5500 cGy) will result in significant endocrinologic deficits in the majority of patients and radiotherapy may have long-term deleterious effects. The latter long-term effects may include the development of vascular malformations (which may be life-threatening) and significant neurocognitive sequelae, especially in very young children.

To delay, if not obviate, the need for radiotherapy, chemotherapy has been used in children with progressive visual pathway gliomas (Packer *et al.* 1997). A variety of different chemotherapeutic agents have been employed and the combination of carboplatin and vincristine has been shown to result in disease stabilization in over 90% of patients with progressive lesions and radiographic shrinkage in 60%. Other drug regimens such as carboplatin alone, or more aggressive regimens, may result in disease control. It is unclear whether these more aggressive regimens are needed to halt disease progression. Also, such regimens carry with them increased risk, including a higher potential for mutagenesis, infection, and associated hearing loss (if cisplatinum is utilized). Such hearing loss may be extremely deleterious in a child who is already visually impaired.

For children with neurofibromatosis type I and visual pathway gliomas, interventions must be undertaken cautiously (Listernick *et al.* 1995). The natural history of tumors of the optic nerve or visual pathway is extremely erratic in patients with neurofibromatosis type I. The majority of children diagnosed on screening examinations not to be clearly symptomatic or progressive will require no immediate treatment. Management includes careful neurologic, visual, endocrinologic, and neuroradiographic follow-up and treatment only if there is clear-cut progression. Because of the potential risks of radiotherapy, patients with progressive disease are often initially treated with chemotherapy.

Cortical gliomas

Up to one-half of cortical gliomas are located in the cerebral hemispheres. The remainder occurs in the deep midline structures of the diencephalon and basal ganglia. Children may often have mixed neuronal-glial tumors (Table 14.6). Diencephalic gliomas, including visual pathway gliomas, are discussed separately. The major clinical signs at diagnosis are nonspecific and nonlocalizing features related to increased ICP (headache, morning emesis, lethargy) occurring in up to 75% of patients regardless of tumor histology and location. Seizures, most frequently grand mal, are present at diagnosis in at least 25% of patients. Although as many as one-third of patients with high-grade tumors have seizures, the frequency is actually higher in the more slowly evolving low-grade tumors, where they may precede diagnosis by months to years. Seizures are a particularly common feature of ganglioglioma and oligodendroglioma.

Neuroimaging

Cortical tumors have a wide variety of appearances, reflecting their different histologies, but all have in common involvement of the peripheral gray matter. The ganglioglioma and dysembryoplastic neuroepithelial tumor (DNET) are well-defined tumors, commonly found in the temporal lobe. The ganglioglioma is generally of a mixed solid-cystic composition, showing hypodensity on CT, hypointensity on T1-weighted imaging, hyperintensity on T2-weighted imaging and variable enhancement. The DNET may present as an enlarged gyrus, showing a lobulated contour. Again hypodense on CT and hyperintense on T2WI, approximately one-third of cases show calcification or enhancement. Both tumors remodel the inner table of the skull and show little or no surrounding edema. The desmoplastic infantile ganglioglioma presents as a very large hemispheric mass with both cystic and solid components. The solid regions tend to be located more peripherally and show a slight increase in density on CT and isointensity on T2-weighted imaging. They strongly enhance the result of an intense desmoplastic reaction. The pleomorphic xanthoastrocytoma (PXA) commonly presents as a large cystic intracranial mass, with a mural nodule, adjacent to the peripheral leptomeninges. It is hypodense on CT, hypointense on T1-weighted MR imaging and iso to hyperintense on T2-weighted imaging. The mural nodule commonly enhances.

Microscopy

Diffuse, fibrillary astrocytomas (WHO grade II), composed of infiltrating, neoplastic astrocytes with scant cytoplasm and nuclear atypia, but without mitoses and higher grade tumors such as anaplastic astrocytomas (WHO grade III) with increased cellularity, cellular pleomorphism, nuclear hyperchromasia and mitotic activity (Fig. 14.8). The highest grade of astrocytic origin tumor is the glioblastoma multiforme, rare in children, that adds to the previously described characteristics higher cellularity, greater pleomorphism with possible giant cells, pseudopalisading necrosis, exuberant microvascular proliferation appearing as glomeruloid tufts and numerous mitoses.

Oligodendroglioma (WHO grade II) are composed of cells with uniform round to ovoid nuclei and empty-looking cytoplasm (fried-egg artifact), bounded by distinct cell membrane producing a classical, low power "honeycomb" appearance.

Oligodendrogliomas characteristically form perineuronal satellitosis around cortical neurons, subpial aggregation and perivascular association.

High-grade glioma: management and outcome

Radical (>90%) surgical resection is the most powerful predictor of favorable outcome in high-grade glioma (HGG) when followed by irradiation. However, only 49% of tu-

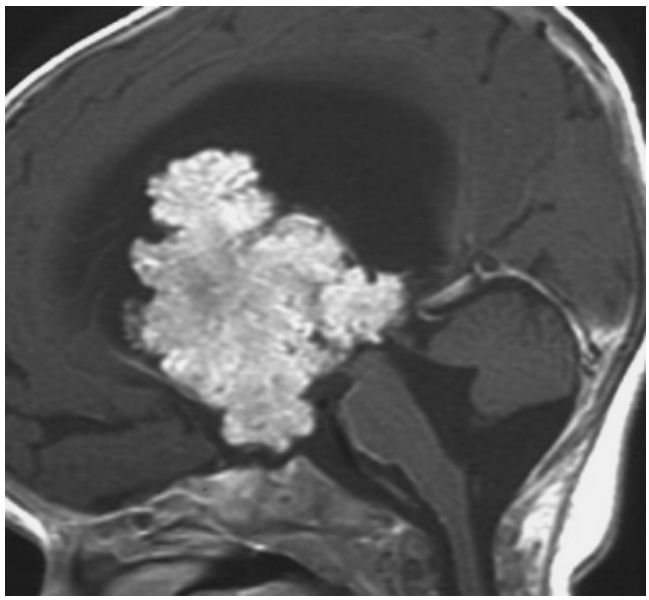

Fig. 14.8 Choroid plexus papilloma. Sagittal postgadolinium T1-weighted image of the brain reveals an extremely large lobulated mass within the third ventricle, showing strong contrast enhancement.

mors in the superficial hemisphere and 8% of tumors in the midline or deep cerebrum are amenable to radical resection. In addition, training of the neurosurgeon (pediatric versus adult neurosurgery) has a significant impact on the extent of surgical resection. Local (2- to 4-cm margin around the area of edema defined by imaging) or wide-field irradiation to 5000–6000 cGy is the mainstay of therapy.

The addition of radiation therapy has improved 5-year survival rates (10–30%) compared to surgery alone (0%). All patients are thus considered candidates for radiotherapy following surgery, with the exception of very young children, in whom attempts have been made to eliminate or delay the use of radiotherapy because of concern regarding neurodevelopmental morbidity. Newer techniques, such as conformal radiation and stereotactic radiosurgery ("gamma knife"), which allow for higher doses of radiation delivered to the tumor bed while minimizing exposure of adjacent normal tissue, are currently under investigation. To date, no large randomized prospective clinical trial has clearly demonstrated a benefit of adjuvant chemotherapy.

The outcome of children with high-grade cortical gliomas remains poor. The 5-year survival rate ranges from 16% to 46% with the use of postoperative radiotherapy and chemotherapy. Patients may have significant neurocognitive, neuroendocrine, and other neurologic deficits as a result of the tumor's location and the secondary effects of surgery, irradiation, and chemotherapy.

Low-grade gliomas: management and outcome

Complete surgical resection is curative for most low-grade gliomas (LGG), and even with incomplete excision, long-term progression-free survival is common. If subsequent progression occurs then re-resection is generally first undertaken. Surgical morbidity depends largely on tumor location and is highest in diencephalic tumors, in which the incidence of hemiparesis or visual field deficits may be 10–20%. Gross total excisions are possible in up to 90% of hemispheric tumors. For patients with progressive disease not amenable to resection, local conformal irradiation to 5000–5500 cGy to the area of the tumor plus a 2-cm margin is warranted. The use of chemotherapy as initial treatment in newly diagnosed LGG involving the optic chiasm and hypothalamus has become a standard approach only among very young children and infants in whom the goal is to avoid radiation neurotoxicity, but has not been used widely for gliomas of the cerebral hemispheres, thalamus or basal ganglionic area. The use of such therapy in older patients is questionable since outcome is generally good with surgery and irradiation. Overall, 5-year survival for low-grade cortical glioma is 95%, while progression-free survival is 88%.

Craniopharyngiomas

Despite over 70 years of experience in the neurosurgical arena, successful treatment of craniopharyngiomas remains open to controversy (Scott *et al.* 1994). They account for 5–10% of all childhood brain tumors. Although these tumors are benign and represent embryonic remnants of Rathke's pouch in the region of the sella; their location in proximity to the hypothalamus, optic pathways, carotid vessels and the propensity to grow to large sizes as well as develop calcification, make their safe and total removal exceedingly difficult. A bimodal incidence is seen with children between the ages of 6–10 years as well as 11–15 years and gender predilection appears to be equal, although some studies support a slightly greater male incidence. Clinical presentation may be variable and may include symptoms secondary to increased intracranial hypertension due to hydrocephalus or from direct tumor/cyst extension. Headaches, nausea, vomiting, visual changes, hormonal insufficiency, memory deficits, and seizures are commonly seen in the setting of craniopharyngioma. Visual symptoms are noted in approximately 50% of affected individuals and compression of the optic chiasm constitutes an emergent clinical situation to preserve vision. Hormonal insufficiency is common (>70%) and may include failure of growth, delayed sexual maturation, excessive weight gain and in 10–20% of children, diabetes insipidus is present.

Neuroimaging

The adamantinomatous craniopharyngioma, most common in children, presents as a well-defined, lobulated, heterogeneous mass. The tumor almost always contains cystic components, which may appear hyperintense on T1-weighted imaging due to high cholesterol content. These cysts are typically brighter on T2-weighted imaging than the solid tumor components that are usually also present. Calcification is almost universal, occurring either as a thin rim around a cyst or larger internal foci. Both the solid areas of tumor and the rim of the cystic components enhance.

Management and outcome

Therapeutic direction must take into account numerous factors, which not only include surgical consideration of tumor size and location but also reflect whether the tumor is primary or recurrent, as well as preoperative visual and endocrinological status. Preoperative evaluation should include formal visual field testing as well as extensive endocrine and metabolic evaluation. Not uncommonly, patients with craniopharyngiomas may demonstrate endocrine dysfunction without overt symptoms.

The surgical goal remains total extirpation, if possible. Owing to the proximity of the carotid vessels, optic chiasm, and hypothalamus; tumors with significant adherent calcification may prevent total excision in a safe fashion. Although this has been a contentious issue for many clinicians up until recently, recent studies appear to support the role for limited resection of craniopharyngiomas when vital structures are at risk. Residual tumor may be subsequently treated with stereotactic radiosurgery, intracavitary brachytherapy utilizing ^{32}P or ^{90}Y, cyst aspiration, as well as intracavitary bleomycin. Indications for type of treatment as well as long-term outcome are still in evolution, although irradiation has been demonstrated to offer 50–90% 5-year and 10-year disease-free survival. Primary tumors presenting within the sella occur 3–15% of the time and may be removed successfully via a transphenoidal approach, with an attendant reduction in overall risk to the patient. Whereas peril to the chiasm and carotid vessels is diminished, endocrine disturbances are expected if the pituitary stalk is not preserved.

Total resection, confirmed by postoperative radiographs, is now possible in 80–90% of individuals whereas mortality has decreased to 0–2% over the past decade. Hormonal replacement is necessary in approximately 80% of pediatric patients and most frequently involves diabetes insipidus, requiring DDAVP therapy in 75% of children, as well as thyroid and cortisol supplementation. Visual deterioration is seen in nearly 20% of patients, whereas 50–60% will show improvement. Neuropsychological impact remains controversial, and is dependent upon baseline memory and intelligence. Recent studies however have demonstrated normal psychosocial integration as well as academic performance in 70–87% of children treated by experienced surgeons and centers.

Germ cell tumors

Germ cell tumors may arise throughout the neuraxis with a propensity to occur in a suprasellar location and more commonly in the pineal region (Packer *et al.* 2000). Confirmed tissue histology prior to the advent of adjuvant therapy remains a cornerstone of pineal/suprasellar tumor therapy, except for those tumors which can be diagnosed by measurement of cerebrospinal fluid markers.

Because germ cell tumors generally arise in the midline pineal area, the dominant signs and symptoms of these tumors are typically the nonspecific and nonlocalizing features of increased intracranial pressure secondary to tumor extension and compression of the third ventricle. Other findings depend on the location and extent of tumor spread. Tumors extending to the midbrain (tectum) may cause varying degrees of vertical gaze palsy characteristic of Parinaud's syndrome. Tumors that infiltrate the thalamus may cause hemiparesis, incoordination, visual deficits, or movement disorders. The suprasellar region also frequently harbors germ cell tumors that may produce pituitary and hypothalamic dysfunction, including diabetes insipidus, hypothyroidism, precocious puberty and emotional as well as thermoregulatory dysfunction.

Neuroimaging

Germinomas usually present as well-defined, homogenous masses, although when large they may show internal heterogeneity. Germinomas commonly show strong uniform enhancement. Close evaluation should be made for accompanying metastatic spread throughout the cerebrospinal fluid. By comparison, the teratoma is extremely heterogeneous, with evidence of fat, calcification and soft tissue within the tumor. This gives a very varied appearance on CT and MR. Enhancement is unusual unless there has been malignant degeneration. Embryonal cell carcinoma and endodermal sinus tumors have few individual defining imaging features. Choriocarcinoma may undergo hemorrhage and should be considered when a hemorrhagic pineal mass is present.

Microscopy

Germinomas are the most frequently occurring intracranial germ cell tumors and are composed of sheets or lobules of large cells with abundant clear cytoplasm, round vesicular nuclei and prominent nucleoli. Often the tumor cells are intermixed with small T-lymphocytes along fibrovascular septa. Teratomas recapitulate, albeit in disorganized fashion, the somatic differentiation by the embryonic ectoderm, endoderm and mesoderm. These tumors may be mature if they are composed of fully differentiated, "adult-type"

tissue elements or immature if composed of incompletely differentiated elements resembling fetal tissue. Mixed germ cell tumors demonstrate any combination of germinomas and/or teratomas with other malignant component such as embryonal carcinomas, endodermal sinus tumors and choriocarcinomas.

Management and outcome

Patients with acute hydrocephalus may be managed by placement of a ventricular drain, ventriculoperitoneal shunt or with increasing frequency by an endoscopic third ventriculostomy. Placement of a ventricular drain may be done in the acute setting in a safe and effective fashion to gain control over the possibility of intracranial hypertension and subsequent neurological deterioration (particularly during the preoperative evaluation with the need for sedation during numerous radiological studies). Cerebrospinal fluid including alfa-fetoprotein (AFP), beta-human chorionic gonadotrophin (β-HCG), and placental alkaline phosphatase (PLAP) should be measured on ventricular and, if safe, lumbar fluid and compared to serum counterparts. In addition, cerebrospinal fluid is assayed for cytology, as part of a preoperative attempt at diagnosis. Elevated levels of AFP and β-HCG confirm the presence of mixed germ cell tumors, while highly elevated β-HCG is diagnostic of a choriocarcinoma. Mildly elevated β-HCG suggests the syncytiotrophoblastic form of germinoma. In suspected cases of nonsecreting germinomas or nongerm cell pineal region tumor, stereotactic or endoscopic methods of obtaining tissue remain a viable approach to limit perioperative morbidity.

Individuals presenting with hydrocephalus may subsequently be a good candidate for an endoscopic biopsy of pineal region lesions that project into the posterior third ventricle. In addition to relatively minimal morbidity, it is often possible to perform an endoscopic third ventriculostomy at the same sitting.

Patients with radiographic features of benign disease or individuals in whom prior biopsy demonstrates tumor histology insensitive to adjuvant therapy are best served by an attempt at total tumor resection for long-term control of disease. This may be accomplished via an infratentorial approach using a supracerebellar exposure or through a supratentorial avenue via a posterior corpus callosum dissection. In individuals with large lesions extending into both the supra and infratentorial compartments, a combined approach splitting the tentorium may offer excellent visualization of the tumor and surrounding vascular structures. Despite decreasing morbidity over the past decade with improvements in surgical technique and postoperative care, such surgical avenues, while offering the possibility of total tumor resection, still carry significant risks of perioperative morbidity and mortality.

Radiation therapy has traditionally been the mainstay of therapy for these tumors. Craniospinal irradiation (36 Gy for nongerminomatous and 24 Gy for germinomas) had been the standard treatment for all germ cell tumors; however, given the chemo-sensitive nature of these tumors, most investigators now employ adjuvant chemotherapy as a means to eliminate the need for, or reduce, the dose of craniospinal irradiation in tumors without metastatic spread. For nonmetastatic tumors, irradiation to the site of initial disease, up to 54 Gy in nongerminomatous and 45 Gy for germinomas, is used. Metastatic tumors still will require craniospinal irradiation with boost to the sites of disease up to the doses given above. The specific chemotherapeutic regimens vary according to the histology and response to initial treatment; however, most contain regimens with an alkylating agent (ifosfamide or cyclophosphamide), platinum agents (carboplatin or cisplatin), and etoposide.

The most important predictive feature of outcome for germ cell tumors is histologic subtype. Pure germinomas, which have negative serum and CSF markers for malignant germ cell elements (negative alfa-fetoprotein and negative to low beta-human chorionic gonadotropin), are sensitive to irradiation, and as such, have >95% survival rate. Attempts to treat these tumors with chemotherapy alone have shown complete response rates of 78%, but only 60–70% survival. Patients with mixed germ cell tumors have a much worse prognosis. The best results have been obtained with platinum-based chemotherapy and full-dose craniospinal irradiation, although 5-year survival remains 40–50%. Pure teratomas are typically unresponsive to chemotherapy or radiotherapy and surgery is the only proven treatment.

Choroid plexus tumors

Although choroid plexus tumors are uncommon entities and constitute only 1–5% of all pediatric tumors, they nevertheless represent a greater percentage (4–12%) of tumors in patients less than 1 year of age. Due to their intraventricular location, they frequently present with hydrocephalus secondary to CSF overproduction as well as obstruction of intraventricular pathways. Not infrequently, infants are born with large lesions within the ventricles in association with hydrocephalus and may even be identified during prenatal evaluation via ultrasound. In addition to presenting with increased intracranial pressure (macrocephaly, full fontanelle, split sutures, Perinaud phenomenom, vomiting, irritability, etc.), patients may also present with seizures, intraventricualr hemorrhage or focal neurological findings. Tumors may arise from any of the ventricles with 75% occurring in the lateral ventricle, in particular the atrium. While choroid plexus lesions occur most commonly in the fourth ventricle in adults, this location is infrequently seen in children. Extraventricular locations have also been observed, in addition to multiple locations, including metastases, throughout the neuraxis.

Neuroimaging

The papilloma presents as a well-defined, lobulated, mass. On CT, it is commonly iso or hyperdense, occasionally showing punctate calcifications or hemorrhage. MRI reveals T1 isointensity and relative T2 hypointensity (Fig. 14.8). The tumor shows strong homogeneous enhancement. Choroid plexus carcinoma commonly shows a more aggressive appearance, with an irregular contour and invasion of adjacent brain. It shows marked heterogeneity with evidence of necrosis, mixed densities and signal intensities and prominent enhancement. It induces vasogenic edema in surrounding brain.

Microscopy

Choroid plexus tumors manifest pathological features that range from benign, well-delineated papillomas to invasive, poorly differentiated carcinomas. The choroid plexus papilloma has a distinct papillary pattern with a well-vascularized connective tissue core, surmounted by a single layer of cuboidal or columnar epithelium. The tumor is well-circumscribed, without invasion of brain and with low mitotic activity. The malignant counterpart, carcinoma, is characterized by loss of papillary architecture with the neoplastic cells forming large solid sheets. Anaplastic features include increased mitotic activity, nuclear atypia, necrosis and frank invasion of adjacent neuronal tissue.

Management and outcome: choroid plexus papillomas

Therapeutic considerations predominantly involve surgical extirpation, with complete excision of tumor if possible. While placement of a ventricular drain may be necessary in the preoperative stage, placement of a permanent shunt is deferred until after tumor removal. In many instances, the need for permanent CSF diversion may not be necessary after the removal of a hypersecreting tumor. Choice of surgical approach will take into consideration exposure of vascular supply to the tumor as well as adequate visualization to safely complete the resection with a minimum of cortical incision and retraction. Lesions in the lateral ventricle not uncommonly have blood supply from both the anterior and lateral posterior choroidal arteries, whereas third ventricle tumors are supplied from the medial posterior choroidal artery. Tumors arising in the fourth ventricle are vascularized by branches from posterior inferior cerebellar or superior cerebellar arteries. Smaller tumors may often be mobilized to gain access to the vascular pedicle, in turn simplifying total removal of the mass. Conversely, larger tumors often require piecemeal resection to eventually reach their blood supply and may manifest considerable bleeding before vascular control is undertaken. Consequently, removal of large atrial lesions in the newborn carries considerable risk of life-threatening hemorrhage and should be deferred to a later age if possible. Preoperative embolization may also be considered as an adjunct to reducing intraoperative bleeding, but is usually reserved for the older patient with sufficiently larger vessels. Continued advances in surgery have led to decreasing surgical morbidity and mortality, however mortality is still reported to be as high as 24% in some series. Long-term outcome will be dependent upon the degree of tumor resection as well as the histopathology. Benign papillomas with complete resection understandably carry an excellent prognosis, whereas malignant tumors with incomplete resection or those with leptomeningeal spread have a less favorable outcome and require adjuvant therapy. Recent advances in pediatric neuro-oncology have demonstrated the effectiveness of initial treatment with chemotherapy with delayed radiation at a later age. Nevertheless, extent of resection remains the single most important factor in predicting long-term survival.

Management and outcome: choroid plexus carcinomas

Surgical resection is the cornerstone of treatment of choroid plexus carcinoma. The surgical approach chosen depends on the location and vascularization of the tumor. Resection of ventricular tumors can be complicated by hemorrhage from arterial feeding vessels or deep venous drainage vessels and appropriate care must be taken to isolate and ligate these vessels. Preoperative embolization has been used to help mitigate the risk of hemorrhagic complications.

Successful gross total resection (GTR) is the most important predictor of successful therapy for CPC. In 277 patients with CPC, 2-year survival rates were 72% *vs*. 34% for those with GTR or subtotal resection respectively. When not initially possible, a GTR may be possible following adjuvant therapy.

Irradiation may be of benefit for those patients who have had a subtotal resection. Adjuvant therapy has been purported to be necessary in the treatment of subtotally resected CPC. Chemotherapy has also been used as adjuvant therapy in young children as well as in combination with radiation. Chemotherapeutic regimens employed usually include cyclophosphamide, etoposide and a platinum agent. Although responses have been noted, a positive impact on long-term survival has been difficult to gauge owing to the small number of patients in each report and the heterogeneity of chemotherapy regimens.

Atypical teratoid/rhabdoid tumors

The atypical teratoid/rhabdoid tumor was first clearly described in 1987 (Rorke *et al.* 1996). This tumor diagnosed by light microscopy and immunohistochemical findings comprises approximately 10–15% of all embryonal tumors occurring in children younger than 3 years of age. Although its exact incidence is unknown, the ratio of atypical teratoid/rhabdoid tumors to primitive neuroectodermal tumors is

approximately 1:4 in children younger than 3 years of age. More recently, atypical/rhabdoid tumors have been diagnosed in older patients.

Approximately one-half of all atypical teratoid/rhabdoid tumors will arise in the posterior fossa. The tumor has also been found throughout the nervous system including the suprasellar region, pineal region, spinal cord and extramedullary sites. When arising in the posterior fossa, atypical teratoid/rhabdoid tumors present similarly to medulloblastomas. However, there seems to be a prediliction for the cerebellopontine angle with children often presenting with sixth and seventh nerve palsies. Supratentorial lesions tend to be quite large at the time of diagnosis resulting in focal neurologic deficits, as well as symptoms of increased intracranial pressure. Cerebrospinal fluid dissemination occurs at the time of diagnosis in one-third to one-half of patients.

Neuroimaging

These tumors are normally large by the time of presentation and commonly show a heterogeneous appearance, due to tumor necrosis. Solid tumor components often show similar imaging characteristics to medulloblastoma, namely CT hyperintensity, T1 hypointensity and T2 isointensity, as well as contrast enhancement. Surrounding edema is common. The imaging characteristics of atypical teratoid/rhabdoid tumors are not, however, sufficiently distinctive to allow clear differentiation from other posterior fossa tumors.

Microscopy

The typical rhabdoid cell is medium-sized, round to oval with distinct borders, eccentric nucleus and commonly prominent nucleolus (Fig. 14.9). Cytoplasm has a fine granular character or may contain a poorly defined pink "body" resembling an inclusion. Mitoses are abundant and field necrosis is common. The immunophenotype is broad, as the large rhabdoid cells display a range of immunoreactivity with clusters of cells almost always positive for epithelial membrane antigen (EMA) and vimentin. Also frequent is reactivity for GFAP and cytokeratin and less frequent for smooth muscle actin (SMA) and neurofilament protein. The rhabdoid cells are negative for desmin and any of the markers for germ cell tumors.

Management and outcome

The management of atypical teratoid/rhabdoid tumors remains suboptimal. In the majority of patients less than 2 years of age, treatment with chemotherapy alone or chemotherapy plus local radiotherapy will result in a long-term disease control rate of less than 10%. Treatment with chemotherapy followed by early craniospinal and local boost radiotherapy or initial radiotherapy supplemented by high-dose chemotherapy has been shown to result in a better outcome in older patients. The management approaches utilized for patients with poor-risk medulloblastoma are often utilized for children with atypical teratoid/rhabdoid tumors, however, recent studies have suggested that therapy will need to be intensified to improve disease control.

Spinal cord tumors

Spinal cord tumors are relatively rare entities accounting for only 4–10% of all central nervous system neoplasms. A variety

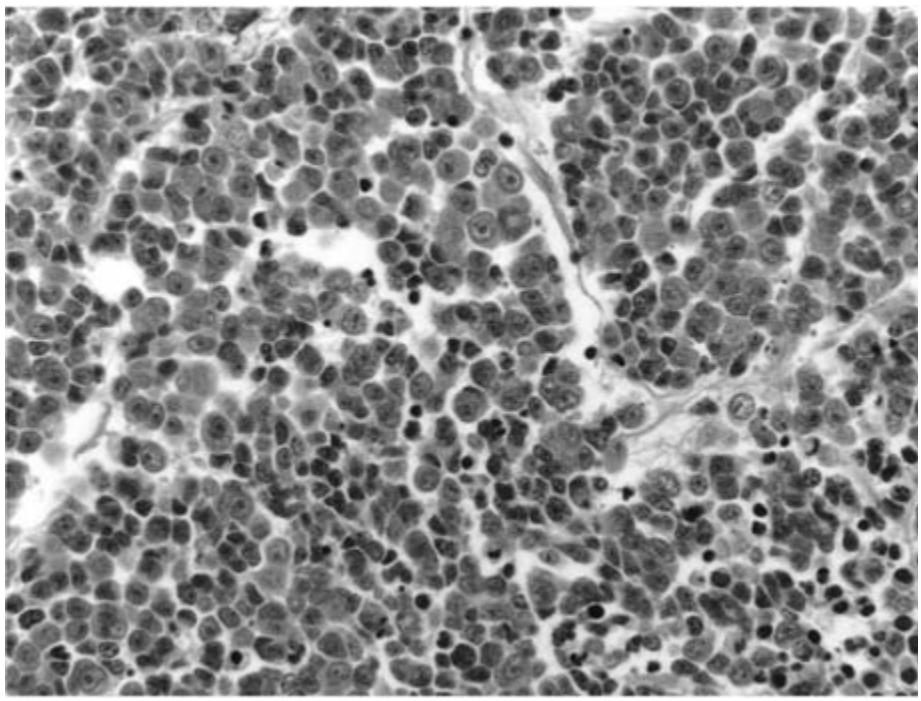

Fig. 14.9 Atypical teratoid/rhabdoid tumor. The cells forming trabeculae have abundant cytoplasm with eosinophilic inclusions, large nuclei and prominent nucleoli (H&E).

PEARLS & PERILS

- In children with visual pathway gliomas, especially optic nerve gliomas, look carefully for stigmata of neurofibromatosis type I.
- Headaches early in the presentation of a brain tumor are usually nonlocalized or nonspecific; however, headaches which are new or have changed significantly in character raise the possibility of an intracranial lesion.
- Crossed hemiparesis with a peripheral facial palsy on one side and hemiparesis on the other strongly suggest the possibility of an intrinsic brain stem process, especially a brain stem glioma.
- An infiltrating chiasmatic mass, especially a chiasmatic glioma, results in complex visual field loss with variable loss of visual acuity than bitemporal hemianopsias.
- Evaluation for tumor dissemination requires both MRI and cerebrospinal fluid; MRI of the entire neuroaxis is best performed prior to surgery.
- The most important determinant of outcome for patients with ependymomas is the degree of surgical resection.
- Not all childhood brain stem gliomas carry a poor prognosis; 20% will be more focal lesions either emanating from the cervicomedullary junction or arising in the tectum.
- Cortical gliomas, especially in infants, may be quite complex and be extremely large at the time of diagnosis, but have a relatively favorable prognosis.
- Although long-term survival is common in children with craniopharyngiomas, quality of life can be greatly impaired in long-term survivors. Sequelae include severe emotional difficulties, obesity, and visual impairment.
- Despite its aggressive nature, choroid plexus carcinomas may require only complete resection for long-term control.
- Children surviving brain tumors are at risk for significant neurologic, neurocognitive, psychological, and endocrinologic sequelae. The success of treatment cannot only be assessed on the basis of survival but also quality of life.

of tumors may arise in the spinal cord as primary lesions or as metastatic secondary masses. The most common primary lesions include astrocytomas, ependymomas, schwannomas, lipomas as well as inclusion cysts (i.e. dermoid, epidermoid). Less common lesions may include ganglioglioma, gangliocytoma, teratoma, hemangioblastoma, germinoma in addition to leptomeningeal metastases from PNET, pineal tumors, ependymomas, and malignant astrocytomas.

Spinal cord tumors may present as intrinsic, intramedullary lesions or as extramedullary masses with extrinsic compression of the cord and adjacent nerve roots. Approximately one-third of pediatric spinal cord tumors are intramedullary with the vast majority of lesions being astrocytomas in the younger patient and ependymomas in the older child. Primary intramedullary tumors (astrocytomas, ependymomas, gangliogliomas) clinically present with intrinsic cord compression and may manifest by weakness, sensory changes including paresthesias, pain, gait changes, scoliosis and bowel or bladder difficulties. Extrinsic tumors, which may include schwannomas, metastases, dermoid/epidermoid, lipomas, etc., frequently present with a combination of myelopathic changes as well as peripheral nerve findings. Peripheral nerve involvement may include back or radicular pain, motor or sensory distubances, spasticity, as well as bowel and bladder changes.

Diagnostic evaluation predominantly involves radiological investigation. EMG/NCV tests are infrequent adjuncts in today's work-up of spinal cord tumors. Somatosensory evoked potentials remain a valuable preoperative as well as intraoperative method of assessing neurophysiological function and integrity of the spinal cord during the course of surgery, alerting the surgeon in the event that manipulation of the cord is causing dysfunction. In addition, urodynamic testing may demonstrate early evidence for neurogenic bladder and may also provide a relative baseline for long-term surveillance.

Neuroimaging

MRI commonly reveals an enlarged, T2 hyperintense cord, although subjects may present with a thin syrinx (Fig. 14.10). Ependymomas may show areas of hemorrhage, detectable asT2 hypointensity, surrounding the tumor. Gadolinium is required to distinguish tumor from surrounding edema or intra- or peritumoral cyst formation, common findings in intramedullary spinal tumors. Almost without exception, spinal cord tumors enhance. Ependymomas tend to be more sharply circumscribed following gadolinium enhancement, however, the rarer germinomas and gangliogliomas also show this finding. By comparison, astrocytomas show a more infiltrative pattern and tumor cells may extend beyond the area of enhancement.

Management and outcome

Current management of spinal cord tumors consists of surgical extirpation in the setting of a majority of benign tumors. Most lesions are low-grade or benign with the greatest challenge resting with defining a surgical plane between normal cord and tumor.

A number of technological advances have played a role in decreasing surgical morbidity over the past decade. The operating microscope in conjunction with intraoperative electrophysiological monitoring as well as the CO_2 or Yag laser, real-time ultrasound and ultrasonic aspiration have all contributed significantly to improve the outcome of these operations. Astrocytomas are often low grade lesions, yet their failure to manifest a clear tumor/cord plane often makes a complete excision impossible to perform,

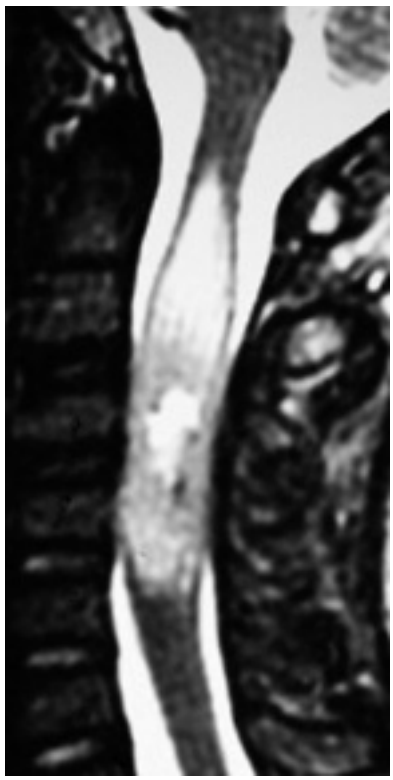

Fig. 14.10 Spinal astrocytoma. Sagittal T2-weighted image of the cervical spine reveals cord expansion and diffuse T2 hyperintensity extending from C2 through C5 levels.

and commonly results in recurrent disease. Benign ependymomas often present with a discernable tissue plane simplifying a possible total removal, whereas more aggressive ependymomas will have a less defined tumor interface and subsequently more often incomplete resection. Other cord lesions, in particular, extramedullary lesions such as inclusion cysts (dermoid, epidermoid) and neurofibromas may be removed in their entirety, with the exception of the congenital lipoma. Postoperative courses may be complicated by neurological deficits (new and/or increased) in addition to infection, CSF leak and kyphoscoliosis. Patients with significant neurological compromise prior to the start of surgery are at considerable risk for increased deficits after surgery. Individuals with extensive laminectomies for tumor removal will be at risk of developing progressive kyphoscoliosis over time.

Outcomes are generally excellent for benign or low-grade lesions. Benign lesions undergoing total excision fare the best with low-grade astrocytomas often enjoying long-term, progression-free survival without adjuvant therapy. Subtotal resection of high-grade lesions such as malignant ependymomas as well as glioblastoma, is followed by radiation therapy as an adjunct therapy. Although patients (especially those less than 5 years of age) are at risk for developing radiation myelitis as well as secondary malignancies at a later date, they are felt to benefit from radiotherapy. Chemotherapeutic approaches have become more commonly employed with variable success to date. Additional protocols are currently in evolution and may benefit from greater molecular understanding of these tumors.

Common long-term sequelae of tumor/treatment

As has been noted in the various general and specific sections in this chapter, childhood brain tumors and their treatment are associated with significant long-term sequelae (Table 14.7). The etiology of the sequelae are often multiple and include factors such as the size of the tumors and its location, the degree of spread of tumor at the time of diagnosis, the presence and degree of hydrocephalus at diagnosis, surgical complications, and short- and long-term effects of radiotherapy and chemotherapy.

Residual neurologic and neurosensory abnormalities have been poorly characterized. In a recent study of over 1800 long-term survivors of childhood brain tumors, it was noted that a significant proportion of patients had permanent focal neurologic deficits including residual hemiparesis and cerebellar deficits (Packer *et al.* 2003). In addition, children with both infratentorial and supratentorial lesions had seizures. Psychological difficulties were common, as were difficulties re-entering into society and holding jobs and having families.

Much of the focus of long-term sequelae research has been centered on the potential detrimental affects of radiotherapy. Radiotherapy tends to induce transient acute neurologic difficulties due to tumor-related swelling, however, the most common difficulties encountered are late effects.

TABLE 14.7

Common Long-term Sequelae of Tumor/Treatment

Neurocognitive dysfunction
- May be related to tumor, hydrocephalus, postoperative complications, delayed effect (progressive) of cranial radiation

Endocrinologic dysfunction
- May be related to hypothalamic/pituitary tumor, late effect of suprasellar/whole brain radiotherapy

Hearing loss
- May be related to cerebellopontine tumors/resection, long-term effect of radiotherapy, cisplatinum use

Secondary tumors
- May be secondary to radiotherapy,? chemotherapy, genetic predisposition

Psychologic/behavioral dysfunction
- May be secondary to tumor (? Cortical, frontal), sequelae of treatment

KEY CLINICAL QUESTIONS

- Prior to initiation of therapy, clinical information which must be addressed for children with medulloblastoma includes:
  - Extent of disease at the time of diagnosis as assessed by neuroimaging of the entire neuroaxis and cerebrospinal fluid cytological examination;
  - Degree of surgical resection, as assessed by postoperative neuroimaging;
  - Other important factors may include the histopathologic appearance of the tumor and specific molecular genetic tumor characteristics
- The key clinical questions in the surgical management of brainstem gliomas include:
  - Is surgery required for diagnosis?
  - Does surgical intervention improve the likelihood of long-term survival?
- Key clinical questions which must be addressed before treatment of childhood visual pathway gliomas include:
  - What part of the visual pathway is involved?
  - Does the child have neurofibromatosis type I?
  - Is there evidence for clear-cut tumor progression at time of diagnosis?
  - What would be the potential detrimental effects of treatment?
- Prior to initiation of therapy of a presumed germ cell tumor, critical questions which must be addressed include:
  - Is surgery necessary for diagnosis, or can diagnosis be made on cerebrospinal fluid markers?
  - Will surgery improve outcome?
  - Is the tumor a pure germinoma or does it have mixed elements?
  - Is chemotherapy indicated to limit the dose and volume of radiotherapy?

CONSIDER CONSULTATION WHEN...

- The triad of morning headaches, vomiting, and lethargy requires referral to a pediatric neurologist or pediatric neurosurgeon and neuroimaging.
- Consider consultation with a neuroradiologist when a brain tumor is believed likely, to determine the optimum imaging that should be undertaken, including the potential utility of MR spectroscopy and functional MRI.
- Early in the course of treatment a pediatric oncologist should be involved to determine the potential benefit of adjuvant chemotherapy.

These delayed sequelae include neurocognitive deficits and endocrinologic sequelae. Whole brain radiotherapy and extensive cortical radiotherapy have been shown to result in overall declines in intelligence, primarily in younger children (especially those younger than 7), and result in significant, albeit more subtle deficits in learning, in older children (Radcliffe *et al.* 1992). The detrimental effects on cognition of more focal radiotherapy, especially radiotherapy given to the posterior fossa, is less clear.

Radiotherapy to the suprasellar region and whole brain radiotherapy has been related to a host of endocrinologic sequelae, most commonly growth hormone deficiency and thyroid deficiency. The impact of growth hormone deficiency is often exacerbated by poor vertebral growth secondary to spinal radiation therapy, required for tumors with a proclivity to disseminate the nervous system. Growth hormonal replacement therapy has been shown to be relatively safe and partially ameliorates growth retardation. Other endocrinologic sequelae also may occur and the issue of gonadal deficiency and fertility is a complex and understudied complication.

Secondary tumors, including primary central nervous system tumors and systemic cancers, are a devastating late occurrence in children with brain tumors. Its exact incidence is not known, but it may occur in as high as 1–2% of long-term survivors. Once again, etiology of this complication is multifactorial and probably relates to genetic predisposition as well as the long-term effects of both radiotherapy and chemotherapy. Primary central nervous tumors which occur most frequently following successful treatment of a brain tumor include high-grade gliomas, which, to date, have been extremely resistant to any form of subsequent therapy, and meningiomas.

Chemotherapy has been employed in an attempt to improve survival and to delay, if not obviate, the need for radiotherapy, but chemotherapy also may result in significant long-term sequelae. Because of the additive neurotoxicity of methotrexate, this drug has not been recently utilized in most chemotherapeutic regimens for children with brain tumors, but is now being reintroduced in some protocols. Methotrexate may result in significant neurologic impairment, including leukoencephalopathy, myelopathy, and if given intrathecally, significant spinal cord dysfunction and radiculopathy. Cis-platinum, which is an active agent in childhood primitive tumors, especially medulloblastoma, often results in significant hearing loss, which may be additive to the effects of radiotherapy delivered to the cochlear region. Vincristine, another commonly used chemotherapeutic agent, often results in some degree of peripheral neuropathy, which may be permanent if this complication is not appreciated early in treatment. The wider use of high-dose chemotherapy carries with it other risks and the use of intensive drug regimens supported by bone marrow transplant or peripheral stem cell rescue may result in significant permanent neurologic difficulties including seizures. Some chemotherapeutic agents, as stated previously, also may increase the risk of mutagenesis.

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CHAPTER 15

Neuromuscular Disease in Children

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OUTLINE

Neuromuscular disorders presenting at birth
Neuromuscular disorders presenting in the infant/toddler
Evaluation of the preadolescent with neuromuscular disease
Appendix

The traditional approach to the topic of neuromuscular disease is to highlight constituents of the lower motor unit and discuss pathological processes that affect particular components, i.e. anterior horn cells, peripheral nerve, neuromuscular junction and muscle. Although this has proven to be a useful pedagogical strategy, it is not economical, practically or intellectually when dealing with children with neuromuscular disorders. An alternative approach is to take advantage of the fact that certain diseases present stereotypically in terms of the clinical features and the age at which they become manifest. Unlike adults, where the age of onset of symptoms may be of little help in suggesting their etiology, the age of presentation and incidence of particular disease entities in this age group can be used to structure a differential diagnosis appropriate to the age of the child.

Neuromuscular disorders presenting at birth

Clinical features

1 Hypotonia at rest
2 No improvement in muscle tone with stimulation
3 Weakness of appendicular muscles
   - diminished grasp (palmar and plantar)
   - inability to raise limbs against gravity (or resistance)
4 Weakness of axial muscles
   - inability to raise head to neutral in Landau posture
   - diaphragmatic breathing
   - respiratory compromise
5 Weakness of facial and bulbar muscles
   - facial diplegia
   - ptosis
   - external ophthalmoplegia
   - swallowing difficulty
   - tongue fasciculation
6 Diminished or absent reflexes

Associated clinical features

- Long, narrow facial features
- Tented upper lip
- High arched palate
- Polyhydramnios
- Arthrogryposis

Associated laboratory features

- Elevated creatine phosphokinase
- Abnormal nerve conduction velocity/electromyography test result
- Bell-shaped thorax on x-ray

Most common neuromuscular disorders presenting at birth

1 Congenital myotonic dystrophy
2 Congenital myopathy
3 Brachial plexopathy
4 Mononeuropathy
5 Neonatal myasthenia gravis
6 Motor neuron disease (usually not spinal muscular atrophy)

Congenital myopathies

Congenital myotonic dystrophy (MD) is probably the single most common neuromuscular disorder presenting at birth. Children with congenital myotonic dystrophy are almost exclusively born to mothers with myotonic dystrophy. Because of the marked variability in gene penetrance, the mother may be unaware of her disorder and her diagnosis may be the byproduct from investigating the cause for weakness in her infant. As is obvious from the above, myotonic dystrophy is a dominantly inherited disorder in which about half of infants of mothers with MD are symptomatic at birth with gradual improvement in the severity of weakness with maturation. The genetic substrate for the disease is an expansion of a CTG repeat sequence within the

3 prime untranslated portion of the DM protein kinase gene (DMPK) on chromosome 19. In normal individuals the CTG repeat may range from 5 to 37 repeats. Individuals affected with MD show greater that 50 repeats and up to 2000. The greater the number of repeats, the earlier and more severe the clinical presentation. The CTG sequence is unstable and with succeeding generations undergoes progressive expansion providing the molecular explanation for the clinical phenomenon of genetic anticipation, or the observation that offspring of affected individuals frequently have an earlier presentation and more severe disease.

Other congenital myopathies may present with a similar clinical picture. These disorders are typically classified by their histopathological features on muscle biopsy. There are a host of myopathic disorders presenting in infancy, some of which have specific and unique gene defects while others are genetically heterogeneous. These disorders are classified on the basis of abnormalities of myofibrillar structure on histochemical studies and on electron microscopy. Some congenital myopathies are identified based on abnormal inclusions such as nemaline or rod-body myopathy or fingerprint body myopathy, while others have myofibrillar abnormalities like central core disease or mini-core disease. Myotubular myopathy, also known as centronuclear myopathy, is characterized by myofibers which are similar to developing muscle in early gestation in which myofibers have a tubular appearance with centrally located nuclei.

The prognosis in these disorders is highly variable as there are, in many cases, multiple genotypes with similar phenotypical expressions. Many severely affected children at birth, even those requiring mechanical ventilatory support, may improve over time and survive into adulthood. Although scientifically unsatisfying, an augury of the prognosis may be observed over the first few months. Those infants who improve will, in general continue to do so. Those who deteriorate progressively worsen, and those with a static course have an indeterminate prognosis, however, the outcome is more likely to be unfavorable.

Congenital muscular dystrophy

The primary distinction between congenital myopathies and congenital muscular dystrophies (CMD) is based on the presence of myofibrillar necrosis and regeneration, along with endomysial fibrosis and deposition of fat on histopathological examination of muscle biopsy in the dystrophic disorders. In addition to weakness and hyporerflexia (usually areflexia) these children may have elevated creatine phosphokinase measurements of several times the upper limit of normal, but not in the range of Duchenne's muscular dystrophy which may reach levels of 50 000 U/L just after birth. Most of these disorders are inherited in an autosomal recessive fashion. The initial step in classifying these diseases is based on the presence or absence of merosin (alpha-2 chain of laminin 2) on immunocytochemical studies of muscle biopsies or Western blots. Absence of the protein can be a primary or secondary phenomenon. Congenital muscular dystrophies, therefore, are described as those which are merosin-deficient or are merosin-positive, the latter of which accounts for about half of CMDs. Some of the CMDs are associated with central nervous system abnormalities including structural abnormalities on MRI and mental retardation. In Japan, the Fukayama type of CMD is the most common form. This disorder is inherited in

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Congenital Myopathies

- Several somatic features are common to congenital myopathies of diverse etiologies. Hypomotility of the extremities *in utero* may result in arthrogryposis multiplex congenita. Although lower extremities typically are more involved, it is rare in the face of hip, knee and ankle joint involvement not to find restricted range of motion at elbow and shoulder joints.
- In a similar vein, bulbar weakness with diminished swallowing *in utero* results in polyhydramnios. During embryogenesis, the palate develops from a narrow and highly arched configuration. The upward pressure from the tongue during the process of swallowing during gestation flattens the palate resulting in horizontal expansion of the midface and transverse orientation of the lips.
- Infants with centronuclear myopathy, like other congenital myopathies, may present with arthrogryposis multiplex congenita. By virtue of the multiple joint contractures, one assumes that joint movement must have been markedly limited during early gestation. Although joint range of motion is restricted, muscle strength may be, paradoxically, only mildly diminished. Centronuclear or myotubular myopathy derives its name from the similarity in appearance of the muscle histology at term in these infants to a much earlier stage in muscle development. Early in gestation, myocytes are multinucleate tubular structures with centrally located nuclei. The metabolic differentiation of myofibers into different fiber types is also rudimentary at that stage. With maturation myofibers expand in caliber with peripheral migration of myonuclei and metabolic differentiation into a normal distribution of types I and II myofibers. Histochemical examination of muscle biopsies from infants with centronuclear myopathy confirms an immature appearance of myofibers with normal biochemical fiber type differentiation. These observations have engendered the hypothesis that centronuclear myopathy, in part, represents a process of delayed myofibrillar maturation with profound weakness early in embryogenesis resulting in restricted joint movement and contracture formation. Muscle strength is thought to improve later in gestation in some infants resulting in only minimal weakness at term.

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Congenital Muscular Dystrophy

- The clinical course in congenital muscular dystrophies is heterogeneous. Some children eventually walk while others grow progressively weaker and die from respiratory failure. Measures of serum creatine phosphokinase levels and pathological features on routine histochemical studies of muscle biopsy specimens are of limited value in discussing prognosis with families.
- As a rule, merosin positive CMDs are more likely to have normal cognitive development, normal cerebral MRI studies and overall a less severe course.
- Severe cognitive impairment along with abnormalities in brain imaging studies is commonly associated with both primary and secondary merosin deficiency.

a recessive mode with a defect in the gene which codes for the protein fukutin. Diminished expression of laminin alpha2 is thought to be a secondary phenomenon in this disorder. The DNA coding for fukatin occupies a 100 kb genomic sequence consisting of 10 exons and 9 introns localized to 9q31. There is typically moderate to severe mental retardation with variable structural brain abnormalities including pachygyria/microgyria, and high signal intensity changes in white matter on T2 MRI sequences. Other examples of congenital muscular dystrophy associated with central nervous system and other somatic abnormalities include Walker–Warburg syndrome and muscle-eye-brain disease.

Congenital myasthenic syndromes

Congenital myasthenia gravis may result in transient weakness in the newborn. This syndrome occurs in infants of mothers with active autoimmune myasthenia. Maternal IgG directed against epitopes associated with the postsynaptic acetyl choline receptor is passively transferred across the placenta in late gestation resulting in receptor blockade with concomitant transient bulbar and somatic weakness. In a poorly controlled myasthenic mother who produces antibodies which cross-react with the fetal AChR, transplacental diffusion of the IgG may result in diminished fetal movement resulting in arthrogryposis. As AChRs mature, they are no longer primarily targeted by the antibody. Other congenital myasthenic syndromes may also present in the newborn period. These are typically inherited disorders with either autosomal dominant or recessive modes of transmission. The electrochemical defect can be presynaptic, postsynaptic or at the end-plate itself. A primary acetylcholine receptor deficiency accounts for most of the nonautoimmune congenital myasthenic syndromes.

Focal nerve injuries

Peripheral nerve injuries are reasonably common including intrauterine, intrapartum and post partum events occurring in the nursery Although the incidence of this collective category is not known, the most frequently encountered of these is brachial plexus injury which has been variously estimated to occur in between 0.4 and 2.3 per 1000 live births. Although most of these injuries are associated with macrosomic infants and often attributed to traction injury during delivery, there are reports of infants with brachial plexopathy after Cesarean section or atraumatic vaginal delivery. Thus, injury during delivery should not be assumed to be the cause of neonatal brachial plexopathy in all cases. The prognosis for recovery in these infants, particularly those with partial plexus involvement involving more proximal myotomes, is usually favorable. Compression neuropathies, especially involving radial and peroneal nerves can be present at delivery, probably related to intrauterine position. Premature infants requiring mechanical ventilation, who have limited tissue mass to protect superficial nerve segments, because of diminished muscle tone, and reduced spontaneous voluntary movement, are vulnerable to postnatal compression nerve palsies.

Disorders of motor neurons

Disorders affecting motor neurons may present in the newborn period. Interestingly, it is rare for spinal muscular atrophy to be diagnosed in the neonatal nursery. For the most part, anterior horn cell diseases which are symptomatic at birth are related to hypoplasia of spinal motor neurons, or to intrauterine injury. Occasionally there is a history of maternal viral-like illness during gestation, however, causality can only be assumed and generally these disorders are considered to be of undetermined etiology. There may be associated arthrogryposis. This group of disorders tends to be nonprogressive and affected infants may demonstrate improvement in motor function over time.

Rational evaluation of the newborn with suspected neuromuscular disease

The essential question which must be addressed by the neurologist in the newborn intensive care unit is whether the infant has central hypotonia or neuromuscular disease. The findings of weakness and areflexia are probably the two most definitive discriminators between the two categories. Although encephalopathy and seizures point to a central cause, a congenital neuromuscular disease does not indemnify the infant against perinatal hypoxia/ischemia. Microcephaly and other congenital anomalies push the clinician to think along the lines of a global disorder affecting the ontogeny of multiple organ systems with cerebral dysgenesis the likely cause for hypotonia. The bedside clinical examination may be sufficient to make the distinction. Ancillary laboratory studies can be useful screening tools. Assuming that perfusion/oxygenation is normal and that the infant is not septic or suffering from

another systemic illness, the following screening tests may be helpful:

- Metabolic screening including blood gas, serum electrolytes, blood ammonia and urine organic acid analysis. These studies will identify most inborn errors of metabolism which are symptomatic in the perinatal period.
- Brain imaging if hypotonia is thought to be on a central basis. Consider performing an EEG to assess physiological maturity/activity.
- Nerve conduction studies and electromyography are extremely helpful in confirming that hypotonia and weakness are due to a neuromuscular disorder and to identify the nature of the disease, i.e. peripheral neuropathy, anterior horn cell disease, etc. The results of the electrophysiological evaluation will direct the subsequent evaluation and biopsy site if appropriate.
- If the nerve conduction studies are normal but electromyography demonstrates widespread denervation, causes of motor neuron disease should be explored. A blood test to evaluate possible mutations in the survival motor neuron gene will detect the majority of cases of spinal muscular atrophy (Werdnig–Hoffman disease) in this age group.
- If the study suggests a myopathic process, careful examination of the parents, especially the mother is essential. Myotonic dystrophy is the commonest inherited neuromuscular disease in the population and often is not recognized in affected adults. Congenital myotonic dystrophy is the single most common specific congenital myopathy in newborns. It occurs in roughly half of offspring from women with myotonic dystrophy. Therefore, clinical examination of the mother will often be consistent with the diagnosis of myotonic dystrophy. The diagnosis can be confirmed with genetic testing.
- If the parents are normal, a muscle biopsy is often the next step in evaluating a patient with congenital myopathy. A caveat which must be confronted, and explained to family members, is that many disorders classified under the broad category of congenital myopathy have nonspecific morphological changes on muscle biopsy, in which case, the biopsy may not lead to more specific understanding of the disorder.

Neuromuscular disorders presenting in the infant/toddler

Typically, in this age group medical attention is sought because of failure to attain motor developmental milestones. Once again, the evaluation requires making a distinction between central hypotonia and neuromuscular disease. Fortunately, this task becomes less difficult as children grow older. It is useful to inquire of the parents, "When the child is very angry or upset, does he display improved muscle strength?" This phenomenon is quite typical of children with central hypotonia. It is often necessary to examine the child when they are very annoyed to confirm the parents' observation.

Clinical features

1. Failure to achieve motor milestones
2. Hypotonia
3. Weakness – generalized or of selected muscle groups
   - Appendicular muscles
     - Difficulty reaching for and grasping objects
     - Inability to bear weight on lower extremities
   - Axial muscles
     - Immature Landau posture
     - Inability to sit up
     - Poor head control
     - Diaphragmatic breathing
     - Respiratory compromise
   - Bulbar muscles
     - Facial weakness
     - Impaired suck/swallow
     - Nasal regurgitation
     - Ptosis
     - External ophthalmoparesis
     - Tongue fasciculations
4. Diminished or absent tendon reflexes

Rational evaluation of the infant/toddler with neuromuscular disease

The clinical picture is usually clearer in this age group than in the newborn where the potential explanation for the child's illness is often multifactorial. There are two typical scenarios when evaluating children in this age group. The first is that of delayed or completely stagnant motor development dating back to birth. The second is that of normal early development with the subacute evolution of neuromuscular symptoms. It is useful to make the distinction between these two presentations to focus the evaluation.

Group I: chronic delay, no clear onset of weakness

The symptoms in this group may be relatively static or indolently progressive, often it is difficult to be certain. Assuming that cognitive development is normal:

- Nerve conduction velocity tests and electromyography are reliable screens for neuromuscular disorders with this type of presentation and will identify the nature of the disorder and direct subsequent workup.
- Spinal muscular atrophy is probably the most common single entity which shows up in this context. The nerve conduction velocity tests and electromyography should localize the disease process to the anterior horn cell. Genetic screening for a mutation in the SMN loci should con-

firm the diagnosis in over 95% of children and obviate the need for biopsy.
- Screening for creatine phosphokinase and aldolase will help to identify myopathic disorders with defective cytoskeletal proteins (dystrophin, sarcoglycan, merosin, etc.) or other disorders with significant myonecrosis (inflammatory myopathies). With the exception of dystrophinopathies, a biopsy will be required for diagnosis, as is also true of other congenital muscle diseases.
- Demyelinating/hypomyelinating neuropathies can present in this age group. Some of those, which are genetically determined, may be may be identified with DNA analysis for associated gene mutations. When these studies are unrevealing, nerve biopsy may be required to more accurately characterize the nature of the disorder.

Common neuromuscular disorders presenting in the infant/toddler: Group I

1 Spinal muscular atrophy
2 Congenital myopathies
3 Congenital muscular dystrophy
4 Genetically determined neuropathy

Spinal muscular atrophies

Spinal muscular atrophy (SMA) types I and II also known as Werdnig–Hoffman disease, are typically diagnosed postnatally when a failure to attain motor milestones is recognized by parents and physicians. Clinical findings are generalized hypotonia, weakness of axial and appendicular muscles with relative sparing of facial and bulbar muscles (early on) and areflexia. Electrodiagnostic testing will document normal sensory nerve conduction with widespread denervation on electromyography. The numerical classification of the SMAs, types I through III (type III is traditionally termed Kugelberg–Welander disease), is based on age of onset of symptoms which can often be difficult to precisely ascertain. A more straight forward nosologic schema is: I – never able to sit independently, II – able to accomplish independent sitting but never walk, and III – achieve the ability to stand and walk. The first of these phenotypes has a high incidence of mortality by 2 years of age.

The disease is caused by a homozygous deletion involving exons 7 and 8 in the survival motor neuron gene (SMN1) and modified by the expression of a second duplicate homologous gene (SMN2). Both are located on chromosome 5q and closely linked, with SMN1 located on the telomeric side of the duplication. Children with severe early onset SMA have typical deletions in SMN1 genes with only one or two residual copies of the SMN2 genes. Those with milder phenotypes have the SMN1 deletions but also possess three of more copies of SMN2. Deletion of both SMN1 and SMN2 genes is probably a lethal permutation since this genotype has not been described in affected humans. Clinical genetics laboratories utilize a polymerase chain reaction methodology to amplify exons 7 and 8 from the SMN genes to analyze the integrity of the SMN1 gene. Quantifying the abundance of copies of the SMN2 gene is usually not readily available, and of little clinical utility at this juncture.

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Spinal Muscular Atrophy

- The spinal muscular atrophies, particularly in children with onset under 1 year of age, are often associated with a defect in omega fatty acid oxidation. During periods of metabolic stress or fasting, which often occur with intercurrent infection, dicarboxyllic aciduria may be present as a manifestation of the metabolic defect. In this setting the child's weakness may precipitously worsen.
- Children admitted because of clinical deterioration with evidence of metabolic decompensation and increasing weakness will often benefit from infusions of high levels of glucose. This approach can help to mitigate the effects of systemic stress, normalize metabolic defects and increase strength. Even modest increases in respiratory muscle strength may be very helpful in the face of impending, or frank respiratory failure.

Chronic symmetrical peripheral neuropathies

Most of the peripheral neuropathies presenting early in life are associated with slowing of sensory and motor nerve conduction velocities and absent or diminished amplitude of sensory nerve action potentials and compound motor action potentials. They are incorporated under the rubric of demyelinating neuropathies, often, more accurately, hypomyelinating neuropathies since there is rarely evidence of formation of normal myelin sheaths on large caliber axons. Congenital hypomyelinating neuropathy may be evident at birth, however, more commonly, it is diagnosed at a later date. Since respiratory muscles and bulbar muscles are usually spared, at least in infancy, in these disorders, normal feeding and respiratory patterns reinforce the perception of normal infant behavior. When examined, these children are typically hypotonic with generalized weakness and absent reflexes. Motor nerve conduction velocities are diminished and may be as slow as 2 m/sec. There is only limited correlation between the magnitude of conduction velocity slowing and the severity of the clinical syndrome. In one series, it was reported that the presence of arthrogryposis multiplex congenita and the absence of onion bulb formations within the endoneurium were histopathological markers associated with a poor prognosis. This category of peripheral neuropathy has been referred to as Dejerine–Sottas syndrome. The term brings with it little specificity since the diagnosis includes children with substantial variability in terms of both genotype and phenotype. In fact, the limita-

tions in nosology closely reflect the reality of the situation; homologous gene defects result in different phenotypes and diverse gene mutations produce similar clinical presentations (see the discussion of hereditary motor and sensory neuropathies below).

Group II: normal early development, subacute onset of symptoms

These children have a history of normal perinatal events and early acquisition of motor skills with a clearly identifiable time of onset of disability. In my experience, the majority of children in this group have disorders of neuromuscular transmission. These children present with bulbar symptoms along with axial and appendicular weakness. In young infants (1–5 months of age) the etiology is usually infant botulism. In older infants/toddlers (12–24 months of age) the cause is often myasthenia gravis. Other acquired, immune-mediated disorders can present in this age although are more common in older children. Metabolic disorders, mitochondrial cytopathies in particular, may present with loss of motor skills, often acutely and related to intercurrent infection.

- Electrodiagnostic testing is highly reliable in confirming the diagnosis of infant botulism long before tests for the organism or toxin are available.
- Confirming a postsynaptic defect in neuromuscular transmission in this age group can be difficult. When a myasthenic syndrome is suspected, a trial of Mestinon may help to clarify the diagnosis.
- Metabolic screening for lactic acidosis, especially during an acute episode along with analysis of urine organic acids and serum amino acids may identify those children with disorders of oxidative phosphorylation. MRI spectroscopy can noninvasively document elevation in intracerebral lactate in children with phenotypical features suggesting a disorder of oxidative phosphorylation. A number of mitochondrial cytopathies can be confirmed by identification of mutations in the mitochondrial genome from DNA extracted from white cells in peripheral blood, without requiring a muscle biopsy. Full sequencing of the mitochondrial genome is most reliable using DNA derived from muscle.

Common neuromuscular disorders in the infant/toddler: Group II

1 Infant botulism
2 Myasthenia gravis
3 Metabolic myopathies
4 Inflammatory myopathies

Infant botulism

This disease results when botulinum spores are ingested, germinate in the gastrointestinal tract and slowly elaborate botulinum toxin which is absorbed and disseminated through systemic circulation, ultimately interrupting neuromuscular transmission. The toxin binds at a presynaptic site on the neuronal membrane at which time it is accessible to antibody directed against epitopes of the toxin. The toxin then traverses the neurolemma, probably by endocytotic mechanisms, and enters the cytoplasm where it binds to acetylcholine release sites and prevents synaptic release of acetylcholine vesicles. Once the toxin is internalized, it is inaccessible to circulating antibody and irreversibly blocks acetylcholine release. The latter steps in this process, internalization of the toxin and blockade of vesicle release, are both temperature and activity dependent. One would, therefore, predict that those neuromuscular junctions, which are warmer and more active, would be the earliest to be affected. In fact, among the earliest manifestations of infant botulism are constipation, external ophthalmoparesis, and feeding difficulty. The clinical severity of the disorder in these infants typically progresses after initial presentation, usually over a relatively short period of time. Many of these patients will require mechanical ventilatory support. Autonomic dysfunction may accompany weakness, especially in the more severely affected infants.

The disease can be caused by several *Clostridium botulinum* species, types A through G which are subclassified based on the characteristics of the elaborated toxin. The vast majority of cases of infant botulism are caused by types A and B. The spores of *C. botulinum* are essentially ubiquitously distributed and typically present in soil. The often-described exposure to honey is over-emphasized and colonization from honey containing spores accounts for essentially an infinitesimal fraction of cases. Types A and B *C. botulinum* have a geographically distinct distribution with type A predominantly found in states from the Rocky Mountains and west while type B is located in regions east of the mountain range. Diagnosis of the disease can be based on typical clinical findings in the context of the subacute evolution of symptoms in a previously healthy infant including the external ophthalmoparesis, bulbar dysfunction, generalized weakness and, most commonly, areflexia. A firm diagnosis can also be based on the electrophysiological characteristics from nerve conduction studies and electromyography. The nature and presynaptic localization of neuromuscular blockade in these infants results in a reproducible constellation of findings. Sensory nerve conduction studies are normal while motor nerve conduction velocities are normal usually with diminished compound motor action potential (CMAP) amplitudes. The hallmark features of electrodiagnostic testing are the presence of a decremental response in the CMAP amplitude with low frequency repetitive motor nerve stimulation (2–3 Hz) and a marked increment with higher rates of stimulation (10–50 Hz). Electromyography reveals mixed features including widespread fibrillation potentials due to chemical denervation of myofibers along

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Infant Botulism

- The time course and severity of infant botulism caused by type A toxin tends to be shorter and less severe that type B.
- A hallmark feature in Eastern, or type B, infant botulism is the presence of internal and external ophthalmoparesis. Observers in Rocky Mountain states and West describe this phenomenon in a minority of cases related to the type A toxin.
- Some authors have suggested that the typical (virtually diagnostic) electrophysiological findings on repetitive motor nerve stimulation in infants with botulism are often absent or inconclusive. This may be related to the nature and number of muscles tested. Ideally, repetitive stimulation should be performed on a muscle in which the compound motor action potential amplitude is only mildly to moderately diminished. One may be unable to demonstrate a meaningful increment or decrement in a severely affected muscle in which the majority of neuromuscular junctions are inactivated.

with abundant small amplitude, short duration, myopathic appearing motor unit potentials also called brief, short duration action potentials (BSAPs) because of fragmentation of motor units. This latter finding is related to the electrochemical inexcitability of myofibers scattered within the motor unit resulting in motor unit potentials with reduced amplitude and a polyphasic morphology.

Despite the severity of the clinical syndrome, with adequate supportive care, the vast majority of these infants recover fully. The mechanism of recovery from the disease is probably multifactorial. The first step is likely recognition of the toxin by the immune system and elaboration of an antibody response to the toxin. During, and in some cases, after recovery, toxin can still be recovered from the gastrointestinal tract. If there is sufficient binding and internalization of toxin at a particular neuromuscular junction, transmission at that junction is permanently blocked with subsequent degeneration of that nerve terminal. Neuromuscular transmission to that myofiber is reestablished by sprouting of a new axon from the distal nerve fiber and the generation of a new neuromuscular junction. The pace of recovery can be enhanced by administration of an antibody directed toward botulinum toxin which has recently become commercially available.

Myasthenia gravis

Myasthenia gravis is an autoimmune disorder which is characterized by a deficiency of acetylcholine receptors on postsynaptic nerve terminals at neuromuscular junctions. The salient clinical manifestation of this disorder is weakness. The most common expression of myasthenia gravis (MG) is ptosis with variable involvement of other muscles. Conventionally, MG has been said to comprise three clinical syndromes: ocular, bulbar, and generalized myasthenia. Pure ocular MG accounts for about 15–25% of autoimmune myasthenia in children depending on the age group and ethnic background. It is often the herald symptom, antedating the appearance of weakness in other muscle groups. Among those children who present with symptoms of ocular MG, roughly 75% will progress to involve bulbar muscles or develop generalized MG. Ptosis with variable degrees of external ophthalmoparesis can develop at any age, including children and adults and evolve to include nearly any combination of striate muscles. Most children who present with ocular symptoms which later generalize do so within the first year. The symptoms typically wax and wane over time and may be exacerbated by intercurrent infection which up-regulates activity of the immune system. There is also, typically, fluctuation in the severity of symptoms in proportion to the degree of exertion, hence the frequently heard complaint that ptosis and other weakness increases during the course of the day. Myasthenia gravis may take a heavy toll from the patient's psychological well-being, especially in older age groups. This is engendered because of the marked fluctuations in strength and function in some myasthenic patients. The patient may exhibit normal, or nearly so, functional abilities at one point, and within a short period of time become progressively weaker to the point of requiring mechanical ventilatory support.

As stated above, MG is an immune-mediated disorder with predominantly IgG class of antibodies directed toward various epitopes of the postsynaptic acetylcholine receptor (AChR). These antibodies are detectable in 50–75% of children with generalized MG (seropositive) and cannot be identified in the balance of (seronegative) children with MG. Although the pathogenesis of the disease is thought to be mediated predominantly via anti-AChR antibodies, there is evidence that suggests cellular immune mechanisms also play a role in orchestrating the elimination of postsynaptic receptors. Roughly 25–50% of children, especially in younger age groups, will be found to be seronegative. It is difficult to quantitate precisely, but a proportion of these seronegative patients, influenced again by age and ethnic background, have pathogenic autoantibodies to muscle specific tyrosine kinase (MuSK). MuSK is localized on the sarcolemmal surface of the neuromuscular junction. This kinase participates in the agrin-induced clustering of AChRs on the postsynaptic nerve terminal during the ontogenesis of the neuromuscular junction. The role this molecule plays in the mature neuromuscular junction is not precisely understood. It is thought, however, that immune-mediated reduction in MuSK results in diminished numbers or inappropriate distribution of AChRs at the postsynaptic nerve terminal. Anti-AChR antibodies and anti-MuSK antibodies appear to be mutually exclusive in that these two antibody species do

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Myasthenia Gravis

- The first line of therapy in myasthenia gravis is usually pyridostigmine. It is most useful in patients with pure ocular involvement in whom immunosuppression may not be warranted. There is little data on which to base recommendations for an optimal therapeutic allgorhythm. Corticosteroids are almost always efficacious, however, side effects may become unacceptable when prolonged high dose treatment is necessary.
- Incorporation of both plasmapheresis and IVIg administration should be considered as steroid sparring strategies. The latter usually is accompanied by fewer logistical impediments, however, may have a longer latency between treatment initiation and therapeutic response.
- Cyclosporine A is a particularly useful adjunct therapeutic agent. Because toxicities are, for the most part, dose-dependent, the ability to monitor drug levels provides a mechanism to adjust dosage to achieve blood concentrations of the drug within the desired range, and to avoid toxic levels with anticipated side effects.
- There is a paucity of data regarding the long-term outcome in patients with myasthenia, especially children who have the highest potential for a protracted course. Thymectomy increases the likelihood of achieving remission in generalized myasthenia and appears to be most effective when performed within a year of the onset of symptoms.

not coexist in individual patients with myasthenia. The autoimmune-mediated attack directed at epitopes from either of these entities results in similar clinical manifestations.

Metabolic myopathies

The topic of metabolic disorders affecting muscle is a broad one which prohibits detailed elucidation in the context of this chapter. The topic will be addressed superficially and the condensed picture painted with broad brush strokes. The majority of metabolic myopathies can be classified into three broad categories: glycogen storage disorders, defects in fatty acid oxidation, and mitochondrial cytopathies. It is axiomatic that these metabolic disturbances often affect other organ systems and weakness may not be the predominant factor which precipitates seeking medical attention.

A common clinical theme with many of the glycogenoses is the presence of exercise intolerance and muscle cramps. Many of the disorders which present in this fashion may also be associated with episodic myoglobinuria. Four of the more well recognized glycogen storage disorders are myophosphorylase deficiency (glycogenosis type V or McArdle's disease), phosfructokinase deficiency (glycogenosis type VII or Tauri's disease), alpha-glycosidase deficiency (glycogenosis type II or Pompe's disease) and debrancher enzyme deficiency (glycogenosis type III or Forbes disease). The first two of these disorders may have similar clinical manifestations often presenting with exercise intolerance and muscle cramps as the herald symptoms. Either disease can present at almost any age, however, they are more likely to present in mid-childhood or later at a time when strenuous physical exertion is more likely to occur. Prolonged exercise may result in rhabdomyolysis and pigmenturia. In severe cases this can result in transient or permanent renal failure. In a similar vein, alpha-glucosidase deficiency and debrancher deficiency may present in children or adults, but both may cause hypotonia and weakness in infancy or early childhood. These later disorders are not typically associated with episodes of rhabdomyolysis. In addition to involvement of striate muscle, both of these diseases may involve other organ systems, with progressive encephalopathy in Pompe's disease and cardiomyopathy a prominent feature in both.

Carnitine polmitoyltransferase II (CPT II) deficiency is arguably the most often identified disorder of fatty acid oxidation. Like many enzyme deficiency diseases, it is genetically determined and has an autosomal recessive mode of inheritance. The salient clinical feature of the disorder is recurrent rhabdomyolysis. Unlike the glycogenoses, there is usually no exercise intolerance in CPT II deficiency. Affected individuals will generally not experience muscle pain or cramping during vigorous exertion. Rather, after an episode of prolonged exercise, they will develop muscle pain followed by pigmenturia. Often, similar bouts will occur spontaneously or in association with intercurrent infection. Between bouts of rhabdomyolysis, these individuals appear normal and very rarely develop weakness. The most important risk from CPT II deficiency is renal failure induced by myoglobinuria. For unclear reasons, the frequency and severity of episodes of rhabdomyolysis seem to improve with maturation.

Another well recognized category of fatty oxidation disorders are the various species of acyl-CoA dehydrogenase or deficiency or CAD. The acyl-CoA dehydrogenases participate in the process of mitochondrial B-oxidation and are specific for the length of the associated fatty acid, short chain (4 carbon), medium chain (8 carbon), and long chain (up to 18 carbon) acyl-CoA dehydrogenase. Again, at the risk of over-simplification, children with these disorders most commonly present with an acute encephalopathy, nonketotic hypoglycemia and features suggestive of Reye's syndrome. These episodes may be associated with rhabdomyolysis, however, this is usually a less dramatic feature of the diseases. The episodes are often precipitated by prolonged fasting. This often occurs in the setting of intercurrent infection. Over time, slowly progressive weakness may evolve, particularly in SCAD and LCAD. There are many other enzymatic defects which result in impaired fatty acid oxidation which are beyond the scope of the current discussion.

In recent years there has been increasing recognition and understanding of disorders of oxidative phosphorylation or mitochondrial cytopathies. This group of disorders is multifaceted in molecular etiology and protean in clinical manifestations. The prototypical mitochondrial disorder is the Kearns–Sayre syndrome. The clinical characteristics of this disorder include: short stature, external ophthalmoparesis, myopathy, pigmentary retinopathy and cardiac conduction defects. When followed over the long term, the majority of these patients will develop cardiomyopathy, progressive encephalopathy and blindness. Like many of the classic, phenotypically characterized, mitochondrial disorders such as MERRF (myopathy encephalopathy and ragged-red fibers), MELAS (myopathy encephalopathy lactic acidosis and stroke-like episodes) or Leigh's syndrome, Kearns-Sayre syndrome is inherited via the maternal transmission of the defective mitochondrial gene. In addition to the clinical features enumerated above, mitochondrial cytopathies almost always ultimately demonstrate multiorgan involvement which may include ataxia, deafness, anemia, liver or kidney failure, gastrointestinal hypomotility, autonomic failure and peripheral neuropathy.

There may be considerable variability in the severity of the expression of homologous gene defects in members of the same kinship. The variable phenotypical manifestations of the disease in different individuals and different organ systems is thought to be attributable to at least two independent factors. The first is determined by the basal metabolic requirements of particular cell and tissue types. Those organ systems with the highest energy substrate requirements are likely to be preferentially susceptible to injury due to defective production of high-energy phosphate intermediates. Inheritance of mitochondrial DNA occurs through the maternal lineage in which the gene may be heterogeneous for mutations, with each cell containing both mutated and normal mitochondrial DNA within the cell cytoplasm. This results, during the earliest phases of embryonal development, in primordial stem cells with variable ratios of abnormal to normal mitochondria. This heterogeneous group of embryonic cells is segregated into progenitor cell lines, which develop into tissues with variable burdens of dysfunctional mitochondria. These factors result in a mismatch between the level of basal energy substrate requirements in a particular tissue and the ability of that tissue to generate the required amount of energy. Hence, different thresholds for energy failure among different organ systems and individual patients.

Only a minority of mitochondrial disorders are maternally inherited due to mutations of the mitochondrial genome. The majority of these diseases are related to mutations of nuclear encoded genes or their processing. A prototypical disease in this category is Friedreich's ataxia. Friedreich's ataxia is inherited in a recessive mode due to an expanded GAA repeat sequence on chromosome 9q resulting in defective expression of the protein frataxin. This protein is thought to regulate iron content within mitochondria with diminished amounts of frataxin resulting in increased iron concentrations within mitochondria resulting in diminished thresholds for oxidative stress, and consequent cell injury. Analogous to other mitochondrial diseases, Friedreich's ataxia exhibits multiorgan involvement with cardiac muscle, motor neurons and subpopulations of sensory neurons within dorsal root ganglia being preferentially affected.

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Metabolic Myopathy

- The symptoms of exercise intolerance, myalgias and episodic rhabdomyolysis are shared by all three categories of metabolic defects described above. An optimal sequence of diagnostic investigations is difficult to codify. Measurement of serum lactate, pyruvate and quantitative amino acids along with determination of quantitative organic acid concentrations in urine are effective screening tools.
- Some children will require skin biopsy and isolation of cultured fibroblasts for studies of lipid metabolism. In selected patients, muscle biopsy may be necessary for enzyme determination, oxidative phosphorylation studies, mitochondrial DNA analysis, routine histochemistry and ultrastructural studies of muscle.
- Careful electrodiagnostic studies may help to identify those children in whom mitochondrial disease is more likely. Evidence of what may be clinically inapparent peripheral neuropathy on nerve conduction studies is often present in mitochondrial cytopathies, often with features of demyelination. Mild myopathic characteristics seen in proximal muscles in these patients may be obscured by changes due to denervation in distal muscles. This combination (peripheral neuropathy with mild myopathic changes in proximal muscles) is typical of mitochondrial disorders but may be overlooked unless specifically sought for.

Evaluation of the preadolescent with neuromuscular disease

The chief complaint by the parents and family members with the onset of neuromuscular disease in this age group (roughly 3–10 years of age) is commonly clumsiness or loss of balance. In children with myopathic processes, this perception is due to the inability of the child to right themselves when their center of gravity is displaced from its point of equilibrium due to weakness of proximal hip girdle muscles. In peripheral neuropathies, the weakness of foot dorsiflexors results in "tripping" when the child encounters trivial environmental obstacles. In both cases the family will complain that the child is falling down. Generally, by the time these

phenomena are apparent, muscle weakness is quite evident on examination. A more subtle manifestation is loss of endurance. A careful history will often reveal that inability to keep up with peers and diminished endurance antedated the onset of falling down. In cases of very mild weakness, early fatigueability may be the only historical feature and examination may be normal or nearly so. In patients with peripheral neuropathies, in addition to a history of weakness or foot drop, it is necessary to inquire about "weak ankles," high arches and hammer toes in family members in order to confirm the hereditary nature of the disease. The most common chronic neuromuscular disorders to present in this age group are genetically determined: Duchenne's and Becker's muscular dystrophies and Charcot–Marie–Tooth disease or the hereditary sensory-motor neuropathies.

Clinical features

1 Loss of motor skills, apparent loss of balance
2 Decreased endurance
3 Weakness – generalized or of selected muscle groups
   - Appendicular muscles
     - Diminished grasp
     - Gower's maneuver
     - Foot drop
   - Axial muscles
     - Inability to do a sit-up
     - Poor head control
   - Bulbar muscles
     - Facial weakness
     - Nasal regurgitation
     - Ptosis
     - External ophthalmoparesis
     - Tongue fasciculations
4 Diminished or absent tendon reflexes

Associated clinical features

- Exaggerated lumbar lordosis
- Muscle pseudohypertrophy
- Pes cavus deformities
- Hammer toes
- Cutaneous nodules
- Toe walking
- Muscle wasting
- Pes planus deformities
- Heliotrope malar rash

Common neuromuscular disorders presenting in the preadolescent period

1 Duchenne's/Becker's muscular dystrophy
2 Hereditary sensory and motor neuropathies
3 Myasthenia gravis
4 Inflammatory myopathies
5 Guillain–Barré syndrome
6 Chronic inflammatory demyelinating neuropathy

Duchenne's/Becker's muscular dystrophy

These disorders are probably the commonest, and also most clinically stereotypical, among diseases affecting males in this age group. The Duchenne's variety generally presents early in the first decade of life while the Becker phenotype may not become clinically evident until late adolescence. These boys exhibit proximal weakness and muscle pseudohypertrophy and most will have a mutation in the dystrophin gene. Dystrophin itself is a cytoskeletal protein which, among others, is critical in stabilizing the link between the intracellular contractile apparatus, the sarcolemmal membrane, and the extracellular matrix. In the absence of the protein, the sarcolemmal membrane is fragile and susceptible to fenestration during myofibrillar contraction and relaxation. Defects in the sarcolemma result in permeability to extracellular ions and subsequent accumulation of intracellular calcium which initiates several pathways which ultimately result in cell death.

Although the clinical features of the disorder are quite stereotypical, several laboratory studies can reinforce the diagnostic impression. A markedly elevated level of creatine phosphokinase in serum is often on the order of fifteen to twenty five thousand units in boys between 2 and 5 years of age. The findings on electrodiagnostic testing are often nonspecific and indicative of a myopathic process. DNA analysis from peripheral blood samples can be diagnostic with a deletion at Xp21 which can be demonstrated in about two-thirds of these boys with traditional DNA screening. In the absence of an identifiable deletion, full length screening of the coding sequences of the dystrophin gene is now available and will define a mutation in an additional segment of the boys in whom there is no detectable deletion. A small but significant group of boys with presumed dystrophin mutations are not identified by DNA analyses and will require muscle biopsy for confirmation of the diagnosis. As noted above, a serum creatine phosphokinase which is elevated 50 to 100-fold is nearly pathognomic for dystrophinopathy in this age group although other defects in cytoskeletal proteins can mimic dystrophin deficient muscular dystrophy (e.g. sarcoglycan deficiency or **S**evere **C**hildhood **A**utosomal **R**ecessive **M**uscular **D**ystrophy: SCARMD) along with other limb-girdle muscular dystrophies which are most often inherited in an autosomal recessive fashion and, therefore may affect either sex. Patients with Kugelberg-Welander disease or SMA type III may occasionally exhibit 5 to 10-fold elevations in creatine phosphokinase with the expected proximal weakness along with hypertrophic calves. Electrodiagnostic testing will confirm the neurogenic nature of their illness.

As noted above, DNA analysis is a readily available tool and will identify a mutation in the majority of boys with Duchenne's/Becker's muscular dystrophies. The accuracy

Muscular Dystrophy

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- Conventional wisdom is that children with Duchenne's type muscular dystrophy present at between 3 and 5 years of age with a complaint of weakness. In fact, parents often notice symptoms at a much earlier stage and may have brought their concerns to the child's pediatrician but were reassured that all was well.
- Parents frequently state the reason for bringing their child with muscular dystrophy for evaluation is clumsiness or impaired balance.
- Pseudohypertrophy in DMD is not restricted to calves, but may also involve proximal leg, and shoulder girdle muscles.
- Although not established in controlled trials, patients with Becker's muscular dystrophy may respond well to treatment with corticosteroids often at a low dose (<0.5 mg/kg/day).

with which the molecular geneticist can predict the disease phenotype (Becker's or Duchenne's) varies considerably from lab to lab and in the nature of the mutation. When there is no family history to suggest the likely rate of progression of the myopathy, a muscle sample for immunocytochemical staining or Western blot analysis of the dystrophin protein will distinguish between the Duchenne's and Becker's variants.

Inflammatory myopathy

Inflammatory myopathies, although relatively rare in childhood, when they occur, are commonly seen in this age group. These disorders are conventionally divided into three broad categories: infectious myositis, autoimmune polymyositis and dermatomyositis. There are a host of viruses with myotrophic properties which can produce focal or generalized muscle inflammation and injury. A not unusual scenario is a child in the mid-first decade of life who, rather acutely, complains of calf pain and is reluctant or unable to walk. In general there will be tenderness to palpation in affected muscles. Serum creatine phosphokinase and muscle transaminases may be elevated. These symptoms usually resolve over several days and further evaluation is rarely necessary.

Autoimmune inflammatory myopathies, for the most part, fall into the category of polymyositis or dermatomyositis. There are rare myopathies associated with other connective tissue disorders, systemic vasculitities or paraneoplastic syndromes. These will not be addressed in this chapter. Although many authors have written that polymyositis is exceedingly rare in childhood and that dermatomyositis is much more common, this has not been my experience. Many children present with complaints of fatigue or weakness with or without muscle swelling or tenderness and absent cutaneous abnormalities. Electrodiagnostic testing will confirm a myopathic disorder, frequently without "irritable" features typically associated with muscle inflammation. The serum creatine phosphokinase level may be mildly or massively elevated with variable elevations in the erythrocyte sedimentation rate and other satellite markers for inflammation or other autoimmune disorders. Magnetic resonance imaging of muscle may demonstrate multifocal areas of increased signal intensity on T2 spin echo sequences. The findings on MRI may provide some guidance for choosing a biopsy site. Muscle biopsy may be normal because of the multifocal nature of inflammation. When an active area of inflammation is sampled, typical features include myofibrillar degeneration and regeneration with primary endomysial inflammation and occasionally perivascular collections of inflammatory cells, without evidence of vasonecrosis.

Dermatomyositis is one of few disorders in clinical neurology where the nosology accurately reflects the pathology of the disease. Children with this disease may present with muscle pain and weakness or with a painful rash as their primary complaint. The classic syndrome features a malar rash, Gottron's papules over extensor surfaces of the fingers, elbows and knees, and subungual flame hemorrhages. As in polymyositis there may be serological evidence of muscle injury and systemic inflammation. Testing in the electrophysiology laboratory may be similar to polymyositis as well and muscle MRI may demonstrate evidence of multifocal myoedema. Dermatomyositis is a vasculitic myopathy so that in addition to the biopsy features seen in polymyositis, there is evidence of frank vasonecrosis indicative of active vasculitis. A hallmark histopathological feature of dermatomyositis is perifascicular myofibrillar atrophy. This is due to the distribution of endomysial blood flow with areas of ischemia most commonly affecting the periphery of the fascicle.

Unlike the situation in adults, where dermatomyositis is commonly a paraneoplastic disease often associated with small cell carcinoma of the lung, neoplasia is almost never a feature of the disease in children. Therapy in both disorders consists of immunosuppression. Again, corticosteroids are probably the first line therapeutic agents. IVIg and methotrexate can be quite helpful in avoiding or reducing chronic steroid side effects.

Hereditary motor and sensory neuropathy

The peroneal muscular atrophy syndrome was originally described in 1886 by Howard Henry Tooth, an English medical student. Later that year, a more detailed description of the disorder was published by the French neurologists Charcot and his pupil Marie. The clinical features of the disease are progressive loss of strength in a fiber length dependent distribution and, usually to a lesser degree, diminished sensation predominantly involving those modalities related to large caliber myelinated axons. Myotactic reflexes are diminished or absent at early stages of the disease.

The initial subclassification of these disorders, for most of the 20th century referred to as Charcot–Marie–Tooth disease, resulted from work by Dyck and Lambert. Electrophysiological testing permitted distinction between kinships with autosomal dominantly inherited neuropathies based on motor nerve conduction velocities in the forearm. Patients with nerve conduction velocity below 40 m/sec were classified as having the demyelinating form of the disease (type I), while those with motor conduction velocity of greater than 40 m/sec were classified as the axonal form (type II). This classification schema was validated by histopathological features on sural nerve biopsies wherein the predominant pathological features were either of axons showing evidence of demyelination and remyelination or features of axonal degeneration and regeneration. Genetic analysis is available to confirm the diagnosis in many HMSN subtypes. The initial mutations identified in autosomal dominantly inherited demyelinating neuropathies were in genes encoding peripheral myelin protein 22 (PMP22) and myelin protein 0 (MPZ). Mutations in the Connexin 32 gene (Cx32) were shown to be responsible for an X-linked pattern of inherited demyelinating neuropathy. Since then numerous genes have been identified to be associated with both axonal and demyelinating subtypes of hereditary sensory motor neuropathy (HMSN). Many authors now argue that a third, intermediate type of HMSN should be added to the nosology. In the last few years enormous strides have been made in identifying genes and specific mutations within those genes responsible for various HMSN categories. In all honesty, the accelerated pace of growth in this field has rendered the literature nearly too voluminous to follow and review articles shortly obsolete.

As noted above, the patterns of inheritance are variable and kinships with autosomal dominant, recessive and sex-linked modes of transmission are reported. There also appear to be instances of spontaneous mutation, although this phenomenon is probably quite rare. To make matters more difficult, mutations in the same gene in different kinships can result in divergent phenotypes with features of either axonal or demyelinating neuropathy. This phenomenon is most likely related to the effect of specific individual mutations at different sites within the gene resulting in altered protein products with differing pathological effects on the functional integrity of schwann cell – axonal relationships.

Hereditary Motor and Sensory Neuropathy

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- The demyelinating forms of HMSN have, in the past, been referred to as hypertrophic demyelinating neuropathies because of nerve enlargement due to endoneurial schwann cell proliferation and collagen deposition. This is manifested by peripheral nerve enlargement which permits distinction between HMSN I and HMSN II phenotypes at the bedside based on the presence of palpably enlarged peripheral nerves.
- Peripheral nerve enlargement can be appreciated in the ulnar nerve at the elbow or the peroneal nerve at the fibular head. After extension and rotation of the head, enlargement of the posterior auricular nerve can be seen and palpated over the posterior-lateral neck.
- When pursuing a family history of genetically determined neuropathy, it is often necessary to inquire about symptoms and signs in family members rather than asking whether peripheral neuropathy is present in the kinship. Useful examples are pes cavus and hammer toes in the family, frequent ankle sprains in childhood and adolescence or inability to roller or ice skate.

Guillain–Barré syndrome

In nations which have in place widespread immunization programs, Guillain–Barré syndrome (GBS) is the single commonest cause of acute flaccid paralysis in children and adults. The incidence of the disease has been variously estimated to be between 0.5 and 1.5/million in children less than 18 years of age. In most series there is male predominance with a male:female ratio of approximately 1.2:1. A typical patient might describe ascending weakness beginning in the legs and advancing to involve the arms associated with moderate to severe back and leg pain. The accepted diagnostic criteria are purely clinical consisting of the subacute or acute onset of progressive weakness involving more than one extremity along with diminished or absent stretch reflexes. Laboratory investigations can serve to reinforce the accuracy of the diagnosis including the presence of albumino-cytologic dissociation on spinal fluid examination and electrodiagnostic findings indicative of a multifocal, acquired, demyelinating neuropathy.

Roughly two-thirds of GBS patients will identify an antecedent event in the 30–60 days prior to the onset of symptoms. These events are diverse in character and dissociate in nature ranging from infections, immunizations, trauma, surgery, parturition to animal exposures and insect bites. When a query regarding the list of antecedent events is narrowed, upper respiratory infection is the most commonly identified. In a series which used serological studies to confirm recent viral infection, cytomegalovirus was the only infection which occurred in patients with GBS more often than controls. Over the past few years it has come to be appreciated that campylobacter enteritis may be the commonest antecedent infection which instigates an immune response resulting in GBS. This is particularly true in developing countries and in areas where the water supply may be contaminated.

The clinical course of GBS conforms to a triphasic model. There is an initial progressive phase which includes the in-

terval from the first appearance of symptoms until the point of maximal clinical severity. This is followed by a plateau phase which lasts until the beginning of recovery. Finally, there is a recovery phase which is typically considerably more prolonged than the progressive phase. Review of several series describing the natural history of GBS in both adults and children reveals remarkable consistency with the mean duration of the progressive and plateau phases each lasting approximately 10–11 days. The recovery phases were much more variable among the different series.

The clinical severity at the nadir of the disease in children hospitalized for GBS was also fairly consistent. Approximately 25% of patients retained the ability to ambulate 5 m without assistance. Roughly 20% of children could ambulate 5 m with assistance or a walker. Forty per cent of children were bed or wheelchair bound with the balance requiring mechanical ventilatory support. The prognosis for recovery is, in general, excellent. A large series from western Europe with consistent follow-up reported that after 6 months all children were ambulatory and, at worst, had minimal functional deficits. In tertiary care centers with sophisticated life support facilities, where most of the more severely affected patients are treated, the mortality in childhood GBS is virtually zero.

The pathobiology of GBS remains incompletely understood and a comprehensive discussion of this topic is outside the scope of this chapter. It is reasonable to conceptualize the pathogenesis as reflecting a series of discrete processes which ultimately orchestrate an immune-mediated attack on the peripheral nervous system. Whether identifiable or not, there must be an event which initiated an autoimmune process. This then is followed by breakdown of immune tolerance. The immune system then targets specific epitopes on schwann cells or axons, or both, within peripheral nerves. Specific immune components including immunoglobulin, T cells, macrophages and proinflammatory cytokines must traverse the blood:nerve barrier. This cascade of events ultimately results in a T cell and immunoglobulin orchestrated, macrophage mediated attack on endoneurial contents.

The specific endoneurial components which are targeted and injured in this autoimmune process determine the electrophysiological, histopathological, and clinical phenotype in the affected child. These criteria have been employed to subclassify GBS into several distinct syndromes. The most common manifestation of GBS in north America and western Europe is acute inflammatory demyelinating polyradiculoneuropathy (AIDP). This disorder accounts for more than 90% of cases of GBS in these regions. These children present with typical ascending paralysis with electrophysiological, and histopathological evidence of multifocal demyelination. A second, much less frequent GBS subtype is acute motor and sensory axonal neuropathy or AMSAN. In this syndrome the electrophysiology and histopathology are indicative of axonal degeneration rather than demyelination affecting both sensory and motor axonal populations. Fisher syndrome is a clinical diagnosis based on the triad of external ophthalmoplegia, ataxia and areflexia. Often children presenting with this clinical triad will develop evidence of more widespread involvement within the peripheral nervous system. This syndrome has been estimated to account for approximately 2% of cases of childhood GBS. A fascinating syndrome which is extremely rare in North America and Western Europe is acute motor axonal neuropathy (AMAN). Electrodiagnostic testing in this syndrome reveals normal motor and sensory nerve conduction velocities with preservation of sensory nerve action potential amplitudes. Histopathological studies have demonstrated sparing of sensory axons with axonal degeneration discretely limited to the motor axonal population.

When the predominant changes in peripheral neuropathy are axonal loss, nerve conduction velocities are typically within the normal range. There will be progressive decline in the action potential amplitudes in proportion to the severity of axonal loss. Although rare in the United States, this disorder may account for up to 40% of cases of GBS in China, South America and elsewhere. There is a significant correlation with campylobacter infection and the absence of water treatment facilities. In China, where the disorder has been best characterized, this is a disease of children from predominantly rural regions. Other GBS subsyndromes have been reported, however, their incidence is insignificant compared to those described above.

There is no scientific rationale on which to base a decision regarding optimal treatment of children with GBS. There are numerous case series in the literature, some employing historical controls, examining the efficacy of both plasmapheresis and human intravenous immunoglobulin (IVIg) in the treatment of children with GBS. Many of these series describe a more rapid recovery in children treated with either modality. There have been no randomized controlled trials of treatment for GBS in children. Data are available for several large randomized trials in adults with GBS using both plasmapheresis, IVIg and a combination. The eligibility criterion for most of these trials is loss of independent ambulation with one of the endpoints being the time to regain the ability to walk 5 m unaided. Both treatments appear to reduce the time to recover independent walking by about 30–35%. These treatments have also been compared and have been found to be equivalent in reducing morbidity in GBS. The individual treatments of plasmapheresis and IVIg have also been compared to a combination of both and each of the three arms of this randomized controlled trial showed equivalent paces of recovery. Several trials have documented an increased incidence of adverse events in the plasmapheresis treated cohorts compared to the patients treated with IVIg. Extrapolating from the experience in adults, it would seem reasonable to choose a therapy based on logistical issues and the adverse event profiles in adult trials. Based on these con-

Guillain–Barré syndrome

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- Guillain–Barré syndrome can occur in any age group including neonates. Passively transferred antibodies have even produced the disorder *in utero* with clinical findings evident at birth.
- Pain is often the presenting complaint and in children, may obscure weakness in the early stages of the disease. These painful symptoms are commonly attributed to arthralgia and the neurologist may be the second or third specialist consulted, after orthopedics and rheumatology.
- Pain is a component of the morbidity in GBS in the majority of cases. In children with severe disease, those requiring mechanical ventilation in particular, it is nearly ubiquitous and is, in some cases, excruciating. Pain should be treated aggressively and the clinician should not hesitate to incorporate narcotic analgesics into the therapeutic armamentarium.
- It is likely that in GBS the majority of peripheral nerve injury occurs at the outset, within the first few days of symptoms. Unless underlying CIDP is suspected, repeat treatment episodes with plasmapheresis or IVIg are unlikely to alter the clinical course.
- GBS is a disease in which rehabilitation needs to begin in the intensive care unit. Early, proactive attention to potential contractures and other complications from prolonged immobility will enhance long-term outcomes.

siderations, many neurologists have opined that IVIg is the treatment of choice in pediatric GBS. This opinion is based more on belief than on scientific method. By contrast, in a large multinational survey in western Europe, the authors reported that those children with the most severe clinical manifestations of GBS were substantially more likely to be treated with plasmapheresis than IVIg. This may reflect a subliminal bias in favor of plasmapheresis in the most severe cases. Clearly, neither position would withstand objective scrutiny. Resolution of these issues will require carefully controlled clinical trials.

Chronic inflammatory demyelinating neuropathy

Chronic inflammatory demyelinating neuropathy (CIDP) is to neurology as lupus is to internal medicine. The disorder is reasonably easily identified when it presents acutely mimicking GBS followed by sequential relapses or the symptoms of the disorder evolve subacutely in the context of a previously well child. In some cases, however, the onset is indolent with slow progression. In this setting CIDP can mimic virtually any inherited neuropathy and should always be kept in mind in a child with neuropathy when no other evidence of disease can be confirmed in the kinship. Because many of the inherited neuropathies are transmitted in a dominant mode, careful family history, and when practical, examination of available family members may establish a presumptive genetic cause for the neuropathy. On occasion, electrodiagnostic testing will distinguish hereditary from acquired neuropathies, however, asymmetrical slowing of nerve conduction velocities, conduction block and other features suggestive of an acquired demyelinating neuropathy may not be evident. To additionally muddy the waters, electrodiagnostic features may be indicative of an axonal neuropathy. DNA analysis for common mutations associated with hereditary neuropathies may clarify the issue if a mutation is detected which appears consonant with the clinical picture. In the absence of a detectible mutation, however, it may be necessary to perform a nerve biopsy or undertake a trial of an immunosuppressant in order to sort these issues out.

Several immunosupressant agents have been shown to be effective in the treatment of CIDP. The choice of an optimal treatment in this disorder is personal and idiosyncratic. Corticosteroids are often a first line therapy because they are relatively inexpensive and because the majority of children with CIDP initially respond well to this treatment. If there is an inadequate response or if cumulative side effects occur because of an ongoing high dosage requirement, additional steroid sparing strategies can be employed. Plasmapheresis, IVIg, cyclosporine, azathioprine and cyclophosphamide all have been used with variable success.

Chronic Inflammatory Demyelinating Neuropathy

PEARLS & PERILS

- As alluded to above, clinical manifestations of CIDP may be protean. Any sensory-motor modality that relies on peripheral nerve for executive or reporter functions may be affected.
- Despite obvious sensory ataxia, careful examination may document little or no impairment of proprioception. Vibratory sensation, in this scenario, will commonly be more obviously diminished. Bulbar involvement, which is more frequent in AIDP, may be present in CIDP. Cranial neuropathies including optic nerve involvement with papilledema have been reported.
- Peripheral neuropathy associated with mitochondrial diseases can replicate the clinical, electrophysiological and histopathological characteristics of CIDP.

KEY CLINICAL QUESTIONS

- Is the infant's diminished spontaneous movement due to a neuromuscular disorder or a systemic disease?
- Is the hypotonia due to a central or peripheral process?
- Does hypotonia improve with stimulation?
- Are reflexes normal or diminished?
- Is motor development improving, static or worsening?
- Is the pattern of weakness predominantly proximal or distal?
- Is there evidence of associated sensory loss?
- Does weakness and sensory loss conform to a length dependent pattern of severity?
- Is diminished sensation predominantly related to dysfunction of myelinated, or unmyelinated axons?
- Is motor dysfunction due to weakness or pain?
- Is internal or external ophthalmoplegia present?
- Do symptoms fluctuate in the course of the day, during the week, over several months, or at all?
- Is ataxia sensory or cerebellar?

Appendix

Differential diagnosis of neuromuscular disease in the newborn

Anterior horn cell disease
- Intrauterine infection
- Hypoxic/ischemic injury
- Genetic disease – spinal muscular atrophy

Peripheral neuropathies
- Congenital hypomyelinating neuropathy
- Congenital axonal neuropathy
- Immune-mediated demyelinating neuropathy
  - Guillian–Barré syndrome/chronic inflammatory demyelinating neuropathy

Disorders of the neuromuscular junction
- Myasthenia gravis (passive transfer of maternal antibody)
- Congenital myasthenic syndromes
- Hypermagnesemia

Diseases affecting muscle
- Congenital myopathy
  - Congenital myotonic dystrophy
  - Congenital myopathies with specific cytoarchitectural characteristics
    - Myotubular myopathy
    - Centronuclear myopathy
    - Nemaline myopathy
    - Central core disease
    - Congenital fiber type disproportion
- Congenital muscular dystrophy
  - Dystrophin deficiency
  - Fukayama-type dystrophy
  - Dystrophin-associated glycoprotein deficiencies
- Inflammatory myopathy
  - With dystrophic cerebral white matter
  - Without central nervous system involvement

Differential diagnosis of neuromuscular diseases presenting in the infant/toddler

Anterior horn cell disorders
- Infection (polio, enteroviruses, rabies)
- Genetic (spinal muscular atrophies)

Peripheral neuropathies
- Genetically determined neuropathy
  - Hereditary sensory-motor neuropathies (HMSN types Ia, Ib, Ix,II)
- Guillain–Barré syndrome
- Chronic inflammatory demyelinating neuropathy

Disorders affecting the neuromuscular junction
- Myasthenia gravis
- Congenital myasthenic syndromes
- Infant botulism

Disorders affecting muscle
- Congenital myopathy
  - (Not myotonic dystrophy in infants)
- Congenital muscular dystrophy
- Inflammatory myopathy
- Metabolic disorders
  - Hypokalemia
  - Periodic paralysis
  - Metabolic myopathies
    - Pompe's disease
    - Phosfructokinase deficiency
    - Debrancher deficiency
    - Phosphoglycerokinase deficiency
    - Methylglutaconic aciduria
    - Acyl co-A-dehydrogenase deficiency (multiple variants)
    - Mitochondrial disorders

Differential diagnosis of neuromuscular disorders presenting in the preadolescent

Anterior horn cell disorders
- Infection (polio, enteroviruses, rabies)
- Genetic (spinal muscular atrophies)

Peripheral neuropathies
- Genetically determined neuropathies
  - (HMSN types Ia, Ib, Ix, II)
- Guillain–Barré Syndrome
- Chronic inflammatory demyelinating neuropathy

Disorders affecting neuromuscular transmission
- Myasthenia gravis
- Congenital myasthenic syndromes
- Botulism (food-borne or wound)

Disorders affecting muscle
- Duchenne's/Becker's muscular dystrophy
- **S**evere **C**hildhood **A**utosomal **R**ecessive **M**uscular **D**ystrophy and other limb-girdle muscular dystrophies
- Myotonic dystrophy
- Congenital myopathy
- Inflammatory myopathy
- Metabolic disorders
  - Hypokalemia
  - Periodic paralysis
  - Metabolic myopathies

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A substantial text devoted to pediatric neuromuscular disease. Currently, this is the definitive work in the field.

Engel AG: Myology, 3rd edn. New York, 2004, McGraw-Hill Co.

The two-volume text is a comprehensive reference source regarding muscle and disorders of that tissue. Its density suggests consumption in small bites lest the richness overwhelm.

Dyck PJ, Thomas PK: Peripheral neuropathy, 4th edn. Philadelphia, 2005, Saunders.

The 4th edition of this classic is expected to be published in 2005. Anticipating that this iteration conforms to the earlier editions, it is the definitive text regarding the neurobiology of peripheral nerve and peripheral neuropathies.

CHAPTER 16

Order and Disorders of Nervous System Development: Cellular and Molecular Mechanisms

OUTLINE

Overview
Classification
Overview of embryology
Disorders of neurulation
Disorders of prosencephalic development
Disorders of neuronal proliferation
Disorders of neuronal migration
Disorders of myelination and cortical organization
Disorders of vascular supply of brain tissue (known or postulated)
Conclusion

Many neurological conditions represent the consequences of altered nervous system development. These include epilepsy syndromes, attentional and cognitive deficits, autistic spectrum disorders, neurocutaneous syndromes, primitive neuroectodermal tumors (PNET), medulloblastomas and congenital malformations. Evidence indicates that psychiatric diseases, including schizophrenia and bipolar depression, are also secondary to abnormal brain development. Thus, knowledge of current principles of developmental neuroscience may provide insights into disease causation as well as a basis for therapeutic interventions. In Part I normal brain development is reviewed with a focus on cellular and molecular mechanisms. In Part II syndromes known or thought to result from disorders of nervous system development are discussed.

The symptoms of disorders of brain development will depend on which phase of brain development is disrupted and to what degree. In some disorders this occurs very early in fetal development, resulting in a devastating abnormality. In the case of some of the neurocutaneous disorders this may occur after birth, resulting in very mild symptoms or forme fruste that is not even detected until a family member presents with more severe manifestations. In spite of this wide range of presentations, all these conditions represent disorders of brain development, often genetically mediated, thus warrant being discussed as a group.

Order of Nervous System Development

Emanuel DiCicco-Bloom, MD

Overview

Nervous system development is generally conceived of as a sequence of processes including precursor proliferation and cell cycle withdrawal, cell migration, axon and dendrite formation, neurotransmitter system expression, axonal growth to targets, synapse elaboration, and selective neuron survival based on appropriate target innervation. While it is convenient to separate these events into discrete processes, many of them occur simultaneously within brain regions and even in the same cell. This is important to recognize, since it alters the conceptual models we construct regarding the possible effects of changing one process, and how it may alter several concurrent processes. For example, the presence of neurotransmitter receptors on very early precursors, those engaged in cell proliferation, allows neurotransmitters themselves, and therapeutic drugs we administer, to directly affect neuronal cell production during development. Thus, following a general overview of development, we examine several of these processes and describe the

important roles in development and disease pathogenesis of neural patterning genes, extracellular signals regulating neurogenesis, and molecular mechanisms of cell migration and process outgrowth.

In considering brain development, several principles serve to guide our understanding. First, different brain regions and neuron populations are generated at distinct times of development, and exhibit specific temporal schedules. Second, the sequence of cellular processes comprising ontogeny predicts that abnormalities in early events necessarily lead to differences in subsequent stages, though not all abnormalities may be accessible to our clinical tools. Third, it is clear that specific molecular signals, such as extracellular growth factors and cognate receptors, play roles at multiple developmental stages of the cell. Thus changes in expression or regulation of a ligand or its receptor, by environmental insults or genetic mechanisms, will have effects on multiple developmental and maturational processes.

The neural plate and neurulation

The nervous system in the human embryo first appears between 2½ and 4 weeks of gestation. During development, emergence of new cell types, including neurons, results from interactions between neighboring layers of cells. On gestational day 13, the embryo consists of a sheet of cells. Following gastrulation (day 14–15), which forms a two-cell layered embryo consisting of ectoderm and endoderm, the neural plate region of the ectoderm is delineated by the underlying mesoderm, which appears on day 16. The mesoderm forms by cells entering a midline cleft in the ectoderm called the primitive streak. After migration, the mesodermal layer lies between ectoderm and endoderm and induces overlying ectoderm to become neural plate. Induction usually involves release of soluble growth factors from one group of cells, which in turn bind receptors on neighboring cells, eliciting changes in nuclear transcription factors which control downstream gene expression. In some cases, cell-cell contact mediated mechanisms are involved. In the gene patterning section below, the important roles of soluble growth factors and transcription factor expression will be described.

The neural plate, whose induction is complete by 18 days, is a sheet of columnar epithelium, and is surrounded by ectodermal epithelium. After formation, the edges of the neural plate elevate, forming the neural ridges. Subsequently, changes in intracellular cytoskeleton and cell-extracellular matrix attachment cause the ridges to merge in the midline and fuse, a process termed neurulation, forming the neural tube, with a central cavity presaging the ventricular system. Fusion begins in the cervical region at the hindbrain level (medulla and pons) and continues rostrally and caudally. Neurulation occurs at 3–4 week of gestation in humans, and its failure results in anencephaly rostrally and spina bifida caudally. Neurulation defects are well known following exposure to retinoic acid in dermatological preparations, anticonvulsants, especially valproic acid, and diets deficient in folic acid.

Another product of neurulation is the neural crest, whose cells derive from the edges of the neural plate and dorsal neural tube. From this position, neural crest cells migrate dorso-laterally, under the skin to form melanocytes, and ventro-medially to form dorsal root sensory ganglia and sympathetic chains of the peripheral nervous system and ganglia of the enteric nervous system. Neural crest also gives rise to diverse tissues including neuroendocrine, cardiac, mesenchymal and skeletal systems, forming the basis of many congenital syndromes involving brain and other organs. The neural crest origin at the border of neural and epidermal ectoderm, and its generation of melanocytes, is the basis for aberrations in these cells resulting in neurocutaneous disorders, such as tuberous sclerosis and neurofibromatosis. Another non-neuronal structure of mesodermal origin formed during neurulation is the notochord found on the ventral side of the neural tube. The notochord plays a critical role during neural tube differentiation, since it is a signaling source of soluble growth factors, such as sonic hedgehog (Shh), which impact gene patterning and cell determination of the ventral spinal cord and hindbrain.

After closure, the neural tube expands differentially to form major morphological subdivisions that precede the major functional divisions of the brain. These subdivisions are important developmentally since different regions are generated according to specific schedules of proliferation and subsequent migration and differentiation. The neural tube can be described in three dimensions: longitudinal, circumferential, and radial. The longitudinal dimension reflects the rostrocaudal (anterior-posterior) organization, which most simply consists of brain and spinal cord. Organization in the circumferential dimension, tangential to the surface, represents two major axes: in the dorso-ventral axis cell groups are uniquely positioned from top to bottom. In the medial to lateral axis there is mirror image symmetry, consistent with overall right-left symmetry of the body. The radial dimension represents organization from the inner most cell layer adjacent to the ventricles to the outermost surface, and exhibits region-specific cell layering. At 4 weeks, the human brain is divided longitudinally into the prosencephalon (forebrain), mesencephalon (midbrain) and rhombencephalon (hindbrain). These three subdivisions or "vesicles" divide further into five divisions by 5 weeks, with the prosencephalon forming telencephalon (including cortex, hippocampus, and basal ganglia) and diencephalon (thalamus and hypothalamus), the mesencephalon (midbrain), and the rhombencephalon forming metencephalon (pons and cerebellum) and myelencephalon (medulla). Morphological transformation into five vesicles depends on region-specific proliferation of precursor cells adjacent

to the ventricles, the so-called ventricular zones (VZ). Proliferation intimately depends on soluble growth factors made by proliferating cells themselves or released from regional signaling centers. In turn, growth factor production and cognate receptor expression also depend on region-specific patterning genes. We now know that VZ precursors, which appear morphologically homogeneous, express a checkerboard array of molecular genetic determinants that control the generation of specific types of neurons in specific regions. While an individual gene may be expressed over an extensive range, such as the rostral cerebral cortex, a specific combination of partially overlapping genes may define a distinct domain, such as the medial aspect of the superior frontal cortex (see "Patterning genes" section below).

In the circumferential dimension, organization begins very early and extends over many rostro-caudal subdivisions. In spinal cord, the majority of tissue comprises the lateral plates, which later divide into dorsal or alar plates, comprised of sensory interneurons, and motor or basal plates, consisting of ventral motor neurons. Two other diminutive plates, termed the roof plate and floor plate, are virtually absent in maturity, however, play critical regulatory roles as growth factor signaling centers in the embryo. Indeed, the floor plate, in response to the growth factor, Shh, from the ventrally located notochord, produces its own Shh, which in turn induces neighboring cells in ventral spinal cord and brainstem to express region-specific transcription factors that specify cell phenotype and function. For example, in combination with other factors, floor plate Shh induces midbrain precursors to differentiate into dopamine-secreting neurons of the substantia nigra. Similarly, the roof plate secretes growth factors, such as bone morphogenetic proteins (BMPs), which induce dorsal neuron cell fate in spinal cord. In the absence of the roof plate, dorsal structures, such as cerebellum, and midline hippocampal structures, fail to form. In the radial dimension, the organization of layers is subdivision-specific, and is produced by differential proliferation of VZ precursors and selective patterns of neuronal cell migration.

The ventricular and subventricular proliferative zones

The distinct patterns of precursor proliferation and migration in different regions generate radial nervous system organization. In each longitudinal subdivision, control of neurogenesis matches production to the final size of a region. While it is well known that many cells produced during development undergo programmed cell death (up to 10–40%) regulated by genetic programs, initial cell generation roughly matches regional size requirements. This close relationship indicates that neurogenesis itself is controlled to generate the necessary complement of cells. This contrasts with traditional concepts suggesting excess cell production everywhere, with cell number regulation achieved primarily through selective cell death mediated by target-derived survival (trophic) factors. The patterning genes discussed below play major roles in directing regional precursor proliferation that is coordinated with final structural requirements. Consequently in diseases characterized by brain regions smaller than normal, such as schizophrenia, there may be a failure to generate neurons initially, as opposed to normal generation with subsequent cell loss.

The generation of specific cell types involves proliferation of undifferentiated precursor cells (or progenitors), followed by cessation of proliferation (exit from the cell cycle) and expression of specific phenotypic characters, such as neurofilaments and neurotransmitter systems. Precursor proliferation occurs primarily in two densely packed regions during development. The primary site is the VZ lining the walls of the entire ventricular system, which contributes to all brain regions in the rostrocaudal dimension. For select regions, however, including the cerebral cortex, hippocampus and cerebellar cortex, precursors from the VZ migrate out to secondary zones where they generate a more restricted range of cell types.

In the early embryo, neural tube VZ progenitors are arranged as a one-cell layer thick, pseudostratified neuroepithelium. The bipolar VZ precursors have cytoplasmic processes that span from the ventricular to the pial surface. During the cell cycle, the VZ appears multilayered, or stratified, because cell nuclei undergo movements, called interkinetic nuclear migration. The cell cycle, by which new cells are produced, comprises four stages: mitosis (M), when nuclei and cells divide, G1 when cells grow in size before dividing again, S phase, when cells synthesize DNA and replicate chromosomes, and G2, a brief growth period, followed by M phase. Precursor cell division (M phase) occurs at the ventricular margin, producing two new cells. The progeny then re-enter G1 as they move outwards within the VZ towards the pia. Under the influence of extracellular signals, these cells become committed to another round of division, marked by entry into S phase, which occurs near the upper VZ margin. After DNA replication, during G2, the nuclei move back down to the ventricular surface where they undergo mitosis and divide. The role of nuclear migration is not known, though it may allow nuclei access to environmental cues that effect subsequent proliferation and gene expression. Several human genetic mutations interfere with interkinetic nuclear movement and cell migration, producing heterotopic neurons and epilepsy syndromes as well as "smooth brain" or lissencephalies.

At the earliest stages, VZ cells divide to increase the pool of progenitors before producing postmitotic neurons. Then, during neurogenesis, with each cell cycle on average, a cell divides giving rise to both a postmitotic neuron and another dividing precursor. At the end of neurogenesis, precursor division gives rise to two postmitotic neurons only, greatly

increasing neuron production and depleting the precursor pool. The newly born neurons do not remain in the VZ, but instead migrate out to their final destinations, such as the cerebral cortical plate, traveling along the processes of radial glial cells (Fig. 16.1c). Like the bipolar VZ precursors described above, radial glia have one process associated with the ventricular surface and the other reaching the pial surface, a morphology consistent with the recent discovery that radial glia are, in fact, the dividing VZ precursors. The association between newborn neurons and the radial glial process allows cells generated within localized VZ domains, known to express distinct patterning genes, to migrate to specific cortical functional areas. In turn, this suggests that VZ precursors already have their phenotypic fate specified at the genetic level, prior to ceasing cell division and beginning migration. However, there is active debate about the relative roles of early expressed VZ genes versus the thalamic afferents that synapse on cortical neurons in determining neuronal cell fate and function. Unlike rodents, where neurons are generated prior to birth and glia are produced after, in the human brain neuron production largely occurs during the first 4 months of gestation. From 16 weeks to birth neurons undergo migration and glial precursors proliferate, migrate and produce myelin.

Supplementing this general plan of neurogenesis, there are distinct regions where other cells are produced in secondary proliferative zones. For example, in cerebral cortex and thalamus, the subventricular zone (SVZ) produces astroglial cells, though debate continues whether it also produces oligodendrocytes and neurons. In hippocampus, the hilus and later the subgranular zone produce dentate gyrus granule neurons, a lifelong process of neurogenesis. In newborn cerebellum, the overlying external germinal layer (EGL) generates granule neurons for several weeks in rodents and for 7–20 months in humans (a population of cells likely affected by medical treatments administered in the neonatal intensive care unit, such as reported negative neurodevelopmental effects of early postnatal steroids). In contrast to the VZ, secondary zone cells do not exhibit nuclear movements, suggesting distinct mechanisms of regulation. After neurogenesis is complete, the VZ differentiates into ciliated epithelial cells of the ependymal lining. Underlying the ependyma, undifferentiated cells of the SVZ, referred to as subependyma, have been identified as a neural stem cell population, capable of proliferating and generating neurons and glia throughout life. This represents a major change in the traditional model that mammalian neurogenesis, including human, is restricted to gestation.

Radial and tangential patterns of neurogenesis and migration

There are three well-recognized spatio-temporal patterns of neurogenesis which underlie regional brain formation. While extensive description is not warranted, several examples illustrate common principles concerning relationships of cell cycle exit (cell birthday) to final cell position, the roles of radial glia in migration, and the distinct capacities of secondary proliferative zones. There are two radial patterns of cell migration from the VZ, referred to as inside-to-outside and outside-to-inside. The third involves nonradial or tangential migration of cells, some of which originate in secondary proliferative zones. Experimentally, these patterns are defined by marking mitotic cells using nuclear incorporation of labeled DNA precursors, either tritiated (3H)-thymidine or bromodeoxyuridine (BrdU), to identify the last day a precursor is in S phase (its birthday), after which it exits the cell cycle, differentiates, and migrates to its final position.

The two radial patterns of neurogenesis reflect whether a structure is phylogenetically older, such as spinal cord, tectum and hippocampal dentate gyrus, or more recently evolved, like cerebral cortex. In more primitive structures, early generated cells are positioned on the outside, with later born cells residing inside, closer to the VZ. This pattern suggests that as more cells are generated, they passively move previously born cells further away. In the second pattern relevant to cerebral cortex, early born cells are located on the inside, with later born cells migrating past earlier ones to take up position outside. This inside-to-outside gradient requires a more complex mechanism, and cannot rely solely on passive cell movement. While radial glial cell function was initially considered uniquely associated with the inside-to-outside gradient, recent studies indicate that radial glia play roles in both. Additionally, the specific character of a region may be altered by nonradial inward migration of cells generated in other locations, relevant to GABA interneurons in cortex and hippocampus, or granule neurons in cerebellum, hippocampal dentate gyrus and olfactory bulb.

The cerebral cortex is the paradigmatic model of inside-to-outside neurogenesis. Derived from the embryonic forebrain telencephalic vesicles, the characteristic six cell layers represent a common cytoarchitectural and physiological basis for neocortical function. Within each layer, neurons exhibit related axodendritic morphologies, use common neurotransmitters and establish similar afferent and efferent connections. In general, pyramidal neurons in layer 3 establish synapses within and between cortical hemispheres whereas deeper layer 5/6 neurons project primarily to subcortical nuclei, including thalamus, brainstem and spinal cord. The majority of cortical neurons originate from the forebrain VZ. At earliest stages, the first postmitotic cells migrate outward from the VZ to establish a superficial layer termed the preplate. Two important cell types comprise the preplate, Cajal-Retzius cells which form outermost layer 1 or marginal zone, and subplate neurons, which lay beneath future layer 6. These distinct regions form when later born cortical plate neurons migrate within and divide the pre-

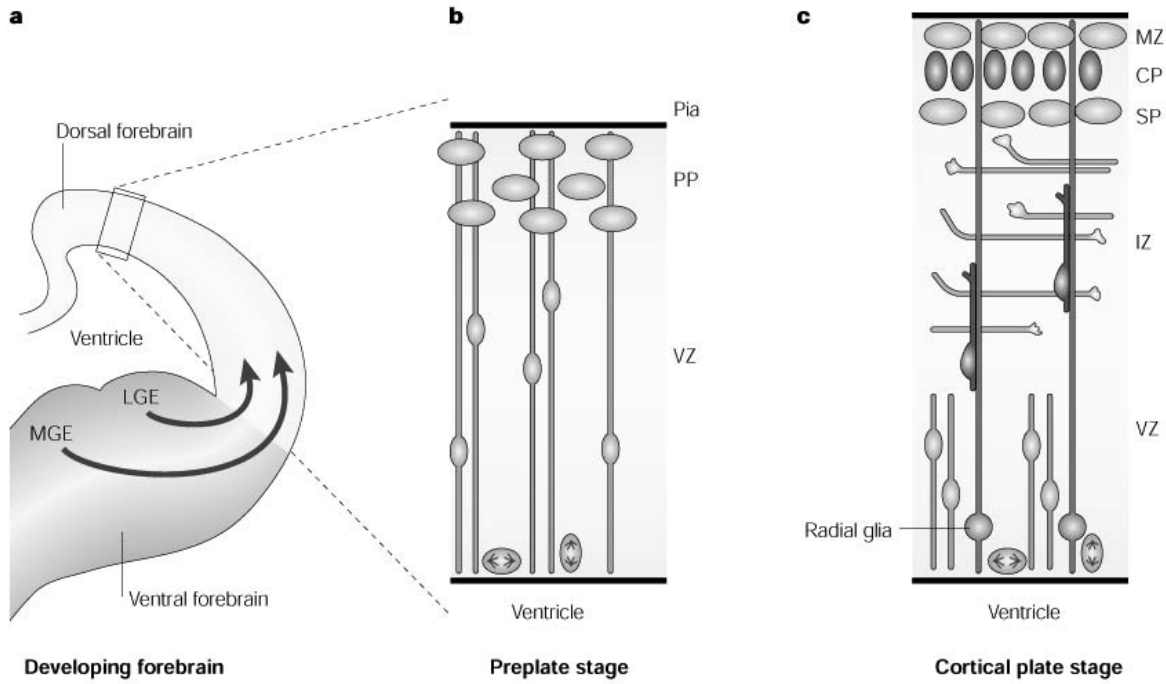

Fig. 16.1 Schematic drawing of radial and tangential migration during cerebral cortex development. (a) A coronal section of one half of the developing rat forebrain. The dorsal forebrain gives rise to the cerebral cortex. The medial and lateral ganglionic eminences (MGE and LGE) of the ventral forebrain generate neurons of the basal ganglia and the cortical interneurons. The arrows indicate the tangential migration route for GABA interneurons to the cortex. The boxed area (enlarged in b and c) shows the developing cortex at early and late stages. (b) In the dorsal forebrain, the first cohort of postmitotic neurons migrate out from the ventricular zone (VZ) and create a preplate below the pial surface. (c) Subsequent postmitotic neurons will migrate along radial glia through the intermediate zone (IZ) and take position in the middle of the preplate, creating a cortical plate (CP) between the outer marginal zone (MZ) and inner subplate (SP). Ultimately, the CP will be composed of six layers that are born sequentially, migrating in an inside-to-outside pattern. Horizontal processes in the IZ represent axon terminals of thalamic afferents. (From Nadarajah & Parnavelas 2002.)

plate in two (Fig. 16.1). Recent neuron tracing experiments in culture and *in vivo* have demonstrated that the neocortex, a dorsal forebrain derivative, is also populated by neurons generated in the ventral forebrain.

Recently, the embryonic preplate has taken on clinical significance. Cajal-Retzius cells produce the extracellular glycoprotein reelin, an important signal for neuronal migration. When reelin gene is genetically deleted in mice, cortical neuron migration is inverted. That is, the usual inside-to-outside gradient of cell generation and laminar position becomes inverted, yielding an outside-to-inside pattern. Thus early born neurons appear furthermost from the VZ, and latest born cells remain closest to the ventricles. Abnormal levels of reelin protein and mRNA have been found in several diseases, including bipolar depression and schizophrenia, and human reelin mutation is associated with lissencephaly (smooth brain), a gyral patterning malformation with loss of gyri and sulci, abnormalities in cerebellum, seizures and mental retardation. On the other hand, the subplate neurons, which persist only until early postnatal development in rodents, play a critical role as temporary targets for thalamic axon terminals on their way to cortex. After pyramidal neurons settle into correct layers in cortical plate, thalamic processes migrate further to reach layer 4 targets, and subplate neurons undergo programmed cell death.

After preplate formation, the cortical VZ generates in inside-to-outside fashion first layer 5/6 neurons, and then more superficial layers in temporal sequence. Thus the day on which a precursor exits the cell cycle in the VZ, its birthday, essentially predicts the kind and localization of the generated neuron. Currently, molecular mechanisms mediating this correlation are being defined, including specific stimulatory and inhibitory proliferative signals. Significantly, the cortical VZ is the primary source of excitatory pyramidal neurons that secrete glutamate.

Unlike the excitatory pyramidal neurons, the overwhelming majority of inhibitory GABA secreting interneurons originate from mitotic precursors of the ganglionic eminences which generate the neurons of the basal ganglia. Subsets of interneurons also secrete neuropeptides, such as NPY and

somatostatin, and express NO generating enzyme, NOS. Not associated with cortical VZ radial glia, these GABA interneurons reach the cortical plate by migrating tangentially, in either the superficial marginal zone or in a deep position above the VZ, the subplate region where thalamic afferents are also growing. Thus, cortical development represents convergence of two principal patterns of neurogenesis, radial and nonradial migration of neurons.

In contrast to the inside-to-outside neurogenesis observed in cortex, phylogenetically older regions, such as hypothalamus, spinal cord, and hippocampal dentate gyrus, exhibit the reverse order of cell generation. First formed postmitotic neurons lie superficially and last generated cells localize toward the center. While this outside-to-inside pattern might reflect passive cell displacement, radial glia and specific migration signaling molecules are clearly involved. Furthermore, cells do not always lie in direct extension from their locus of VZ generation. Rather, some groups of cells migrate to specific locations, as observed for neurons of the inferior olivary nuclei.

The hippocampus demonstrates both radial and nonradial patterns of neurogenesis. The pyramidal cell layer, Ammon's horn CA 1–3 neurons, is generated in a typical outside-to-inside fashion in the dorsomedial forebrain from 7 to 15 weeks of gestation, though migration patterns appear complex. However, the other major population, dentate gyrus granule neurons, start appearing at 18 weeks, and exhibit prolonged outside-to-inside postnatal neurogenesis, originating from several migrating secondary proliferative zones. In rat for instance, granule neurogenesis starts at E16 with proliferation in the dentate VZ of the forebrain. At E18, an aggregate of precursors migrates along a subpial route into the dentate gyrus, generating granule cells nearby the dentate. After birth, there is another migration, localizing proliferative precursors to the dentate hilus, which persists until 1 month of life. Thereafter, granule precursors move to a layer just under the dentate gyrus, termed the subgranular zone (SGZ), which produces neurons throughout life in adult rats, primates and humans. In rodents, SGZ precursors proliferate in response to cerebral ischemia, tissue injury and seizures, as well as growth factors, identifying potential sources for brain response to damage.

A different combination of radial and nonradial migration is observed in cerebellum, a brain region recently recognized to play important functions in nonmotor tasks. Except for granule cells, the other major neurons, including Purkinje and deep nuclei, originate from the primary VZ of the fourth ventricle, coincident with other brainstem neurons. In rat, this occurs at E13-E15 and in humans, 5–7 weeks gestation. The granule neurons, as well as basket and stellate interneurons, originate in the secondary proliferative zone, the external germinal layer (EGL), which covers newborn cerebellum at birth. EGL precursors originate in the fourth ventricle VZ, and migrate dorsally through the brainstem to reach this superficial position. The rat EGL proliferates for 3 weeks, generating more neurons than are present in any other structure, while in humans, EGL precursors exist for at least 7 weeks and up to 2 years. When an EGL precursor stops proliferating, the cell body sinks below the surface, grows bilateral processes which extend transversely in the molecular layer, and then the soma migrates further down into the internal granule layer, the IGL. Cells reach the IGL along specialized Bergmann glia, which serve guidance functions similar to the radial glia. However, in this case, cells originate from a secondary proliferative zone that generates neurons exclusively of the granule cell lineage, indicating a restricted neural fate. Clinically, this postnatal population of neurons causes cerebellar granule neurogenesis to be vulnerable to infectious and other insults of early childhood, and an unintended target of several therapeutic drugs, such as steroids, well known to inhibit cell proliferation.

Specific inductive signals and patterning genes in development

As discussed above, induction of the central nervous system begins at the neural plate stage when the notochord, underlying mesenchyme and surrounding epidermal ectoderm produce signaling molecules that affect the identity of neighboring cells. Specifically, the ectoderm produces bone morphogenetic proteins (BMPs) which promote and maintain epidermal differentiation. Another way of stating this is that neural differentiation is a default state, which occurs unless it is inhibited. In turn, neural induction proceeds when BMP action is blocked. BMP inhibiting proteins, such as noggin, follistatin, and chordin, are secreted by Hensen's node (homologous to the amphibian Spemann organizer), a signaling center at the rostral end of the primitive streak, which blocks skin formation and allows ectoderm to adopt a neural fate. Once the neural tube closes, the roof plate and floor plate become new signaling centers, organizing dorsal and ventral neural tube respectively. As a principle stated earlier, the same ligand/receptor system is used sequentially for multiple functions during development. BMPs are a case in point, since they prevent neural development at neural plate stage, while after neurulation, the factors are produced by the dorsal neural tube itself to induce sensory neuron fates. Consequently, interfering with this single signal will have complex developmental effects.

The spinal cord

The synthesis, release and diffusion of inductive signals from signaling sources produce concentration gradients that impose distinct neural fates in the spinal cord. The notochord and floor plate secrete Shh, which induces motor neurons and interneurons ventrally, while the epidermal ectoderm and roof plate release several BMPs which impart neural

crest and sensory relay interneuron fates dorsally. Growth factor inductive signals act to initiate discrete regions of transcription factor gene expression. For instance, high concentrations of Shh induce the winged helix transcription factor Hnf3β gene in floor plate cells and Nkx6.1and Nkx2.2 in ventral neural tube, while expression of more dorsal genes, Pax6, Dbx1, Dbx2, Irx3 and Pax7, is repressed. In response to Shh, ventral motor neurons express the transcription factor gene Isl1, whose protein product is essential for neuron differentiation; without it, the motoneurons are not produced. Subsequently, ventral interneurons differentiate, expressing En1 or Lim1/2 independent of Shh signaling. In contrast, the release of BMPs by the dorsal cord and roof plate induces a distinct cascade of patterning genes to elicit sensory interneuron differentiation. In turn, dorsal BMPs, and proteins of another signaling family, the Wnts, are signals likely to be regulated by roof plate-specific patterning genes, such as Lmx1 and 2. In aggregate, the coordinated actions of Shh and BMPs induce the dorso-ventral dimension of the spinal cord. Currently under study, Shh may regulate spinal cord patterning genes of the Pax family that interact with the PDGF growth factor receptor and folic acid metabolism, disturbances of which may result in spina bifida.

In similar fashion, other inductive signals determine rostro-caudal organization of the CNS, such as retinoic acid anteriorly, an upstream regulator of Hox patterning genes, and the FGFs posteriorly. The overlapping and unique expression of the many Hox gene family members and Krox20 are important for establishing the segmental pattern in the anterior-posterior axis of the hindbrain and spinal cord, now classic models well described in previous reviews. Similarly several excellent reviews of cerebellum and hindbrain-midbrain development discuss the roles of patterning genes and signaling centers. One patterning gene, the ZIC2 transcription factor, is associated with the hindbrain deformity, Dandy–Walker syndrome, as well as holoprosencephaly (HPE) (see below).

The cerebral cortex

Evidence suggests that forebrain development also depends on inductive signals and patterning genes as observed in more caudal structures. In the embryo, the dorsal forebrain structures include the hippocampus medially, the cerebral cortex dorsolaterally and the entorhinal cortex ventrolaterally, whereas in basal forebrain, the globus pallidus lies medially and the striatum laterally. Based on gene expression and morphological criteria it has been hypothesized that the forebrain is divided into a checkerboard-like grid-pattern of gene expression domains generated by the intersection of longitudinal columns and transverse segments, perpendicular to the longitudinal axis. The columns and segments (prosomeres) exhibit restricted expression of patterning genes, allowing for unique combinations of factors within each embryonic subdivision. Many of these genes, including Hnf3β, Emx2, Pax6 and Dlx2, are first expressed even before neurulation in the neural plate and are then maintained, providing the "protomap" determinants of the VZ described above. As in spinal cord, initial forebrain gene expression is influenced by a similar array of soluble factors arising from signaling centers, such as Shh, BMP and retinoic acid. As the telencephalic vesicles form, signaling centers localize to the edges of the cortex. In the dorsal midline there is the anterior neural ridge, an anterior cranial mesenchyme secreting FGF8, the roof plate, and at the roof plate-vesicle junction, the cortical hem (Fig. 16.2). Other factors originate laterally from the dorsal-ventral forebrain junction, as well as from basal forebrain structures themselves.

Initial forebrain development starts with formation of two telencephalic vesicles from the rostral-most neural tube, the prosencephalon. This process is influenced by secreted signaling molecules, such as FGF8 and Shh, from the anterior neural ridge, followed by the roof plate, the cortical hem (see below: The hippocampus), the choroid plexus and other cells of the meninges and skin. Shh and Six3 are coexpressed in the anterior neural ridge and later in the ventral midline, whereas Zic2 is expressed in the dorsal roof plate.

Genetic studies have begun to provide insight into the mechanisms producing the diversity of cerebral cortical regions. After telencephalic vesicles form, opposing gradients of patterning genes seem to be critical in specifying the rostro-caudal areal characteristics of the cortex. Though likely to become more complex with new discoveries, the current model indicates that rostral/lateral cortex expresses high levels of homeodomain gene Pax6, whereas caudal/medial cortex exhibits Emx2, Lhx2 and Lhx5 (Fig. 16.2). A prediction would be that altering gene expression should cause a change in cortical areas, especially the proportions of motor to sensory cortex. Consistent with this model, expression of motor cortex markers is markedly diminished in mice mutant for Pax6, as well as for downstream bHLH transcription factor, Ngn2, which it regulates. In addition, the reduction in motor cortex characteristics is accompanied by a proportionate increase in caudal sensory cortex traits. Moreover, there is also change in the dorso-ventral dimension: genes usually restricted to the ventral striatum and pallidum, namely Gsh and Dlx, are expressed ectopically in dorsal territory. A similar dorsal shift of ventral genes occurs with combined deletion of another set of dorsal transcription factors, Ngn1/2 and Gli3, yielding loss of the cerebral cortex. These observations indicate that patterning genes exert reciprocal inhibitory functions in several dimensions, a mechanism for establishing developmental boundaries between areas.

The impact of signaling molecules on regional, sensory-motor specification has been elegantly demonstrated in experiments genetically altering levels of FGF8. Over-expression of FGF8 in its normal anterior neural ridge location causes

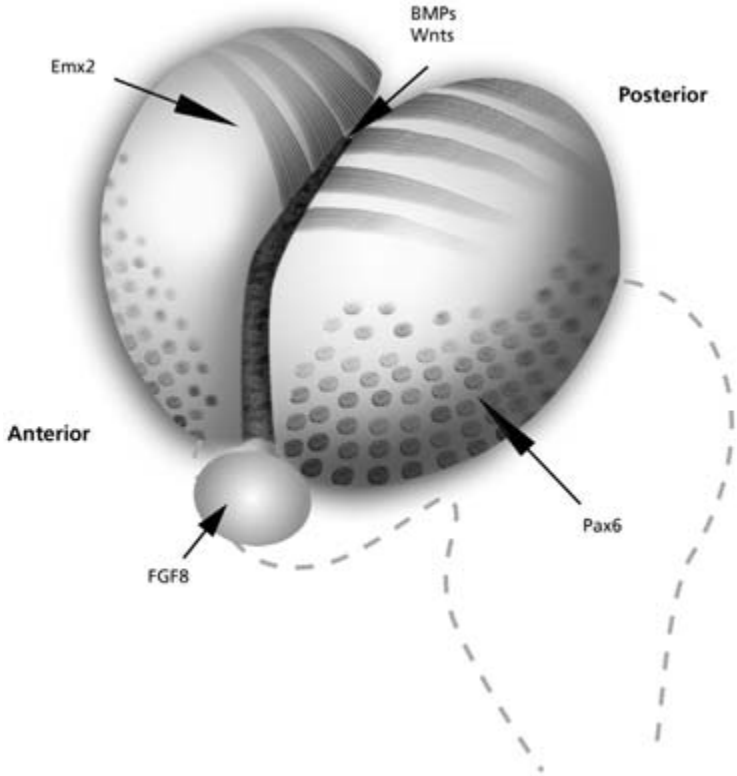

Fig. 16.2 Patterning genes and signaling centers in the developing cerebral cortex. This schematic diagram shows a lateral-superior view of the two cerebral hemispheres of the embryonic mouse, sitting above the midbrain and hindbrain (broken lines). The anterior-lateral extent of *Pax6* gene expression is indicated by circles. The posterior-medial domain of *Emx2* expression is indicated by stripes. The genes exhibit continuous gradients of expression that decrease as they extend to the opposite poles. The signaling factor FGF8 is produced by and released from mesenchymal tissue in the anterior neural ridge, which regulates *Pax6* and *Emx2* expression. In the midline, BMPs and Wnts are secreted from other signaling centers, including the roof plate and the cortical hems. (Designed by E. DiCicco-Bloom, MD, and drawn by Karen Forgash.)

a posterior shift of cortical areas, whereas over-expressing a soluble receptor fragment, which sequesters endogenous factor, shifts borders anteriorly. Furthermore, introducing FGF8 into the posterior cortex where Emx2 predominates induces a duplication of somatosensory organization. These results suggest that FGF8 alters the ratios of Pax6 and Emx2 levels in the cortical neuroepithelium, that is changes the gradients, respecifying the rostro-caudal character that emerges. In addition to FGF8, Wnt and BMP signaling may also directly regulate Emx2 transcription, indicating combinatorial actions of extracellular signals on patterning gene expression, and consequent cortical development. More generally, gradients of patterning genes likely regulate the nature of cortical areas in all three dimensions. Critical patterning gene targets will likely include proteins which mediate cell–cell interactions, such as the adhesive cadherins, membrane-bound ephrins and their Eph receptors, and members of the immunoglobulin superfamily, that play roles in cell differentiation, cell migration and neuronal process outgrowth.

The hippocampus

As a region of major importance in schizophrenia, autism and epilepsy, identifying mechanisms regulating hippocampal formation may provide clues to developmental bases of these disorders. In mouse, the hippocampus is located in the medial wall of the telencephalic vesicle. Where it joins the roof plate, the future roof of the third ventricle, there is a newly defined signaling center, the cortical hem, which secretes BMPs, Wnts, and FGFs (Fig. 16.2). Genetic experiments have defined patterning genes localized to the cortical hem and hippocampal primordia, whose deletions result in a variety of morphogenetic defects. In mice lacking Wnt3a, which is expressed in the cortical hem, the hippocampus is either completely missing or greatly reduced, while neighboring cerebral cortex is mainly preserved. A similar phenotype is produced by deleting an intracellular factor downstream to Wnt receptor activation, the Lef1 gene, suggesting that the Wnt3a-Lef1 pathway is required for hippocampal cell specification and/or proliferation, issues remaining to be defined. When another cortical hem gene, Lhx5, is deleted, mice lack both the hem and neighboring choroid plexus, both sources of growth factors. However, in this case, the cortical hem cells may in fact proliferate in excess, and the hippocampal primordia may be present but disorganized, exhibiting abnormalities in cell proliferation, migration and differentiation. A related abnormality is observed with Lhx2 mutation. Finally, a sequence of bHLH transcription factors plays roles in hippocampal neurogenesis: dentate gyrus differentiation is defective in NeuroD and Mash1 mutants. Significantly, expression of all these hippocampal patterning genes is regulated by factors secreted by anterior neural ridge, roof plate and the cortical hem, including FGF8, Shh, BMPs and Wnts. Moreover, the basal forebrain region secretes an EGF-related protein, TGFα, which can stimulate expression of the classical limbic marker protein, LAMP.

These various signals and genes now serve as candidates for disruption in human diseases of the hippocampus.

The basal ganglia

In addition to motor and cognitive functions, the basal ganglia take on new importance in neocortical function, since they appear to be the embryonic origin of virtually all adult GABA interneurons, reaching the neocortex through tangential migration (Fig. 16.1). Gene expression studies have identified several transcription factors that appear in precursors originating in the ventral forebrain ganglionic eminences, allowing interneurons to be followed as they migrate dorsally into the cortical layers. Conversely, genetic deletion mutants exhibit diminished or absent interneurons, yielding results consistent with other tracing techniques. These transcription factors, including Pax6, Gsh2, and Nkx2.1, establish boundaries between different precursor zones in the ventral forebrain VZ, through mechanisms involving mutual repression. As a simplified model, the medial ganglionic eminence (MGE) expresses primarily Nkx2.1 and gives rise to most GABA interneurons of the cortex and hippocampus, whereas the lateral ganglionic eminence (LGE) expresses Gsh2 and generates GABA interneurons of the SVZ and olfactory bulb. The boundary between ventral and dorsal forebrain then depends on LGE interaction with the dorsal neocortex, which expresses Pax6. When Nkx2.1 is deleted, LGE transcription factor expression spreads ventrally into the MGE territory, and there is a 50% reduction in neocortical and striatal GABA interneurons. In contrast, deletion of Gsh2 leads to ventral expansion of the dorsal cortical molecular markers and concomitant decreases in olfactory interneurons. Finally, Pax6 mutation causes both MGE and LGE to spread laterally and into dorsal cortical areas, yielding increased interneuron migration. The final phenotypic changes are complex, as these factors exhibit unique and overlapping expression, and interact to control cell fate.

Other transcription factors expressed in the MGE and LGE, including Mash1, Dlx1, Dlx2, Dlx5, Dlx6, Lhx6 and Lhz7, appear to regulate both the timing of differentiation as well as the type of interneuron generated. Mash1 is expressed in early born cells, whereas Dlx1/Dlx2 appears in later maturing neurons, having as targets other family members, Dlx5/Dlx6. In the Dlx1/Dlx2 double knock out, there is a 75% reduction in neocortical interneurons, and complete absence in the hippocampus, while olfactory neurons are preserved. A regulatory cascade has been suggested since Mash1 can regulate Dlx expression, while Dlx2 can induce expression of the GABA synthetic enzyme, glutamic acid decarboxylase (GAD) 67. Consistent with this model, the Mash1 deletion mutant exhibits reduced cortical GABA interneurons and striatal cholinergic interneurons. Similarly, Nkx2.1 loss also alters neuron subpopulations, leading to complete absence of all cortical interneurons expressing NPY, somatostatin and NOS. These studies suggest that transcription factors play roles at multiple stages in neuronal production including generic neuronal fate specification, as well as neuron subtype determination.

Neuronal specification

As indicated for basal ganglia, throughout the nervous system transcription factors participate in decisions at multiple levels, including determining the generic neural cell, such as neuron or glial cell, as well as neuron subtypes. Mash1 can promote a neuronal fate over a glial fate, as well as induce the GABA interneuron phenotype. However, another bHLH factor, Olig1/2, can promote oligodendrocyte development, whereas it promotes motor neuron differentiation elsewhere, indicating that the variety of factors expressed in a specific cell leads to combinatorial effects, thus diverse outcomes for cell differentiation. The bHLH inhibitory factor, Id, is expressed at the transition from somatosensory to motor cortex, implying roles of family members in cortical regional (areal) characteristics. In the hippocampus, granule neuron fate is dependent on NeuroD and Math1, with deficient cell numbers when either one is deleted. The role of specific factors in cortical cell layer determination remains an area of active investigation, but likely includes Tbr1, Otx1, and Pax6.

Regulation of neurogenesis by extracellular factors

The interaction of extracellular factors with intrinsic genetic determinants controlling region-specific neurogenesis includes signals that regulate cell proliferation. Patterning genes control the expression of growth factor receptors and the molecular machinery of the cell division cycle. Extracellular factors are known to stimulate or inhibit proliferation of VZ precursors and originate from the cells themselves (autocrine), neighboring cells/tissues (paracrine), or the general circulation (endocrine). Although defined initially in cell culture, a number of mitogenic growth factors are now well-characterized in vivo, including those stimulating proliferation, such as basic fibroblast growth factor (bFGF), EGF, IGF-I, Shh, and signals inhibiting cell division, such as pituitary adenylate cyclase activating polypeptide (PACAP), GABA and glutamate, and members of the TGFβ superfamily. In addition to stimulating re-entry of cells into the cell cycle, a mitogenic effect, extracellular signals also enhance proliferation by promoting survival of the mitotic population, a trophic action. Stimulation of both pathways is necessary to produce maximal cell numbers. These mitogenic and trophic mechanisms during development parallel those identified in carcinogenesis, reflecting roles of c-myc and bcl-2 respectively. Several of the neurotrophins, especially

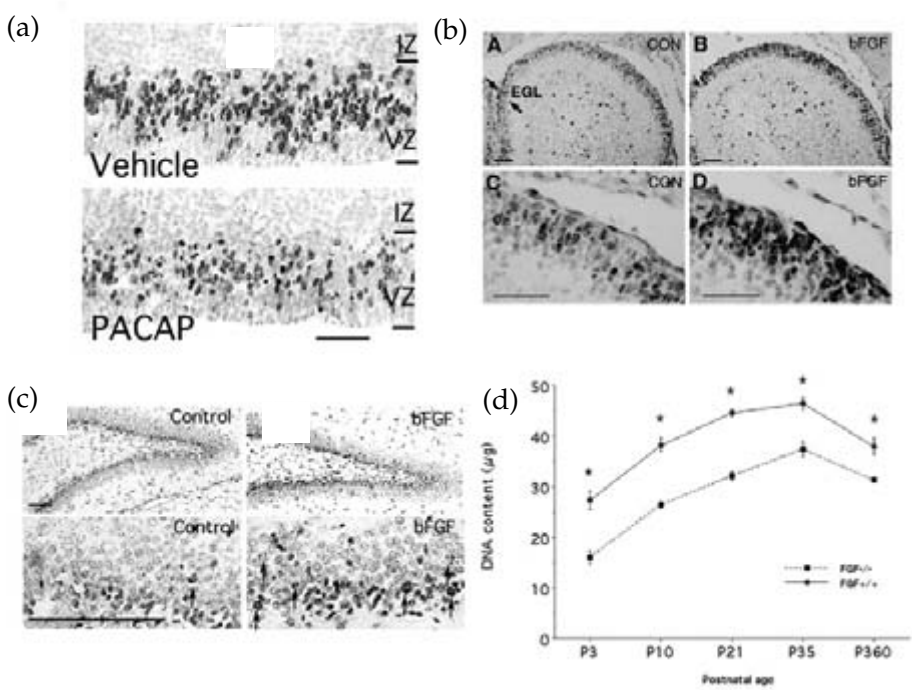

Fig. 16.3 Extracellular growth factors stimulate or inhibit neuronal precursor proliferation during brain development. (a) Intracerebroventricular injection of antimitogenic peptide, PACAP, into the rat embryo *in utero* inhibits mitosis in VZ precursors of the cerebral cortex. Less VZ precursors exhibit nuclear labeling with DNA synthesis marker, BrdU, in embryos exposed to PACAP, indicating that the cells were prevented from entering S phase of the mitotic cell cycle. Three and 5 days later there were ~40% less mitotically labeled neurons in the cortical plate. BrdU positive cells appear brown and toluidine counterstain appears blue. Scale bar = 50 μm. (Suh *et al.* 2002.) (b) Eight hours after subcutaneous injection of bFGF in newborn rat pups, 30% more cerebellar EGL precursors are in mitotic S phase, as indicated by brown nuclear staining compared to saline injected littermates. Thus peripherally injected factors rapidly alter ongoing neurogenesis in the developing brain. A and B low magnification of a single cerebellar folium, C and D high magnification; CON = control saline injection (A and C), bFGF = growth factor injected (B and D). Nuclear BrdU stain appears brown, and basic fuchsin counterstain appears pink. Scale bar = 100 μm. (Tao *et al.* 1996.) (c) Three weeks after bFGF injection at birth, there are many more mitotically labeled (arrows) dentate gyrus granule neurons in the hippocampal formation. BrdU positive nuclei indicated by arrows in control and factor treated animals appear brown, and thionin counterstain appears blue. There were 33% more granule neurons quantified by stereological counting, an increase that was maintained throughout life. The postnatal day 21 dentate gyrus is pictured at low (top) and high magnification (bottom). Scale bar = 100 μm. (Cheng *et al.* 2002). (d) Mice with genetic deletion of bFGF exhibit a lifelong reduction in total cells in the hippocampal formation, reflected by diminished total DNA in microgram per hippocampus. Absolute cell counting revealed 30% decreases in the number of dentate gyrus granule layer neurons as well as astrocytes at 3 weeks of age. (Cheng *et al.* 2002).

BDNF and neurotrophin-3 (NT3), promote survival of mitotic precursors as well as the newly generated progeny.

The developmental significance of extracellular mitogens is demonstrated by factor and receptor expression in regions of neurogenesis, and the profound and permanent consequences of altering their activities during development. Changes in proliferation in prenatal cortical VZ and postnatal cerebellar EGL and hippocampal dentate gyrus produce lifelong modifications in brain region population size and cell composition, potentially relevant to structural differences observed in schizophrenia and autism. In the cerebral cortex VZ of the embryonic rat, proliferation is controlled by promitogenic bFGF and antimitogenic PACAP, which are expressed as autocrine/paracrine signals. Positive and negative effects were shown in living embryos *in utero* by performing intracerebroventricular (ICV) injections of the factors or antagonists. bFGF produced a larger adult cortex composed of 87% more neurons which employed glutamate, thus increasing the ratio of excitatory pyramidal neurons to GABA inhibitory neurons, which were unchanged. Conversely, embryonic PACAP injection inhibited proliferation of cortical VZ precursors by 26%, reducing the number of labeled layer 5/6 neurons by 40% in the cortical plate 5 days later (Fig. 16.3a). A similar reduction was accomplished by genetically deleting promitogenic bFGF, diminishing cortical size. Furthermore, effects of mitogenic signals depended critically on the stage-specific program of regional development, since bFGF injection at later ages when gliogenesis predominates, affected glial numbers selectively. Thus developmental dysregulation of mitogenic pathways due to genetic or environmental factors (hypoxia, maternal/fetal

infection, drug or toxin exposure) may produce subtle changes in the size and composition of the developing cortex. Other signals that may have proliferative roles include Wnts, TGFα, IGF-I, BMPs, and leukocyte inhibitory factor (LIF)/ciliary neurotrophic factor (CNTF).

Similar to cerebral cortex, later generated populations, such as cerebellar granule neurons and hippocampal dentate gyrus cells, are sensitive to growth factor manipulation, especially relevant to therapies administered intravenously to premature and newborn infants in the neonatal nursery. Unlike humans, in the rat cerebellum granule neurons are produced postnatally for only 3 weeks, however, dentate gyrus neurons are produced throughout life in both species. Remarkably, a single peripheral injection of bFGF into newborn rat pups rapidly crossed into the cerebrospinal fluid, and stimulated proliferation in the cerebellar EGL by 30% as well as hippocampal dentate gyrus by 100% at 8 hours, consistent with an endocrine mechanism of action (Fig. 16.3b). The consequences of mitogenic stimulation in cerebellum were a 33% increase in internal granule neuron production and a 22% larger cerebellum. In hippocampus, mitotic stimulation elicited by a single bFGF injection (Fig. 16.3c) increased the absolute number of dentate gyrus granule neurons by 33% at 3 weeks, defined stereologically, producing a 25% larger hippocampus containing more neurons and astrocytes, a change that persisted lifelong. Conversely, genetic deletion of bFGF resulted in smaller cerebellum and hippocampus at birth and throughout life, indicating that levels of the growth factor were critical for normal brain region formation (Fig. 16.3d). Alterations in animal behaviors are currently under investigation. Other proliferative signals regulating cerebellar granule neurogenesis include Shh and PACAP, whose disruption contributes to human medulloblastoma, whereas in hippocampus, the Wnt family may be involved.

There are clinical implications of growth factor effects observed in fetuses and newborns. It is necessary to investigate possible neurogenetic effects of therapeutic agents administered during pregnancy and in the newborn nursery for long-term consequences. bFGF is effective in stimulating neurogenesis in adults and at younger ages since it is transported across the mature blood-brain barrier (BBB); it is possible that other protein factors are transported into brain, potentially altering ongoing neurogenesis (in adult rats, IGF-I stimulates hippocampal dentate gyrus neurogenesis). Other therapeutics which affect neurogenesis cross the BBB efficiently due to their lipid solubility. For example, steroids, which inhibit neurogenesis, are frequently used during the perinatal period to promote lung maturation and treat infections and trauma. At least in very low birth weight premature infants (<1000 g), postnatal steroid use is associated with worse neurodevelopmental outcome, supporting recent cautions about their use in this population. Further, neurodevelopment delay is well known in children experiencing serious systemic illness; to what degree this reflects interference with neurogenesis and concomitant processes, potentially producing long-term sequelae, is an important area for investigation.

Cell migration

Throughout the nervous system, newly generated neurons normally migrate away from proliferative zones to achieve their final destinations. If disrupted, abnormal cell localization occurs, resulting in abnormal function. In man, more than 25 syndromes with disturbed neuronal migration have been described, most of which produce various levels of mental retardation and epilepsy (see below). In developing cerebral cortex, the most well-characterized mechanism is radial migration of immature pyramidal neurons from the underlying VZ to their appropriate cortical layers in inside-to-outside fashion, as described above. However, the inhibitory GABA interneurons are generated in the ventrally located medial ganglionic eminences (Fig. 16.1) and reach the cortex through tangential migration in the intermediate zone along axonal processes or other neurons. The neurons in the developing cerebellum also exhibit both radial and tangential migration. Purkinje cells leave the fourth ventricle VZ and exhibit radial migration, whereas other precursors from the rhombic lip migrate tangentially to cover the cerebellar surface, establishing the EGL, a secondary proliferative zone. From the EGL, newly generated granule cells migrate radially inwards to create the internal granule cell layer. Finally, granule interneurons of the olfactory bulb exhibit a different kind of migration, originating in the subventricular zone (SVZ) of the lateral ventricles overlying the striatum. These neuroblasts divide and migrate simultaneously in the rostral migratory stream in transit to the bulb, on a path comprising of chains of cells that support forward movements. The most commonly recognized disorders of human neuronal migration are the extensive lissencephalies (see below), though incomplete migration of more restricted neuron aggregates (heterotopias) frequently underlies focal seizure disorders.

Animal models have defined molecular pathways involved in neuronal migration. Cell movement requires signals to start and stop migration, adhesion molecules to guide migration, and functional cytoskeleton to mediate cell translocation. The best characterized mouse model of aberrant neuronal migration is reeler, a spontaneous mutant in which cortical neuron laminar position is inverted, being generated in outside-to-inside fashion. Reelin is a large, secreted, extracellular glycoprotein produced embryonically by the earliest neurons in the cortical preplate, Cajal Retzius cells, and also in the hippocampus and cerebellum. Molecular and genetic analysis has established a signaling sequence in reelin activity which includes at least two receptors, the very-low-density lipoprotein receptor (VLDLR) and the apoprotein E receptor 2 (ApoER2), and the intracel-

lular adapter protein, disabled 1 (Dab1), initially identified in the scrambler mutant mouse, which is a reelin phenocopy. Current thoughts consider the reelin system as one mediator of radial glial-guided neuronal migration, though specific functions in starting or stopping migration remain controversial. The roles of the VLDL and ApoE2 receptors are intriguing for their possible contributions to Alzheimer's disease risk. Recent studies have found human reelin gene (RELN) mutations associated with autosomal recessive lissencephaly (see below).

Cell migration also depends on molecules mediating cellular interactions, which provide cell adhesion, or induce attraction or repulsion. Astrotactin is a major glial protein involved in neuronal migration on radial glial processes, whereas neuregulins and their receptors, ErbB2–4, play roles in neuronal-glial migratory interactions. Recent genetic studies find that neuregulin polymorphisms are highly associated with schizophrenia. In addition to adhesion signaling systems, early appearing neurotransmitters, GABA and glutamate, and platelet-derived growth factor (PDGF) appear to regulate migration speed. In contrast to radial migration of excitatory pyramidal neurons from the cortical VZ, GABA interneurons generated in ganglionic eminences employ different mechanisms to leave the ventral forebrain and migrate dorsally into the cerebral cortex. Several signaling systems have been identified, including the Slit protein and Robo receptor, the semaphorins and their neuropilin receptors, and hepatocyte growth factor and its c-Met receptor, all of which appear to repel GABA interneurons from basal forebrain, promoting tangential migration into cortex (Fig. 16.1). Several human forms of congenital muscular dystrophy with severe brain and eye migration defects result from gene mutations in enzymes that transfer mannose sugars to serine/threonine -OH groups in glycoproteins, interrupting interactions with several extracellular matrix molecules, producing type II cobblestone lissencephalies (discussed further below).

Differentiation and neuronal process outgrowth

After newly produced neurons and glial cells reach their final destinations, they differentiate into mature cells. For neurons, this involves outgrowth of dendrites and extension of axonal processes, formation of synapses, and production of neurotransmitter systems, including receptors and selective reuptake sites. Most axons will become insulated by myelin sheaths produced by oligodendroglial cells. Many of these events occur with a peak period from 5 months of gestation onward. During the first several years of life, many neuronal systems exhibit exuberant process growth and branching, which is later decreased by selective "pruning" of axons and synapses dependent on experience. In contrast, myelination continues for several years after birth and into adulthood.

While there is tremendous synapse plasticity in adult brain, a fundamental feature of the nervous system is the point-to-point or topographic mapping of one neuron population to another. During development, neurons in various brain regions extend axons to innervate diverse distant targets, such as cortex and spinal cord. The structure that recognizes and responds to cues in the environment is the growth cone, located at the axon tip. The growth cone has rod-like extensions called filopodia that bear receptors for specific guidance cues, which are present on cell surfaces and in the

KEY CLINICAL QUESTIONS

All Disorders of Brain Development

- Were there any prenatal maternal infections?
- A history of prenatal infections raises the possibility of an environmental, rather than a genetic cause, for brain malformations. Cytomegalovirus can result in polymicrogyria, rubella can cause microcephaly, and toxoplasmosis often leads to scattered calcifications.
- Is there a history of clotting disorders?
- Clotting disorders can cause cerebral infarctions. Early prenatal infarctions may result in porencephaly, which is distinguished from schizencephaly by the gray matter that lines the cleft of a schizencephalic defect. Complete occlusion of both internal carotid arteries results in hydrancephaly, which is distinguished from aprosencephaly by the membranous covering that overlies a hydrancephalic defect.
- Is there a family history of developmental delays, learning disabilities, or seizures?
- Some disorders of brain formation have widely variable clinical phenotypes ranging from mild learning disabilities to severe mental retardation, spastic quadraparesis, and epilepsy. Periventricular nodular heterotopia, for instance, is clinically silent in as many as 25% of affected patients. The mother of an affected patient may herself have the disorder without knowledge of it. A history of mild learning disabilities may be the only sign of maternal involvement.
- How is the child doing developmentally?
- Developmental concerns are common among all disorders of brain formation and are often the presenting sign of the disorder. It is therefore important to review developmental progress and initiate any therapies that are needed.
- Have there been any seizures?
- Seizures are also common among all disorders of brain formation. Infantile spasms are particularly prevalent in lissencephaly and tuberous sclerosis and should always be considered in infants with these conditions.
- Are the parents planning more children in the future?
- Family planning is among the most important considerations for parents of an affected child. It is therefore necessary to pursue genetic testing and provide genetic counseling, particularly for families planning to expand.

extracellular matrix. Interactions between filopodial receptors and environmental cues cause growth cones to move forward, turn or retract. The region-specific expression of extracellular guidance molecules, such as cadherins regulated by patterning genes Pax6 and Emx2, results in highly directed outgrowth of axons, termed axonal pathfinding. These molecules affect the direction, speed and fasciculation of axons, acting through either positive or negative regulation. Guidance molecules may be soluble extracellular factors, or alternatively, may be bound to extracellular matrix or cell membranes. In the latter class of signal is the newly discovered family of transmembrane proteins, the ephrins. Ephrins play major roles in topographic mapping between neuron populations and their targets, and act via the largest known family of tyrosine kinase receptors in brain, Eph receptors. Ephrins frequently serve as chemorepellent cues, negatively regulating growth by preventing developing axons from entering incorrect target fields. For example, the optic tectum expresses ephrins A2 and A5 in a gradient that decreases along the posterior to anterior axis, whereas innervating retinal ganglion cells express a gradient of Eph receptors. Ganglion cell axons from the posterior retina, which possess high Eph A3 receptor levels, will preferentially innervate the anterior tectum, since low level ephrin expression will not activate the Eph kinase which causes growth cone retraction. In the category of soluble molecules, netrins serve primarily as chemoattractant proteins secreted, for instance, by the spinal cord floor plate to stimulate spinothalamic sensory interneurons to grow into the anterior commissure, whereas Slit is a secreted chemorepulsive factor which, through its roundabout (Robo) receptor, regulates midline crossing and axonal fasciculation and pathfinding.

In neocortex, layer 5 and 6 axons exit the hemisphere laterally via the internal capsule to reach subcortical destinations, whereas layer 3 axons extend medially through corpus callosum to innervate the opposite hemisphere. The internal capsule carries bidirectional axons, from cortex to thalamus and beyond, as well as thalamocortical processes, exhibiting precise connections between individual thalamic nuclei and distinct cortical domains. During development, thalamic axons must travel a complex route, passing through lateral ventral thalamus, turning to enter the internal capsule and turning dorsally to reach cortical targets. However, thalamic axons reach the developing neocortex before target neurons have completed their migration to appropriate layers. Instead, the early generated subplate neurons projecting to the internal capsule may function as guidepost cells, serving as temporary targets for thalamic axons. The subplate neurons express two guidance systems, including the chemoattractant netrin 1, and chemorepellant cell surface molecule, ephrin-A5, which is complemented by Eph receptor expression by thalamic axon growth cones. After cortical neurons complete laminar migration, thalamic axons leave subplate neurons, which apparently undergo degeneration, and extend into proper cortical layers guided by a number of cues, including chondroitin sulfate proteoglycans, ephrins and cadherins under patterning gene regulation. In similar fashion, thalamic afferents to limbic cortex, which express Eph A5 receptor, may be repelled from sensorimotor cortex by ephrin A5. Numerous experiments demonstrate misrouted axon terminals in developing brain when ephrin/Eph expression is altered. Thus, changes in ephrin/Eph signaling during brain development may cause abnormal cell migration and/or axonal process termination. Such abnormalities may contribute to cognitive and/or motor dsyfunction of genetic or environmental origin.

Disorders of Nervous System Development

John N. Gaitanis, MD and David E. Mandelbaum, MD, PhD

Classification

Early classification schemes of brain malformations relied on pathology and radiographic findings. More recent classifications have taken genetics into account. Clinicians, radiologists, pathologists, embryologists and geneticists have different areas of focus and each discipline is inclined to align a classification scheme according to their primary area of interest. The fact that a given gene defect can cause different phenotypic expressions and that a single phenotype may have multiple gene abnormalities associated with it illustrates the complexity in attempts at classification.

This chapter arranges cortical malformations according to the earliest embryological stage in which the abnormality has its origin (Barkovich *et al*. 2001). Yet, this too is an artificial distinction since the stages of cortical development overlap in time and lack discrete boundaries. Moreover, some gene defects exert influence in more than one developmental stage. Thus, the classification system presented here will undoubtedly be modified as understanding of these conditions increases.

Overview of embryology

As discussed in great detail in Part I of this chapter, the brain and spinal cord form from the dorsal aspect of the embryo through neurulation, the process of neural tube formation occuring in the third and fourth weeks of gestation. In the fifth and sixth weeks, prosencephalic development, the process by which the brain takes shape, begins. Cortical formation in humans spans weeks 8–24 of gestation (Crino & Eberwine 1997) and can be divided into stages of cell proliferation (both neural and glial precursor cells are generated), neuronal migration (cells travel from the proliferative zone to their designated destination), and cortical organization (cell networks are determined) (Barkovich *et al*. 1996; 2001). Myelination is the final step of brain development and continues well beyond birth (Brody *et al*. 1987). As noted above, assigning strict temporal divisions is misleading, since different stages take place concurrently. It is nevertheless helpful to define stages for the purpose of classification of the disorders.

Disorders of neurulation

Fusion of the neural tube begins at the level of the hindbrain (medulla and pons) and proceeds rostrally and caudally. Failure of rostral fusion results in dysraphic states of the brain (anencephaly, encephalocele – see Table 16.1) and incomplete caudal fusion causes spinal dysraphism (myelomeningocele). The anterior end of the neural tube closes by 24 days and posterior closure, to the level of the lumbar sacral region, happens by day 26 (lower sacral and coccygeal closure occurs by a separate process termed secondary neurulation, which is not complete until after birth). Disorders of neurulation differ in severity depending on the timing of the disruption. The most severe disorder, craniorachischisis totalis, in which the brain and spinal cord fail to develop because of a complete absence of neurulation, occurs no later than 20–22 days of gestation. Anencephaly, a complete failure of anterior neural tube closure resulting in an absence of brain formation, occurs no later than 24 days. Encephalocele, a restricted failure of anterior neural tube closure, happens around day 26. Likewise, myelomeningocele, a restricted failure of posterior neural tube closure, also occurs by day 26.

Myelomeningocele is the most clinically important disorder of neurulation since patients with it usually survive. Its incidence in the United States is approximately 0.2–0.4 per 1000 live births (Yen *et al*. 1992). The neurological features of myelomeningocele relate to the level of involvement, presence of hydrocephalus, and other associated malformations (Table 16.2).

Impairment of motor, sensory, and sphincter function relate directly to the level of involvement. Ambulation is one of the most important clinical concerns, and retained strength of the iliopsoas and quadriceps muscles are required for walking. Lesions at or below S1 rarely affect ambulation, whereas higher defects, above L2, almost always do. Among patients with intermediate lesions (L3, L4, L5), approximately half will walk, but braces or other assistive devices may be required. A clinical adage, while a bit simplistic, summarizes it as follows: "if they can move their hips they can walk and if they can move their knees they can run."

FEATURES

Table 16.1 Encephalocele

Discriminating features

1. Meningeal extrusion through bony defect
2. Abnormal cortical tissue extending through defect

Consistent feature

1. Midline skull defects

Variable features

1. Location
2. Other CNS structural abnormalities
3. Cognitive function
4. Anomalies of other systems

FEATURES

Table 16.2 Myelomeningocele/Spina Bifida

Discriminating features

1. Absence of overlying skin
2. Absence of meninges
3. Malformed spinal cord

Consistent features

1. Failure of vertebral arch fusion
2. Arnold–Chiari malformation

Variable features

1. Extent and levels of cord malformation
2. Number of vertebral arches involved
3. Extent of skin defect
4. Other CNS abnormalities
5. Cognitive function
6. Presence of seizure disorder
7. Tethered cord below lesion

Hydrocephalus is seen in approximately 90% of patients with lumbar lesions. The usual signs of increased intracranial pressure (lethargy, irritability, limited upward gaze, rapidly expanding head circumference) are not essential for diagnosis and are present in only 15% of newborns with myelomeningocele. If clinical signs are present, they usually develop 2–3 weeks after birth and are almost certain to be present by 6 weeks. Their frequent absence necessitates serial neuroimaging for the prompt diagnosis of hydrocephalus. Infants demonstrating hydrocephalus at birth require shunt placement immediately following myelomeningocele closure (usually within a single sedation). The closure stops CSF leakage, and can therefore worsen hydrocephalus if a shunt is not placed.

When myelomeningocele and hydrocephalus are combined with inferior displacement of the medulla and lower cerebellum through the foramen magnum, it is termed the Arnold–Chiari malformation (Chiari type II). Other features of this disorder include elongation and thinning of the upper medulla and pons and bony defects of the foramen magnum, occiput, and upper cervical vertebrae. Brain stem and cortical malformations are common. Resulting brainstem dysfunction is a significant cause of morbidity and mortality. It may result in apnea, stridor, cyanotic spells, and dysphagia. The overall mortality rate in patients with brainstem dysfunction is 21%, but when all four symptoms are present, the mortality rate is as high as 60%. Cortical malformations are an important cause of morbidity such as intellectual disability and epilepsy. They are also very common in patients with Arnold–Chiari malformations, being present in as many as 92% (Table 16.3).

Treatment of myelomeningocele and Arnold–Chiari malformation begins prior to birth. Delivery by cesarean section before the onset of labor is necessary to preserve motor function. Animal models of myelomeningocele have shown that intrauterine repair results in improved outcome. This suggests that the exposed spinal cord undergoes progressive *in utero* damage (Walsh *et al*. 2001). Whether this is relevant to human forms of myelomeningocele, and whether intrauterine repair would be beneficial is, as yet, unknown. Following delivery, early closure of the myelomeningocele prevents infection. Closure typically takes place within the first week, often in the first 48 hours. Early diagnosis and treatment of hydrocephalus is necessary, and placement of a ventriculoperitoneal shunt, if needed, should take place early into the infant's course. There is evidence to suggest that shunt placement at the time of myelomeningocele closure can reduce back wound morbidity without increasing shunt complications (Miller *et al*. 1996).

Brainstem dysfunction is less easily managed. Decompressive upper cervical laminectomy has been used and is best performed within the first weeks after birth. Otherwise, treatment is largely symptomatic and focuses on maintaining a patent airway and preventing aspiration.

Avoiding urinary tract complications begins with urodynamic evaluation. Daily catheterization is often required to prevent urinary tract infections in patients with incoordination of the detrusor muscle and external urethral sphincter. For patients who are nonambulatory, close orthopedic follow-up is needed for prevention and management of scoliosis and contractures. Given the wide range of systems affected in myelomeningocele, multidisciplinary clinics are helpful for coordinating care.

FEATURES

Table 16.3 Arnold–Chiari Malformation

Discriminating feature

1. Myelomeningocele combined with inferior displacement of medulla and lower brainstem

Consistent features

1. Elongation of cerebellar tonsils through foramen magnum
2. Elongation and thinning of upper medulla and pons
3. Bony defects of the foramen magnum, occiput, or upper cervical vertebra

Variable features

1. Progressive hydrocephalus
2. Presence and degree of brainstem dysfunction
3. Presence of cortical malformations
4. Presence and degree of cognitive impairment
5. Presence of seizure disorder

Disorders of prosencephalic development

Prosencephalic development is the process in which the forebrain (telencephalon and diencephalon) takes shape. It begins during the fifth week and continues through the second and third months of gestation. Prosencephalic development also influences formation of the face, and a severe disruption at this stage will result in characteristic facial anomalies. Development of the forebrain can be divided into three stages: formation, cleavage, and midline development. The resulting disorders depend on the stage affected. Disruption of prosencephalic formation results in the most severe anomalies, including aprosencephaly (complete absence of the telencephalon and diencephalons) or atelencephaly (with preservation of the diencephalon). Maintenance of the skull and dermal covering readily distinguish these from anencephaly. Because disorders of prosencephalic formation are not compatible with life, they bear little clinical relevance in comparison to disruption of prosencephalic cleavage or midline development.

Holoprosencephaly

Included among disorders of prosencephalic cleavage is holoprosencephaly (HPE), in which disruption of the roof plate and absence of hemispheric separation result in a single, large, forebrain ventricle. In its most severe form, alobar HPE, the brain is a single spherical structure with a common ventricle and a malformed cortical mantle. The optic nerves are dysplastic and the olfactory bulbs and tracts may be absent. The hypothalamus does not separate normally into two halves. Facial anomalies, ranging from cyclopia to a single central incisor, are observed. Less severe forms, semilobar and lobar HPE, have lesser degrees of the same anomalies. For instance, in semilobar HPE, the frontal and parietal lobes remain fused and the interhemispheric fissure is only present posteriorly. In contrast, in lobar HPE most of the left and right hemispheres and lateral ventricles are separated and fusion is seen only at the most ventral aspect of the frontal lobes. Clinical severity relates directly to the degree of structural change. Neurological dysfunction inversely correlates with the degree of hemispheric separation, with less separation resulting in greater impairment. Endocrinopathies correlate with the severity of hypothalamic separation. Associated cortical malformations frequently cause epilepsy, which is often refractory. Careful attention to the neuroimaging features is necessary in providing an accurate prognosis (Plawner *et al*. 2002) (Table 16.4).

HPE is a heterogeneous condition, with both genetic and environmental causes. The most common environmental cause is maternal diabetes, which carries a 1% risk of HPE (200 times greater than in the normal population). Cytogenetic abnormalities account for approximately 25–50% of holoprosencephaly cases, with trisomy 13 and 18 being the most common. Single gene mutations are found in roughly 25% of patients. Several genes are known to be causative.

PEARLS & PERILS

Holoprosencephaly

- Craniofacial anomalies accompany HPE in about 80% of patients, but patients with all types of holoprosencephaly can have relatively normal facial appearances. A correlation often exists between the facial anomalies and the subtype of holoprosencephaly.
- Ventricular enlargement of the occipital horns, termed colpocephaly, is a common finding in holoprosencephaly and does not reflect progressive hydrocephalus.
- Clinically, infants with septo-optic dysplasia have impaired vision (often presenting with nystagmus) and endocrine dysfunction (hyponatremia, hypoglycemia, and impaired growth).
- Agenesis of the corpus callosum in combination with chorioretinal lacunas, mental retardation, and infantile spasms constitutes Aicardi's syndrome.

FEATURES

Table 16.4 Holoprosencephaly

Discriminating feature

1. Impaired forebrain cleavage

Consistent feature

1. Incomplete separation of forebrain

Variable features

1. Degree of cleavage defect (alobar, semilobar, lobar)
2. Endocrinopathies
3. Associated cortical malformations
4. Cognitive impairment
5. Optic nerve dysplasia
6. Presence of seizure disorder

The first gene discovered, the sonic hedgehog gene (Shh) at 7q36, appears to be the most common. Shh plays an important role in dorsal-ventral patterning – the process by which the dorsal and ventral regions of the nervous system acquire their anatomical and functional properties (Thakur *et al*. 2004). Genetic testing is currently available for seven different single gene mutations, and many more may exist. HPE is also seen in cases of Smith–Lemli–Opitz syndrome, in which a defect in the biosynthesis of cholesterol leads to reduced Shh activity. Assuming a clear environmental cause is not found, the evaluation typically begins with a karyotype followed by molecular genetic testing if the karyotype is unremarkable. Genetic counseling is important given the heterogeneity of these disorders.

Abnormalities of midline prosencephalic development are typically less severe than HPE. They include agenesis of the corpus callosum and septo-optic dysplasia (SOD). Agenesis of the corpus callosum can be either partial or complete. With partial agenesis, the posterior portion is more affected. It is commonly associated with other brain anomalies including Arnold–Chiari II malformations and neuronal migration disorders. SOD, on the other hand, is characterized by optic nerve hypoplasia in combination with absence of the septum pellucidum and pituitary dysfunction. Clinically, it may present with visual impairment (which may be recognized because of congenital nystagmus), endocrinopathies, or both. The causes are heterogeneous, including both environmental and genetic etiologies. One gene associated with SOD is HESX1, a homeobox gene essential for pituitary and forebrain development.

Disorders of neuronal proliferation

Neuronal proliferation takes place between the second and fourth months of gestation (Volpe 2001). Radial glial cells, which play a critical role in neuronal migration, are also formed at this time. Neurons and glia have their origin in the

ventricular and subventricular zones. In the earliest phases of neuronal proliferation, neuronal-glial stem cells divide to form further stem cells (Rakic 1988; 1995). Later, stem cell division becomes asymmetric so that one daughter cell is postmitotic while the other remains a stem cell. Eventually, fewer and fewer stem cells are produced and all of the neurons within the proliferative unit are postmitotic (Kornack 1998). Abnormal neuronal proliferation may result in conditions characterized by too many or too few neurons. Incomplete differentiation of postmitotic neurons is included within this category.

Decreased proliferation

Microcephaly/microlissencephaly

Primary microcephaly (microcephaly vera) is diagnosed when the head circumference at birth is three or more standard deviations below normal (Table 16.5). Primary microcephaly is a heterogeneous condition and can be caused by destructive processes (hypoxia-ischemia, intrauterine infections) or from a genetically determined reduction in neuronal proliferation. Most genetic forms are recessively inherited. The most common of these conditions may be microcephaly 5 (MCPH5), caused by mutations in the abnormal spindle-like microcephaly associated gene (ASPM) (Bond 2003). ASPM may be essential for normal mitotic spindle activity in neuronal progenitor cells and its disruption therefore affects neuronal proliferation (Bond 2002). Mental retardation and a generalized simplification of the gyral pattern are common, but more severe gyral abnormalities have not been described.

Microcephaly is sometimes associated with a more simplified gyral pattern or, in severe cases, with a smooth cortex, termed microlissencephaly (Dobyns 1995; Barkovich *et al*. 1998). These cases can be associated with cerebellar and callosal abnormalities (Barth 1982) in addition to extracranial dysmorphism (McComb 1991). Seizures and global developmental delays are uniformly present (Kroon 1996). Microlissencephaly is thought to be distinct from the syndrome of microcephaly with simplified gyral pattern (Dobyns 1999).

FEATURES

Table 16.5 Primary Microcephaly

Discriminating feature

1. Head circumference >3 standard deviations below normal at birth

Consistent feature

1. Developmental delay (cognitive and/or motor impairment)

Variable features

1. Etiology (destructive *vs*. genetically determined)
2. Degree of gyral simplification

Disordered proliferation

Hemimegalencephaly

When there is enlargement of just one cerebral hemisphere, it is termed hemimegalencephaly. It probably results when a disturbance of cellular differentiation and proliferation interacts with the genetic expression of body symmetry (Flores-Sarnat 2002) (Fig. 16.4). In addition to increased size of the affected hemisphere, neuroimaging may reveal abnormal gyration, ventriculomegaly, and increased T2 signal of the white matter (Sasaki 2000; Flores-Sarnat 2002). Histology reveals disorganized cortical lamination, subcortical heterotopia, and large, dysmorphic neurons, termed balloon neurons (DeRosa 1992; Crino 1997a; Woo 2001). The opposite hemisphere may be normal or have mild dysplasia and heterotopia (Crino 1997b). Hemimegalencephaly can be associated with tuberous sclerosis complex (Galluzzi 2002), hypomelanosis of Ito (Woo 2001), and linear nevus sebaceous syndrome (Herman 2001). All patients have epilepsy; hemispherectomy is often required for intractable cases (Flores-Sarnat 2002; Devlin 2003).

Abnormal neuronal differentiation/maturation

In abnormalities of maturation or differentiation, neurons exhibit immature or glial features. The large, dysplastic neurons of cortical dysplasia possess markers of neuro-

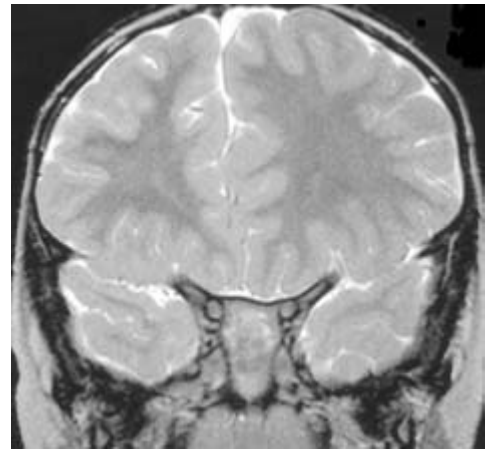

Fig. 16.4 When unilateral enlargement of just one cerebral hemisphere exists, it is termed hemimegalencephaly. It probably results when a disturbance of cellular differentiation and proliferation interacts with the genetic expression of body symmetry.

Tuberous Sclerosis Complex

PEARLS & PERILS

- About 25% of children with infantile spasms have tuberous sclerosis.
- Vigabatrin may be preferable to ACTH for the treatment of infantile spasms in patients with tuberous sclerosis
- Cranial imaging, abdominal (renal) ultrasound study, and echocardiograms should be considered in screening parents of patients with tuberous sclerosis for manifestations of the disease.
- Surgical decompression, possibly percutaneous, may ameliorate clinical symptoms of renal cysts.
- Retinal hamartomas are not symptomatic and do not change significantly with age.
- Pulmonary lymphangiomyomatosis, although very rarely seen in tuberous sclerosis, is pathognomonic for the disorder.
- The fat content of hepatic angiomyolipomas is diagnostic on ultrasound or CT.
- Dental enamel pitting can be easily demonstrated with plaque-disclosing solution and dye. The diffuse small pits have been seen in 75–100% of adults with tuberous sclerosis.

nal immaturity, such as microtubule associated protein 2c (MAP2c), MAP 1B, and nestin (Yamanouchi 1996; Crino 1997a). Balloon neurons contain abnormally large amounts of cytoplasm and stain for both neuronal and glial markers (Barkovich *et al*. 2001), indicating a failure to commit to a specific cell lineage (Robain 1996). Balloon and dysplastic neurons are seen in cortical dysplasia and in the cortical hamartomas of tuberous sclerosis complex (Crome 1957; Cravioto 1960). Evidence of disrupted neuronal migration, including disorganized or absent lamination, malpositioned neurons, and heterotopic neurons within the white matter (Crino 1997b) are also present in these disorders. Such conditions must, therefore, involve abnormalities of both maturation and migration, indicating that dysplastic and balloon neurons lack the cellular machinery to migrate properly through the cortical plate (Crino 1997b).

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a multisystem, dominantly inherited condition. It has a high rate of spontaneous mutations and approximately half of all patients do not have an affected parent. Two genes have been cloned for TSC. Both result in similar clinical features. The TSC1 gene, located on chromosome 9q34, codes for a novel protein called hamartin, which indirectly links the cell membrane to the cytoskeleton (Narayanan 2003). TSC2, located at chromosome 16p13.3 encodes for the protein tuberin, which may function in cellular signaling pathways (Narayanan 2003). Hamartin and tuberin interact together as part of a larger protein complex (Narayanan 2003).

The clinical diagnosis of TSC is divided into three subheadings: definite, probable, and suspect, based on the type and number of abnormalities (Roach 1992). The clinical expression of TSC is based on the location and severity of organ involvement. The primary targets are the skin, kidneys, heart, and central nervous system. Hypopigmented macules (Fig. 16.5) are the most common skin lesions and are present in as many as 90% of affected patients. Adenoma sebaceum, an angiofibromatous lesion occurring in a butterfly distribution about the nose and cheeks, is seen in 50% (Fig. 16.6). Other skin lesions include the shagreen patch (over the lumbosacral or gluteal region), café-au-lait spots, and subungual fibromas. Tumors are common and are seen in multiple organs, such as renal angiomyolipomas, cardiac rhabdomyomas, and retinal hamartomas (Table 16.6).

In the brain, the characteristic features include cortical hamartomas (cortical tubers), subependymal hamartomas (subependymal nodules), and giant cell astrocytomas. Cortical tubers are firm and nodular, with a consistency resembling the potato tubers for which they are named. On MRI cortical tubers appear as enlarged, atypically shaped gyri

Fig. 16.5 Hypopigmented macule: hypopigmented macules (ash-leaf spots) are the most common skin lesions in tuberous sclerosis and are present in as many as 90% of affected patients.

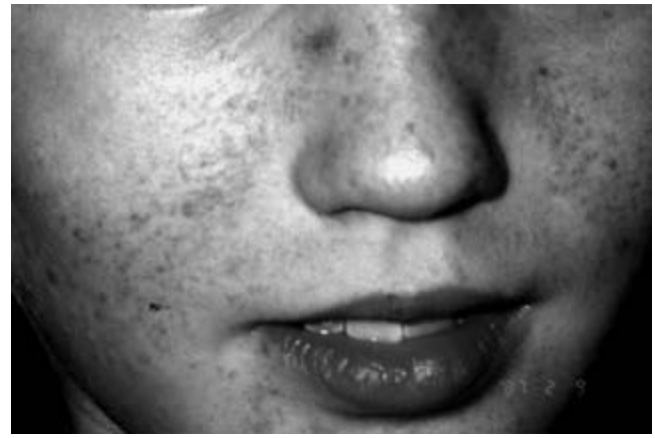

Fig. 16.6 Adenoma sebaceum, an angiofibromatous lesion occurring in a butterfly distribution about the nose and cheeks, is seen in 50% of patients with tuberous sclerosis and typically develops in adolescence.

FEATURES

Table 16.6 Tuberous Sclerosis Complex

Discriminating features

1. Cortical and retinal hamartomas (tubers)
2. Dermal angiofibromas
3. Multiple renal angiomyolipomas

Consistent feature

1. Hypomelanotic macules

Variable features

1. Epilepsy, including infantile spasms
2. Mental retardation
3. Cardiac rhabdomyomas
4. Thyroid adenoma
5. Gingival fibromas
6. Shagreen patch
7. Subungual fibromas
9. Adenoma sebaceum
10. Subependymal nodules
11. Subependymal giant cell astrocytoma

From Roach ES, Smith M, Huttenlocher P, Bhat M, Alcorn D, Hawley L: Diagnostic criteria: tuberous sclerosis complex. Report of the Diagnostic Criteria Committee of the National Tuberous Sclerosis Association. *J Child Neurol* 7:221–224, 1992.

with abnormal signal intensity in the subcortical white matter (Barkovich *et al*. 1995). Microscopically, they resemble focal cortical dysplasia (Taylor 1971) with disorganized lamination and balloon neurons (Crino 1997b). Beneath the cortex, subependymal nodules are at risk of transforming into subependymal giant cell astrocytomas (Kwiatkowski *et al*. 2003).

Cortical tubers often result in epilepsy. Under 1 year of age, infantile spasms predominate. Vigabatrin is a particularly effective treatment for infantile spasms in TSC patients (Elterman 2001), and is widely considered to be first line therapy in this setting (Chiron 1997; Hanock 1999). Later in life, generalized tonic–clonic seizures predominate, but simple and complex-partial seizures are also common. Refractory epilepsy is a common problem in TSC; surgical resection of an epileptogenic cortical tuber is possible, and is most successful when a single epileptogenic area is identified (Guerreiro 1998).

The presence of epilepsy is a predictor of cognitive impairment – this is particularly true when seizures develop under 2 years of age or when infantile spasms occur. Cognitive impairment can also be predicted by the burden of cortical tubers, with more tubers correlating with greater impairment (O'Callaghan *et al*. 2004). Autism is common in patients with TSC. It is more likely to develop in those with temporal tubers, seizure onset before age 3, or a history of infantile spasms (Bolton *et al*. 2002). Attention, language and behavioral problems are also seen. Most of these patients have epilepsy as well. In general, only those TSC patients who are cognitively normal are seizure-free, and vice versa.

Nodular, periventricular collections of small cells resembling candle drippings are termed subependymal nodules. In some instances, they will transform over time into subependymal giant cell astrocytomas (SEGAs). SEGAs typically develop in the region of the foramen of Monro and can obstruct cerebral spinal fluid flow, resulting in hydrocephalus. Presenting symptoms include headache, vomiting, obtundation, or focal neurological deficits. Early recognition is important. Incompletely calcified periventricular nodules greater than 5 mm, and nodules demonstrating gadolinium enhancement are at greater risk of transformation. Yet, the most important criterion for recognizing SEGAs is progressive enlargement of the lesion. Neuroimaging is recommended prior to 2 years to screen for such lesions, and yearly follow-up may be necessary if suspicious periventricular nodules are discovered (Nabbout 2001).

Focal cortical dysplasia

Focal cortical dysplasia (FCD) strongly resembles the cortical tubers of TSC. Macroscopically, the lesions display wider than normal gyri and blurring of the gray–white junction (Cotter *et al*. 1999). Microscopic findings include disordered cortical lamination with dysplastic, cytomegalic-appearing neurons and balloon cells. The underlying white matter is hypomyelinated and contains radially oriented balloon cells (Urbach *et al*. 2002). The histology of FCD resembles tuberous sclerosis to such an extent that they have been postulated to be the same entity, with FCD representing a forme fruste of TSC. Although patients with FCD do not demonstrate the cutaneous or other systemic manifestations of TSC, they have the same genetic alterations as TSC, an increase in TSC1 polymorphisms and loss of heterozygosity at the TSC1 locus (Becker *et al*. 2002), suggesting a common pathway in these two disorders. On MRI, FCD are slightly hyperintense on T2-weighted sequences. The hyperintense regions have a funnel-shaped appearance, with the base of the funnel oriented towards the pial surface and the tip extending to the white matter (Urbach *et al*. 2002). Seizures resulting from FCD are commonly refractory to pharmacotherapy and surgical resection is often required to control the seizures (Urbach *et al*. 2002).

Hypomelanosis of Ito

The brain malformations of hypomelanosis of Ito (HI) include abnormalities of neuronal differentiation such as cortical dysplasia and hemimegalencephaly. Malformations characteristic of later stages of brain development (heterotopia, polymicrogyria) are also seen, suggesting heterogeneity within the disorder. The skin lesions of HI consist of whorls and streaks of decreased pigmentation, which follow the

FEATURES

Table 16.7 Hypomelanosis of Ito

Discriminating feature

1. Characteristic hypomelanotic skin lesion or lesions (prominent over the ventral surface of the torso and on the flexor surface of the extremities)

Consistent feature

1. Characteristic hypomelanotic lesion

Variable features

1. Mental retardation
2. Epilepsy
3. Central nervous system migration defects (heterotopia, polymicrogyria)
4. Hemihypertrophy
5. Syndactyly

PEARLS & PERILS

Hypomelanosis of Ito

- Genetic mosaicism has been discovered in children with the disorder. Circulating lymphocytes do not demonstrate the chromosomal variations; skin fibroblasts are needed.
- If a clear family history is present, the possibility of the wrong diagnosis exists. Patients with incontinentia pigmenti may have similar appearing skin signs, which are distinguishable by biopsy.
- Although half the children with hypomelanosis of Ito have clear, hard neurological abnormalities, the prevalence of less severe problems (such as migraine, attention deficit, or learning disabilities) may be higher than expected in the other half of the population.

lines of Blaschko. There are no preceding inflammatory or vesicular eruptions as in incontintia pigmenti (see below) and the palms, soles, and mucous membranes are spared. The skin lesions are more prominent over the ventral surface of the torso and on the flexor surface of the extremities. They may be unilateral, in which case they exibit a midline cutoff. In patients with HI and hemimegalencephaly, the skin lesions are contralateral to the brain abnormality. Hypohydrosis is present over the hypopigmented areas and can be diagnosed by applying iodine and starch on the skin, followed by subcutaneous injection of pilocarpine hydrochloride. Systemic manifestations include ophthalmologic, cardiac, musculoskeletal and genital anomalies (Table 16.7).

The neurological manifestations include epilepsy and mental retardation. Generalized tonic–clonic seizures are the most common, but infantile spasms, focal, and myoclonic seizures are also observed. Autistic behaviors are sometimes seen and are usually present in children with epilepsy. Pathology may reveal polymicrogyria, heterotopia, cortical dysplasia, or hemimegalencephaly. The etiology of HI is likely to be heterogeneous; several different choromosomal abnormalities have been associated with it, but the responsible genes remain unknown.

Schizencephaly

The term schizencephaly refers to a cleft extending between the pial and lateral ventricular surfaces. Lining the cleft on both sides are abnormally small gyri, termed polymicrogyria. The presence of polymicrogyria helps distinguish this malformative lesion from destructive disorders (i.e. porencephaly) with a similar appearance (Yakolev *et al*. 1946). Schizencephaly is heterogeneous in appearance. Lesions vary in size from small closed-lip to large open-lip schizencephaly and it may occur in one or both hemispheres. Possible etiologies are similarly heterogeneous. Environmental causes, such as fetal hypotension, exposure to organic solvents, and viral infections, may be causative (Denis *et al*. 2000). Vascular anomalies have also been reported in association with schizencephaly (Denis 2000). Familial cases exist, indicating a genetic mechanism in some instances. In 1996, Brunelli *et al.* reported heterozygous mutations in the homeobox gene EMX2 in seven sporadic cases (Brunelli *et al*. 1996). The same group later reported two brothers with the same EMX2 deletion and different degrees of schizencephaly (Granata *et al*. 1997). The authors postulate that although the gene mutation is causative, environmental factors may impact on severity (Table 16.8).

The clinical severity relates to the degree of structural involvement. Unilateral clefts commonly present with hemiparesis and mild, if any, cognitive delay. Bilateral clefts, on the other hand, are associated with quadriparesis and significant cognitive impairment (Denis *et al*. 2000). Likewise, the size of the lesion is an important determinant of outcome. For example, patients with large or medium open-lip schizencephaly display significantly worse motor and

FEATURES

Table 16.8 Schizencephaly

Discriminating feature

1. Cleft extending between the pial and lateral ventricular surfaces

Consistent feature

1. Polymicrogyria lining the cleft

Variable features

1. Size of cleft (open or closed lip)
2. Unilateral or bilateral clefts
3. Epilepsy
4. Motor impairment
5. Cognitive impairment
6. Etiology (environmental versus genetic)

PEARLS & PERILS

Schizencephaly

- The walls of the schizencephalic cleft are lined by polymicrogyria. Without the adjacent gray matter, the defect is more likely to be a porencephalic cleft.
- The septum pellucidum is absent in 80–90% of patients with schizencephaly. Septo-optic dysplasia has also been described.
- Intractable seizures are common in schizencephaly. Several different seizure types (including generalized tonic–clonic, simple partial, complex partial, and infantile spasms) can exist. The severity and subtype of schizencephaly do not correlate with the presence of or type of epilepsy.

intellectual function than patients with close-lip or small open-lip lesions (Barkovich & Kjos 1992b). The severity of epilepsy, however, is generally unrelated to the structural findings (Packard *et al*. 1997).

Disorders of neuronal migration

Migration takes place between the third and fifth months of gestation (Volpe 2001). During migration, postmitotic neurons move from the ventricular and subventricular layers to their final sites within the cerebral cortex. Migration occurs in radial (perpendicular to the pial surface) and tangential (parallel to the pial surface) fashions.

Heterotopia

Heterotopia are collections of ectopic neurons located outside of the cortex (Barkovich *et al*. 2000). Unlike cortical dysplasia, the neurons within heterotopia are normal. Thus, on imaging, heterotopia are isointense with normal gray matter, lacking the abnormal signal intensity seen in dysplasia. The cortex overlying heterotopia may be abnormally thin with shallow sulci (Barkovich *et al*. 2000).

Familial periventricular heterotopia (PH) are characterized by periventricular nodules of neurons resting beneath an otherwise normal-appearing cortex (Dobyns *et al*. 1996). The nodules are rounded, irregular and separated from each other by myelinated fibers (Fig. 16.7). In PH, some neurons migrate fully to form a normal-appearing six-layer cortex, while others have a complete failure of migration and remain in nodular collections within the subependymal region. The cortex functions surprisingly well and most patients have normal intelligence. Epilepsy is common and generally develops in the midteenage years (Fox & Walsh 1999) (Table 16.9).

Familial PH commonly displays X-linked dominant inheritance and is lethal in hemizygous male embryos (Eksioglu *et al.* 1996). Approximately half of patients have a *de novo* mutation. Because epilepsy is mild or absent in approximately one-quarter of all patients, a family history is not always confirmed until neuroimaging of a patient's mother is performed. PH most often results from a mutation of the Filamin A (FLNA) gene on chromosome Xq28, which encodes a large actin-binding protein involved in structuring actin networks at the leading edge of motile cells, thus necessary for migration (Fox *et al*. 1998; Fox & Walsh 1999).

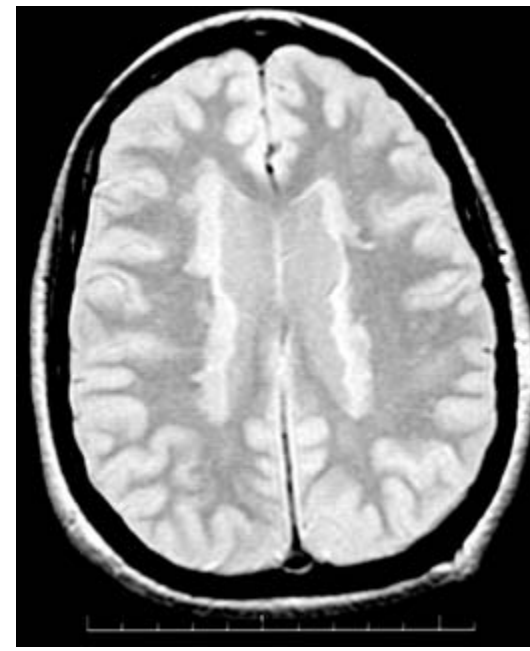

Fig. 16.7 Periventricular heterotopia (PH) are characterized by periventricular nodules of neurons resting beneath an otherwise normal-appearing cortex. The nodules are rounded, irregular and separated from each other by myelinated fibers.

FEATURES

Table 16.9 Periventricular (Nodular) Heterotopia

Discriminating feature

1. Nodular collections of neurons within the subependymal region

Consistent feature

1. Rounded nodules of neurons resting beneath an otherwise normal-appearing cortex

Variable features

1. Cognitive impairment
2. Epilepsy

Lissencephaly

Lissencephaly refers to a paucity of normal gyri and sulci resulting in a "smooth brain." It is a heterogeneous condition, which is traditionally divided into two pathologic subtypes: classical (type I) and cobblestone (type II). Radio-

PEARLS & PERILS

Familial Periventricular Heterotopia

- Nearly 25% of patients are reported to be asymptomatic, but some of these patients may actually have undiagnosed learning disabilities or other subtle deficits.
- Male patients have been described and may represent a distinct genetic cause from FLNA.

graphically, the cortex appears smooth in both types, but beyond that, few similarities exist. Classical lissencephaly results from an arrest of neuronal migration whereas cobblestone lissencephaly results from overmigration. In both cases, lissencephaly is associated with epilepsy and severe developmental delay.

Classical lissencephaly (agyria–pachygyria complex)

Most patients with classical (type I) lissencephaly have a combination of agyria (a total absence of gyri) and pachygyria (a reduced number of abnormally large gyri). Radiographically, the surface of the brain appears smooth in agyria, with diminished white matter and shallow sylvian fissures (Barkovich *et al*. 2000). In pachygyria, gyri are reduced in number and abnormally broad and flat (Barkovich *et al*. 2000). Microscopically, agyria has a disorganized outer cortical layer and a thick layer of ectopic neurons in the periventricular region; pachygyria displays better cortical organization (Table 16.10). Clinical severity is largely related to the degree of structural abnormality, with greater gyral simplification resulting in greater clinical impairment. In cases of agyria, epilepsy is universal and infantile spasms are a particularly common seizure type. Electroencephalography reveals characteristic, high-voltage beta activity (Liang *et al*. 2002). Neurodevelopmental disabilities are severe; many patients have mental retardation, spastic quadriparesis, and microcephaly. In patients with pachygyria, particularly when focal and unilateral, epilepsy and developmental delays remain common but are less severe (Çakmakçi *et al*. 2004).

Classical lissencephaly is most commonly caused by a disruption of the platelet-activating factor acetylhydrolase gene (PAFAH1B1; also known as LIS1) located on chromosome 17p13.3 (Reiner *et al*. 1993). The LIS-1 gene product interacts with microtubules, and related motor components, dynein and dynactin, as well as doublecortin, a protein that may regulate microtubule stability. Almost all patients have spontaneous, heterozygous deletions of LIS1, which are not present in the parents. The risk of having a second affected child is therefore low. When a large deletion occurs, other congenital anomalies (craniofacial, renal, cardiac, or gastrointestinal malformations) can result and together are termed the Miller–Dieker syndrome (Dobyns *et al*. 1993).

Abnormalities of the doublecortin (DCX or XLIS) gene, located on the X chromosome, are also known to cause classical lissencephaly (Gleeson *et al*. 1998). In hemizygous males, the phenotype is nearly indistinguishable from LIS1. Yet, in heterozygous females, a disorder termed double cortex (DC), also known as subcortical band heterotopia, results. In DC, the outer cortex displays normal six-layered architecture, but an inappropriate accumulation of neurons exists in the subcortical white matter (Fig. 16.8). Random inactivation of the X chromosome accounts for this pattern. Half of the neurons express a normal copy of the doublecortin gene and undergo normal migration, whereas the other half express the mutant copy and remain arrested in the subcortical white matter. In males, only one X chromosome exists, so the mutation affects all neurons. Hence, the more severe phe-

FEATURES

Table 16.10 Classical (Type I) Lissencephaly

Discriminating feature

1. Smooth cerebral cortex (agyria and pachygyria)

Consistent features

1. Abnormally thick cortex
2. Disorganized cortical lamination
3. Cognitive and motor impairment
4. Epilepsy

Variable features

1. Degree of motor and cognitive impairment
2. Severity of epilepsy
3. Etiology (LIS1 *vs*. DCX mutations)
4. Craniofacial or systemic malformations

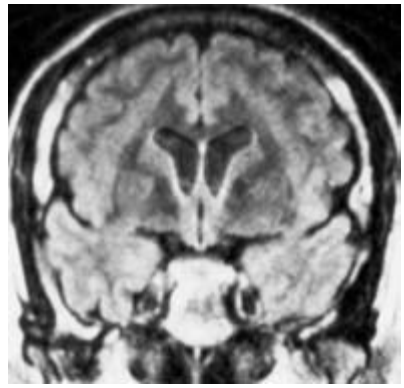

Fig. 16.8 In double cortex (DC), females heterozygous for a doublecortin gene mutation display two discrete areas of cerebral cortex. The outer layer may appear normal and has an appropriate six-layered architecture, but an inappropriate accumulation of neurons also exists in the subcortical white matter. X-inactivation likely accounts for this divergent pattern of neuronal migration. In males, only one X chromosome exists, so the mutation affects all neurons and the more severe phenotype of classical lissencephaly occurs.

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Classical (Type I) Lissencephaly

- Facial anomalies can be associated with isolated lissencephaly sequence and offer clues as to the underlying genetic defect. In Miller–Dieker Syndrome (associated with LIS1 defects), a prominent forehead, low nasal bridge, or short nose can be seen. These facial changes may become less prominent with age. In X-linked lissencephaly (XLIS), a low nasal bridge, prominent epicanthal folds, and flat midface can be seen.
- The pattern of gyral abnormality also differs between LIS1 and XLIS. Mutations of LIS1 generally have a posterior-to-anterior gradient, with agyria being most prominent posteriorly and increasing pachygyria anteriorly. Mutations of XLIS, on the other hand, are associated with an anterior-to-posterior gradient of lissencephaly.
- Cerebellar hypoplasia is more common in XLIS than LIS1 and is also seen in abnormalities of the RELN gene.
- If the birth head circumference is less than three standard deviations below normal, microlissencephaly (which is genetically distinct from LIS1 and XLIS) is the likely diagnosis.

notype of classical lissencephaly occurs in males. Females with DC display mild to moderate mental retardation and their epilepsy is generally less severe than in males with lissencephaly (Berg *et al*. 1998).

Cobblestone (type II) lissencephaly

Cobblestone lissencephaly develops from an over-migration of neurons beyond the pial surface and onto the overlying subarachnoid tissue. Cobblestone lissencephaly is sometimes associated with congenital muscular dystrophy and eye abnormalities, e.g. Fukuyama congenital muscular dystrophy (FCMD), Walker–Warburg syndrome (WWS), and muscle-eye-brain disease (MEB). These disorders are believed to result from an impairment of glycosylation (Grewal *et al*. 2003). More specifically, they affect O-mannosylation, which is important to brain, nerve and skeletal muscle, explaining the distribution of involved tissues in these disorders (Endo et al. 1999).

Of all three disorders, WWS has the most severe phenotype and is often fatal in the first year of life (Dobyns *et al*. 1989). In addition to cobblestone lissencephaly, patients with WWS sometimes display agenesis of the corpus callosum, cerebellar hypoplasia, hydrocephaly, and encephalocele. Neuroimaging reveals a thickened cortex with few, abnormally shallow sulci. The gray–white matter junction is irregular due to disorganized collections of neurons misplaced in the white matter. Hypomyelination is common (Barkovich *et al*. 2000). Ocular anomalies include microphthalmos and

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Cobblestone (Type II) Lissencephaly

- Fukuyama congenital muscular dystrophy, muscle-eye-brain disease of the Finnish type (MEB), and Walker–Warburg syndrome present in infancy with hypotonia, severe weakness, and a poor suck and cry. Walker–Warburg is the most severe form and Fukuyama congenital muscular dystrophy is the mildest of the three, but considerable overlap exists and the three disorders are sometimes difficult to distinguish on clinical grounds only.

congenital glaucoma (Barkovich *et al*. 2000). Genetically, WWS is recessively inherited. The syndrome results from mutations in the O-mannosyltransferase 1 (POMT1) gene (Beltrán-Valero de Bernabé *et al*. 2002), implicating a failure of glycosylation as the primary defect (Table 16.11).

MEB is also an autosomal recessive condition and is most prevalent in Finland. The clinical severity is intermediate to WWS and FCMD (Santavuori *et al*. 1989) as is the radiographic appearance (Barkovich *et al*. 2000). MEB results from loss of function mutations in the gene encoding protein O-linked mannose β1,2-N-acetylglucosaminyltransferase 1 (POMGnT1) (Yoshida *et al*. 2001). A genotype-phenotype correlation exists in MEB patients with mutations close to the 5′ terminus of the POMGnT1 gene resulting in a severe clinical picture and mutations at the 3′ terminus leading to milder impairments (Taniguchi *et al*. 2003).

FCMD is the mildest of the three disorders. It presents with hypotonia and global developmental delays. Seizures develop in the first year of life in half of patients (Toda *et al*. 2000). FCMD is associated with mutations of the gene fukutin on chromosome 9q31 (Toda *et al*. 1993). The exact function of fukutin is unknown, but its structure predicts

FEATURES

Table 16.11 Cobblestone (Type II) Lissencephaly

Discriminating feature

1. Excessive number of abnormally small cortical gyri (polymicrogyria)

Consistent features

1. Thickened cortex with few, abnormally shallow sulci
2. Cognitive and motor impairment

Variable features

1. Ocular abnormalities
2. Muscle abnormalities
3. Epilepsy
4. Degree of cognitive and motor impairment

it to be an enzyme involved in the modification of surface glycoproteins or glycolipids (Aravind & Koonin 1999).

FCMD is seen primarily in Japan, where 94% of the affected individuals share a common haplotype, indicating a single founder in the Japanese population (Kobayashi *et al.* 1998). Patients who are homozygous for the founder mutation have a higher residual activity of fukutin and a milder phenotype than patients with a spontaneous point mutation on the second allele (compound heterozygotes) (Toda *et al.* 2000). It is difficult to distinguish severely affected FCMD cases from WWS patients. Recently, two Turkish individuals with mutations of fukutin were reported as displaying a WWS phenotype (Beltrán-Valero de Bernabé 2003; Silan 2003). Such overlap implies a shared pathway in the pathophysiology of these disorders.

Symmetric polymicrogyria

Polymicrogyria is thought to develop at the latest stages of neuronal migration or the earliest phases of cortical organization (Barkovich *et al.* 2001). It often results from external causes such as intrauterine cytomegalovirus infection (Barkovich *et al.* 1994) or placental perfusion failure (Baker *et al.* 1996). Yet, genetic causes do exist and tend to result in focal but symmetrical lesions. Syndromes affecting every conceivable region – fronto-parietal, perisylvian, parieto-occipital – have been observed. Epilepsy and cognitive delays are common among all of the syndromes; additional symptoms depend upon the specific region(s) affected.

Bilateral frontoparietal polymicrogyria (BFPP) is characterized by bilateral, symmetric polymicrogyria in the frontoparietal regions (Chang *et al.* 2003). There is a decreasing gradient of severity from the anterior to posterior direction. The white matter is thin with areas of T2 prolongation, the ventricles are enlarged, and the pons and cerebellar vermis are abnormally small (Chang 2003). The clinical manifestations are consistent: motor abnormalities, seizures, and global developmental delay are universal (Guerrini R 2000; Chang *et al.* 2003). Cerebellar abnormalities and dysconjugate gaze are also common (Chang *et al.* 2003). The disorder has been mapped to chromosome 16q12.2–21 (Piao 2002; Chang *et al.* 2003). BFPP patients are characteristically from the Middle East or Indian subcontinent, and many share a single haplotype, indicating a common founder mutation (Piao *et al.* 2002; Chang *et al.* 2003).

Bilateral perisylvian polymicrogyria (BPP) results in a clinical syndrome manifested by mild mental retardation, epilepsy, and pseudobulbar palsy (Kuzniecky *et al.* 1993). The pseudobulbar palsy specifically affects expressive speech and feeding. BPP is often a sporadic condition. It has been described in association with unrelated disorders including neurofibromatosis type I (Balestri *et al.* 2003) and Kabuki syndrome (Powell 2003). BPP is therefore likely to be heterogeneous. In some pedigrees, BPP follows an X-linked inheritance pattern, and linkage analysis places the critical region at Xq28 (Villard *et al.* 2002). Sixty-six genes are known to exist in that interval, including the Filamin A gene.

Disorders of myelination and cortical organization

Cortical organization and myelination are the final steps of brain development and continue well after birth. Abnormalities at these stages may be less obvious on neuroimaging than earlier malformations, but they nonetheless have profound effects. Cognitive and motor impairments are common associated with both abnormalities; spasticity is more specific to problems with myelination, whereas hypotonia is frequently seen in disorders of cortical organization.

Cortical organization begins in the fifth month of gestation and continues through the first several years of life. Abnormalities of cortical organization are commonly associated with mental retardation. The most consistent anatomical correlates of mental retardation are dendritic anomalies, such as deficient branching. Such abnormalities cannot be detected by neuroimaging, explaining why many patients with mental retardation have normal MRIs.

Myelination begins in the second trimester of pregnancy and continues into adulthood. Normal myelination is impaired when oligodrendrocytes are deficient in number (either from injury or failure to proliferate) or are unable to deposit myelin around axons. Insufficient oligodendrocytes are observed in periventricular leukomalacia, in which differentiating oligodendroglia are injured and therefore unable to produce myelin. Other disorders, such as hypothyroidism, malnutrition, amino and organic acidopathies (maple syrup urine disease, homocystinuria), cause functional impairment of myelination. Primary disturbances of myelination are distinguished from leukodystrophies in that leukodystrophies result from injury to previously myelinated axons.

Neurofibromatosis type I

The primary disorder in NF relates to oncogene regulation and tumor formation, but the white matter abnormalities seen in NF can be categorized as a disorder of myelination. Additionally, a study showing increased volume of gray and white matter in children with NF1 suggests that brain overgrowth is an intrinsic component of this disease (Greenwood *et al.* 2004).

Neurofibromatosis type 1 (NF1), also known as peripheral neurofibromatosis, is an autosomal dominant, single gene defect affecting multiple organ systems. The NF1 gene localizes to chromosome 17q11.2 and encodes the protein product neurofibromin. The incidence of NF1 ranges between 1 in 3000 to 1 in 4000. Approximately 50% of patients with NF1 lack a family history and likely represent new mutations (Lynch 2002). The diagnosis is based on NIH consensus criteria and requires two or more of the following: six or

more café-au-lait spots (0.5 mm or larger in prepubertal and 1.5 mm or larger in post pubertal individuals), two or more neurofibromas of any type or one plexiform neurofibroma, axillary or groin freckling, two or more Lisch nodules, optic nerve glioma, dysplasia of the sphenoid bone or long bone cortex, or a first degree relative with NF1 (Table 16.12). Of these features, café-au-lait spots are the most easily recognized and are often the presenting feature of the disease (Fig. 16.9). They are evenly pigmented macules, which increase in size and number with age. They may be the only sign present in infancy, making a definitive diagnosis difficult to establish until later in life.

In childhood, the most common complication of NF1 is cognitive impairment. A broad range of effects are seen including low IQ, behavioral problems, and learning disabilities. IQ scores in NF1 patients have a bimodal distribution; some children have intellectual impairment whereas others do not. This separation may have its basis in the white matter T2 hyperintensities, also known as unidentified bright objects (UBOs), common to NF1 patients. They represent dysplastic glial proliferation and aberrant myelination in the underdeveloped brain. When compared to children without T2 hyperintensities, those with the lesions have significantly lower mean values for IQ and language scores and significantly impaired visuomotor integration and coordination (North 1995). T2-hyperintensities in childhood are also a predictor of cognitive dysfunction in adulthood (Hyman 2003). Denckla *et al.* (1996) found that children with NF1 had a lowering of their IQ score as a function of the distribution of UBOs, rather than the number of lesions. A study showing a correlation between increased white matter volume and visual-perceptual deficits suggests that brain overgrowth may be a factor in the associated cognitive deficits (Greenwood *et al.* 2004).

Tumors and malignancies are common in NF1, and are a major cause of morbidity. Neurofibromas, the tumors for which the disorder takes its name, are peripheral nerve sheath tumors with unpredictable growth patterns. They are benign tumors without risk of malignant transformation, and typically develop in adolescence. Although they are unlikely to cause neurological deficit, spinal neurofibromas arising from the dorsal nerve roots can lead to severe pain. Plexiform neurofibromas, on the other hand, are more likely to be present at birth. They can be found anywhere within the body and cause a variety of presenting symptoms depending on their location. Serious complications include pain, spinal cord compression, and spread to the orbit with

FEATURES

Table 16.12 Neurofibromatosis Type I (NF1)

Discriminating features

1. Plexiform neurofibromas
2. Optic nerve glioma

Consistent features

1. Multiple café-au-lait spots
2. Lisch nodules
3. Autosomal dominant inheritance

Variable features

1. Neurofibromas
2. Pilocytic astrocytoma
3. Axillary or groin freckling
4. White matter T2 hyperintensities (unidentified bright objects)
5. Macrocephaly
6. Cognitive impairment
7. Epilepsy

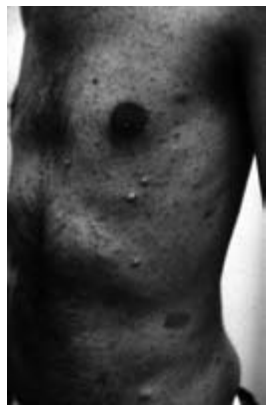

Fig. 16.9 This patient with neurofibromatosis type I demonstrates multiple cutaneous neurofibromas and café-au-lait spots.

PEARLS & PERILS

Neurofibromatosis Type I (NF1)

- Hyperpigmented patches over the midline of the back indicate an underlying neurofibroma involving the spinal cord or adjacent roots.
- The characteristic bony lesions, sphenoid wing hypoplasia, and tibial and radial pseudoarthroses should be considered diagnostic for neurofibromatosis in children
- Probably the most common false-positive diagnostic sign is multiple café-au-lait spots. Very few patients with neurofibromatosis have these features as the only markers of the disorder.
- The subcutaneous nerves in the neck are easily seen on clinical examination. They are often the nerves first recognized as involved by neurofibromatosis.
- Slit-lamp ophthalmologic examination of parents is a rapid, accurate screen for the presence of the gene.
- Pigmentary skin features are more useful in prepubertal siblings.
- Genetic testing is of limited sensitivity and a negative study does not exclude the disorder.

resulting sphenoid wing dysplasia and pulsating exophthalmos. Plexiform neurofibromas can undergo transformation to malignant peripheral nerve sheath tumors.

Optic nerve gliomas are pilocytic astrocytomas involving the optic nerve, chiasm, or tract. They usually develop prior to age 7 and can be insidious in their onset. Yearly ophthalmologic assessments are therefore important for early diagnosis and management of these tumors. Abnormalities on the ophthalmologic exam necessitate an MRI. Treatment should be withheld for stable, nonprogressive tumors, since it adds to neurological, endocrine, or visual morbidity (Tow 2003). Progressive tumors, however, do require treatment. Intraorbital tumors are best managed with resection, whereas posterior (chiasmatic or optic tract) tumors are treated with radiotherapy. Given the young age of most of these children, endocrinopathies and cognitive impairment from radiotherapy are major concerns. Chemotherapy has recently been tried as a means of either avoiding or delaying radiotherapy; initial results suggest that this approach spares the intellectual impairments common to radiotherapy (Lacaze 2003). Further study is needed to determine what the role of chemotherapy should be in these patients.

Other malignancies observed in NF1 include CNS tumors (particularly astrocytomas), pheochromocytomas, and leukemia. Given the prevalence of tumors in NF1, it should come as no surprise that an oncogene is responsible for the condition; neurofibromin functions as a tumor suppressor protein, the loss of which promotes tumor formation.

The work-up for NF1 is aimed at the early identification of potential complications, with tumor formation being the main concern. The American Academy of Pediatrics Committee on Genetics recommends yearly physical examinations and ophthalmologic assessments. The physical examination focuses on the organ systems involved. The skin is screened for new neurofibromas or plexiform neurofibromas. Blood pressure is followed to assess for renal (renal artery stenosis) or endocrine (pheochromocytomas and adrenal tumors) abnormalities. A skeletal examination looks for pseudoarthrosis of the tibia, bowing of the long bones, scoliosis, and orbital defects. The neurological examination may reveal macrocephaly, learning disabilities, or cognitive impairment. The ophthalmologic evaluation helps exclude optic nerve gliomas, choroidal hamartomas, and Lisch nodules.

Laboratory investigations confirm the diagnosis and explore any abnormalities disclosed on the physical examination. Molecular genetic testing is available for NF1, but the size and complexity of the gene combined with the genetic heterogeneity of the disorder have been obstacles to routine DNA testing. Gene testing is nonetheless helpful for genetic counseling and even makes preimplantation diagnosis possible (Verlinsky 2002). Because tumors are the most serious consequence of NF1, neuroimaging, preferably with MRI, is an important tool for management of this condition. Imaging is required whenever the history or physical examination raise a question of tumor development.

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Neurofibromatosis Type II (NF2)

- A careful family history should be obtained from all patients with acoustic neuromas. The younger the patient, the more likely the diagnosis of NF2.
- The tumors of NF2 do not seem to respond to hormonal changes as do those of NF1.

Neurofibromatosis type II

Like NF1, neurofibromatosis type II (NF2), is an autosomal dominant, single gene deficit, which, in NF2, localizes to chromosome 22. The gene product, merlin, also has tumor suppressor function. Tumors and malignancies are, therefore, common in both conditions. Beyond that, few similarities exist. Café-au-lait spots are rarely seen in NF2 and neurofibromas are surprisingly uncommon considering that the disorder takes its name from this tumor type. NF2 is seen much less commonly than NF1, with an incidence of only 1:30 000 to 1:40 000.

Common tumors in NF2 include schwannomas (which are usually multiple), meningiomas, ependymomas, and gliomas. Vestibulo-cochlear schwannomas are particularly common and sometimes bilateral (in which case, a diagnosis of NF2 is certain). Roughly half of NF2 patients present because of hearing loss, tinnitus, and vertigo resulting from a vestibulo-cochlear schwannoma. The peak age of diagnosis is the third decade. In children, ocular abnormalities (diplopia, vision loss) are the most common presenting symptoms (MacCollin *et al.* 1998). These are caused by hamartomas of the retina, optic nerve sheath meningiomas, or juvenile posterior subcapsular lenticular opacities (a specific type of cataract). Meningiomas at a young age should also raise a suspicion of NF2; both intracranial and spinal meningiomas occur. Schwannomas and ependymomas may develop in the spine, in which case, back pain and paraplegia may result (Table 16.13).

Disorders of vascular supply of brain tissue (known or postulated)

The following disorders result from vascular abnormalities, and are therefore difficult to organize within the embryological classification presented above. However, each results in developmental abnormalities of the brain, justifying inclusion in this discussion.

FEATURES

Table 16.13 Neurofibromatosis Type II

Discriminating features

1. Bilateral acoustic neuromas
2. Multiple schwannomas
3. Multiple meningiomas

Consistent features

1. Bilateral deafness
2. Fewer than five café-au-lait spots
3. Autosomal dominant inheritance

Variable features

1. Tinnitis
2. Headaches
3. Cranial nerve palsy
4. Retinal hamartomas

Bilateral parasagittal parieto-occipital polymicrogyria

Unlike the other symmetrical polymicrogyria syndromes, bilateral parasagittal parieto-occipital polymicrogyria is unlikely to have a genetic basis. Of nine patients described, none had a familial distribution. Given that the lesion occurs in a vascular watershed region, perfusion failure is postulated to be the cause. All patients develop seizures and cognitive abilities range from normal to mild retardation (Guerrini 1997) (Fig. 16.10).

Incontinentia pigmenti

Incontinentia pigmenti is a rare, X-linked, dominant, neurocutaneous disorder with the onset of skin changes in the first 6 weeks of life. The cutaneous disorder follows a characteristic evolution from vesicular to verrucous to hyperpigmented and finally atrophic changes. The vesicles and bullae from the original eruption in infancy later give rise to the characteristic swirling pattern of hyperpigmentation. Hair, nail, dental and ophthalmologic abnormalities are also observed. Neurologically, these infants may develop epilepsy, mental retardation, microcephaly, spasticity, or ataxia. A recent case report demonstrating periventricular hemorrhagic infarctions in infancy strongly suggests microangiopathy as the cause of the neurological changes (Hennel 2003). The gene for incontinentia pigmenti has been mapped to Xq28, and is thought to be lethal in males, accounting for the 20:1 female to male predominance (Table 16.14).

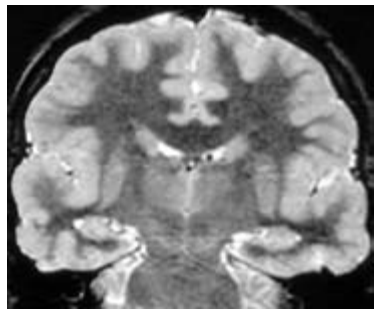

Fig. 16.10 Bilateral perisylvian polymicrogyria (BPP) results in a clinical syndrome manifested by mild mental retardation, epilepsy, and pseudobulbar palsy. The pseudobulbar palsy specifically affects expressive speech and feeding, as would be predicted by the motor homunculus.

PEARLS & PERILS

Incontinentia Pigmenti

- Boys with the disorder have been diagnosed (14 out of 255 cases). Some have had polyploidy of the X chromosome, notably Klinefelter's syndrome.
- Children with incontinentia pigmenti are small-for-gestational-age infants more frequently than predicted in the general population.
- Retrolental fibroplasias in an infant not exposed to a high concentration oxygen should suggest the diagnosis of incontinentia pigmenti.

Sturge–Weber syndrome

Sturge–Weber syndrome is characterized by angiomata of the leptomeninges and skin (Fig. 16.11). The cutaneous lesion, also known as a port-wine stain, typically involves the ophthalmic and maxillary distributions of the trigeminal nerve. The leptomeningeal angiomata may be either unilateral or bilateral, but unilateral lesions are more common. The specific neurological effects are dependent on the location of the lesion, which is most commonly parietal or occipital. Neurological impairment results in large part from stasis and a vascular steal phenomenon. Laminar cortical necrosis with neuronal loss, gliosis, cerebral atrophy, and calcifications are seen histologically. The calcifications take on a classic train-track appearance on plain films and CT. MRI, if done, should be performed with gadolinium to allow for appreciation of the angiomata. The clinical manifestations include hemiparesis, stroke-like episodes, mental

FEATURES

Table 16.14 Incontinentia Pigmenti

Discriminating feature

1. Characteristic swirled hyperpigmented lesions

Consistent feature

1. Female sex

Variable features

1. Mental retardation
2. Epilepsy
3. Hemihypertrophy

Fig. 16.11 This patient with Sturge–Weber syndrome demonstrates the typical leptomeningeal angiomata (port-wine stain) of the ophthalmic and maxillary distributions of the trigeminal nerve. Leptomeningeal angiomata may be either unilateral or bilateral, but unilateral lesions are more common.

retardation, epilepsy, and headaches. Epilepsy is present in 75–90% of patients, and the seizures are typically focal. Many patients have refractory epilepsy, in which case cortical resection and possibly hemispherectomy are considered. An important non-neurological effect is glaucoma, which can occur at any age (Table 16.15).

Ataxia-telangiectasia

The reader is referred to Chapter 9 on Movement Disorders for a discussion of this condition.

Clinical aspects of nervous system malformations

Clinical-radiographic correlation

Structure predicts function. Hence, most cerebral malformations display a clinical-radiographic correlation. Diffuse lesions, such as classical lissencephaly, are associated with severe global developmental delay. Bilateral, focal lesions may result in bilateral motor dysfunction and moderate to severe developmental impairment (Barkovich & Kjos 1992a). Unilateral lesions can be associated with contralateral hemiplegia and mild, if any, cognitive delay. The size of focal lesions is an important determinant of outcome. For example, patients with large or medium open-lip schizencephaly display significantly worse motor and intellectual function than patients with close-lip or small open-lip lesions (Barkovich & Kjos 1992b). Location is also relevant; frontal dysplasia and polymicrogyria are strongly associated with motor impairment (Barkovich & Kjos 1992b; Guerrini *et al.* 2000).

FEATURES

Table 16.15 Sturge–Weber Syndrome

Discriminating features

1. Port-wine stain (nevus flammeus) in trigeminal distribution
2. Ipsilateral meningocortical venous malformation

Consistent features

1. Progressive cortical deficits
2. Epilepsy (focal)
3. Glaucoma

Variable features

1. Cutaneous vascular malformations on trunk or limbs
2. Mental retardation
3. Hemihypertrophy/hemiatrophy

PEARLS & PERILS

Sturge–Weber Syndrome

- Hemihypertrophy, seen in the disorder, is usually associated with a vascular malformation of the affected limb or limbs. A similar enlargement is seen in the skull ipsilateral to the port-wine stain.
- Migraine is more common in Sturge–Weber patients than in the general population, and it is more likely to occur at younger ages and be associated with neurological deficits.

Clinical-genetic correlation

Genetic heterogeneity makes it difficult to predict the clinical phenotype solely from knowing the gene involved. Nonetheless, occasionally, knowledge of the details of the mutation aid in determining the prognosis. In general, the degree of residual protein function correlates with severity. Function can range from complete absence of protein production, as is seen in large deletions, to normal production with reduced activity, which may occur with certain point mutations. Such is the case with lissencephaly/subcortical band heterotopia from DCX mutations. Familial cases, most of which possess missense mutations, have a milder phenotype than sporadic cases in which protein truncation mutations are more common (Matsumoto *et al.* 2001). For X-linked disorders, X inactivation is tremendously important in determining the phenotype, but is nearly impossible to study since brain tissue, which is optimal for looking at this question, is difficult to obtain. Cultured fibroblasts or lymphocytes can be used as a substitute, but the results from these tissues are less conclusive. In deletions, it is important to consider the impact of contiguous genes, since their involvement can alter the clinical phenotype. Such is the case in Miller–Dieker syndrome, where impairment of genes contiguous to LIS1 accounts for a more severe degree of lissencephaly and other systemic anomalies (Cardoso *et al.* 2003). Gene–gene interactions are also relevant. In periventricular heterotopia, only some of the neurons demonstrate a failure of migration whereas others go on to form a normal six-layered cortex. Traditionally, this was attributed to genetic mosaicism from random X-inactivation. Yet, males

CONSIDER CONSULTATION WHEN…

Endocrinology

- Consider an endocrinology consultation for patients with holoprosencephaly, septo-optic dysplasia, or other abnormalities of prosencephalic development. Consultation with an endocrinologist is essential if hypoglycemia, diabetes insipidus, growth hormone deficiency, or other signs of hypothalamic-pituitary dysfunction are present.
- Also consider an endocrine consultation for patients with catamenial epilepsy who are refractory to traditional antiepileptic agents.

Ophthalmology

- Patients with septo-optic dysplasia or other abnormalities of prosencephalic development are at risk of optic nerve atrophy. Patients with severe cortical malformations, such as lissencephaly, are more likely to have cortical visual impairment. Walker–Warburg, muscle-eye-brain, and Fukuyama congenital muscular dystrophy patients may exhibit myopia, strabismus, congenital glaucoma, retinal folds, and retinal and optic nerve hypoplasia.

Orthopedics

- Axial hypotonia with spasticity of the extremities is common in many cortical malformations such as lissencephaly. Such patients often require bracing, botulinum toxin, or surgery to reduce spasticity and contractures. In disorders with accompanying muscle disease, such as Fukuyama congenital muscular dystrophy, severe hypotonia and weakness place patients at risk of developing scoliosis.

Cardiology

- For patients with Miller–Dieker syndrome, consideration should be given to performing an echocardiogram, since congenital heart disease can associated with the disorder.
- Cardiac rhabdomyomas may be found in children with tuberous sclerosis. They are generally clinically insignificant and usually regress over time, but they may cause mechanical obstruction, heart failure or arrythmias.

Pulmonary/Gastroenterology

- Patients with severe motor impairment from their cortical malformations are at risk of developing aspiration pneumonia. A swallow study should be considered if coughing or gagging develop with feeds. G-tube placement and cessation of oral feeds may be required in patients with aspiration.

Genetics

- Family planning is one of the most important social issues related to brain malformations. Consultation with a geneticist and genetics counselor is strongly advised, particularly for parents who are considering having more children.

with PH from FLNA mutations have been described (Sheen *et al*. 2001), arguing against X-inactivation as the basis for the divergent behavior of neurons in PH. The highly homologous protein, Filamin B (FLNB), may help compensate for the loss of FLNA function and allow for proper neuronal migration of some neurons (Sheen *et al*. 2002).

As a result of genetic heterogeneity, abnormalities of a given gene can result in a wide spectrum of different phenotypes. Conversely, a single phenotype may be caused by different genes. An important issue for the clinician to recognize is that the initial description of genetic conditions is biased towards more severe phenotypes. Over time, as more patients are evaluated for a given genetic condition, the known phenotypes broaden to include more subtle cases.

Conclusion

For children with disorders of nervous system development there are few specific therapeutic interventions available beyond physical, occupational and speech therapy and remedial education. Epilepsy resulting from brain malformations is often refractory to pharmacotherapy but surgical resection of epileptogenic cortical malformations may be an option for some of these children. A crucial role for the treating physician is to provide counseling and guidance. This is particularly important in newly diagnosed children whose parents are burdened by uncertainty. A thoughtful, compassionate approach to the radiographic and genetic assessment can offer the parents insight to their child's condition, even given the limitations in predicting outcome. The genetic evaluation is particularly important for purposes of family planning.

Annotated bibliography

Barkovich AJ, Kuzniecky RI, Dobyns WB, Jackson GD, Becker LE, Evrard P: A classification scheme for malformations of cortical development. Neuropediatrics 27:59–63, 1996.

Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB: Classification system for malformations of cortical development. Neurology 57:2168–2178, 2001.

In the above papers, Barkovich et al. identify a classification scheme for disorders of cortical development, arranging them based on the earliest embryological stage in which the malformation has its origin. The more recent paper serves as an update to the original.

Taylor DC, Falconer MA, Bruton CJ, Corsellis JAN: Focal dysplasia of the cerebral cortex in epilepsy. J Neurol Neurosurg Psych 34:369–387, 1971.

Taylor describes the neuropathology of focal cortical dysplasia. This description includes features such as giant dysmorphic neurons and balloon cells. Focal cortical dysplasia with these features is now referred to as Taylor-type dysplasia

Tassi L, Colombo N, Garbelli R et al.: Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. Brain 125:1719–32, 2002.

In this paper, three subtypes of focal cortical dysplasia, along with their clinical and radiographic correlates, are described. Patients with Taylor-type cortical dysplasia have readily identifiable lesions on imaging and the best surgical outcome postoperatively with 75% being seizure-free after 1 year of follow-up. This study highlights the relationship of pathology to the clinical phenotype.

Barkovich AJ, Kjos BO: Nonlissencephalic cortical dysplasias: correlation of imaging findings with clinical deficits. AJNR 13:104–106, 1992a.

Barkovich AJ, Kjos BO: Schizencephaly: correlation of clinical findings with MR characteristics. AJNR 13:104–106, 1992b.

Both of the above papers highlight the clinical-radiographic correlation of brain malformations. The first focuses on cortical dysplasias and the second on schizencephaly. In both cases, the anatomy of the lesion, as identified based on neuroimaging, is shown to correlate with the clinical outcome.

Cardoso C, Leventer RJ, Ward HL et al.: Refinement of a 400-kb critical region allows genotypic differentiation between isolated lissencephaly, Miller–Dieker syndrome, and other phenotypes secondary to deletions of 17p13.3. Am J Hum Genet 72:918–30, 2003.

Toda T, Kobayashi K, Kondo-Iida E, Sasaki J, Nakamura Y: The Fukuyama congenital muscular dystrophy story. Neuromusc Dis 10:153–159, 2000.

Both of the above papers demonstrate genotype-phenotype correlations. The first demonstrates how deletions of contiguous genes in the 17p13.3 locus can result in varied clinical phenotypes, ranging from isolated lissencephaly to the Miller–Dieker syndrome. In the second, Fukuyama congenital muscular dystrophy patients homozygous for the founder mutation of fukutin are demonstrated to have a milder phenotype of the disorder than those with a spontaneous point mutation on the second allele.

CHAPTER 17

Disorders of Motor Execution I: Cerebral Palsy

Barry S. Russman, MD

OUTLINE

Introduction and definition
Historical review
Classification
Epidemiology
Pathogenesis
Diagnosis
Evaluation of a patient with cerebral palsy
Associated problems
Common health problems
Treatment
Prevention
Prognosis
Prognosis for vocation
Conclusions and summary

Introduction and definition

Cerebral palsy is "characterized by aberrant control of movement or posture of a patient, appearing early in life (secondary to a central nervous system lesion, damage or dysfunction), and not the result of a recognized progressive or degenerative brain disease" (Nelson & Ellenberg 1978). In addition to motor deficits, the patient may suffer from other manifestations of cerebral dysfunction, including mental retardation, epilepsy, sensory deficits (hearing or visual loss), learning disabilities and emotional problems, but these problems are not implied by a diagnosis of cerebral palsy. The diagnosis is established by a history that the patient is not losing motor skills (i.e. the patient does not have a progressive disease). Physical examination (which may change over time because of tone changes and contracture development with growth), supplemented by laboratory tests when needed, localizes the problem to the central nervous system and not to the motor unit (anterior horn cell, peripheral nerve, nerve-muscle junction, or muscle). Efforts to establish an etiology should be made. Understanding the etiology, together with the specific type of cerebral palsy (spastic, dyskinetic, etc.) can lead to a prognosis and rational treatment program.

Cerebral palsy often has been referred to as a "wastebasket" term. The entity cerebral palsy is delimited chiefly for purposes of treatment: individuals with conditions designated by this term often have similar needs for rehabilitation, education, medical and social services.

Historical review

The words cerebral palsy became prominent as a result of the work of Little, an English surgeon in the l860s. He defined a specific type of cerebral palsy, namely, spastic diplegia, which is still referred to as Little's disease. In addition, he is responsible for the generally erroneous suggestion that birth anoxia was the primary cause of cerebral palsy. Sigmund Freud in his classic l897 text, *Infantile Cerebral Palsy*, emphasized the existence of associated problems such as mental retardation, epilepsy and visual disturbances and was the first to suggest that cerebral palsy was not primarily caused by birth anoxia (Freud 1968).

During the early twentieth century, most cerebral palsy research was related to the development of different treatment programs. The gamut ranged from inhibiting movement with braces to facilitating movement with various stimulation techniques (Weiss & Betts 1967). Much of the confusion and disagreement regarding treatment related to a lack of knowledge regarding the etiology and pathology. Further, an acceptable classification system that would allow comparison of similar patients and treatment programs had not yet been developed.

In l956 a classification system finally was established. Also, epidemiologic studies were launched in the United States, Western Australia, and Sweden (Nelson & Ellenberg 1978; Stanley & English 1986; Hagberg *et al.* 2001). The study by Nelson and Ellenberg, the National Collaborative Perinatal Project (NCPP), deserves special mention, as it is the only prospective one. Twelve hospitals in the United States enrolled over 50 000 pregnant mothers the first time they presented themselves for prenatal care. Each mother's pregnancy, labor and delivery were monitored using a carefully designed protocol. The child was evaluated in the delivery room, at 1 day of age, 3 days of age, and at periodic intervals until 7 years of age. Included in these evaluations were developmental, neurological and psychological examinations. Much of the information presented in the following sections

of this chapter will be summaries of the studies from the NCPP, as well as from the Swedish and Western Australian reports.

Classification

The classification system in common use today was published in 1956, the effort of a committee of the American Academy of Cerebral Palsy (Minear 1956) (Table 17.1). The system is a clinical one based on the physiology of the motor dysfunction and the number of limbs involved. The system establishes an orderly approach to describing a patient's disability. However, it does not afford insight into the etiology, pathology or the patient's functional deficits. Although this classification system is widely used, there are problems with it. Blair and Stanley showed that the inter-observer diagnostic agreement did not exceed 55% even after training in the use of the system (Blair & Stanley 1985).

Physiologic (motor) grouping

Table 17.1 summarizes the motor and anatomic groupings. *Spasticity* is defined as a velocity-dependent increased muscle tone, determined by passively flexing and extending muscle groups across a joint (Lance 1980). A satisfactory, reproducible system of grading muscle tone has never been developed, although the Ashworth and Tardieu scales are commonly used in research (Boyd & Graham 1999). Most physicians describe the tone as being normal, increased or decreased. Associated with spasticity are enhanced deep tendon reflexes, usually associated with clonus and extensor plantar responses. However, the latter are sometimes difficult to elicit in the infant and even in the older child with spastic cerebral palsy.

Dyskinesia is defined as abnormal motor movements that are most obvious when the patient initiates a movement. The motor patterns and posture of patients with dyskinesia are secondary to inadequate regulation of muscle tone and coordination (Brun & Kyllerman 1979; Kyllerman *et al.* 1982; Kyllerman 1982). When the patient is totally relaxed, usually in the supine position, a full range of motion and decreased muscle tone may be found. Dyskinetic patients are subdivided into two subgroups. The hyperkinetic or *choreo-athetoid* children show purposeless, often massive involuntary movements with motor overflow, that is, the initiation of a movement of one extremity leads to movement of other muscle groups. The *dystonic* group manifest abnormal shifts of general muscle tone induced by movement. Typically, these children assume and retain abnormal and distorted postures in a stereotyped pattern (Fig.17.1). Both types of dyskinesia may occur in the same patient. Dystonia may be confused with spasticity in that passive range of motion in both situations may be difficult. Examining the patient in the supine position commonly will *not* alter the muscle tone in the spastic patient, but usually reveals low tone in the patient with dystonia. It is important to distinguish the specific physiological abnormality as far as possible because the etiology, treatment, associated problems and prognosis are different (see sections on diagnosis and treatment).

Patients with *ataxias* have a disturbance of the coordination of voluntary movements due to muscle dyssynergia. These patients may be *hypotonic* during the first 2 or 3 years of life. They commonly walk with a wide-based gait and have a mild intention tremor (dysmetria). A rare subgroup in the ataxia category is called the disequilibrium syndrome (Sanner & Hagberg 1974). These patients not only have dysmetria but also a pronounced difficulty in maintaining posture and equilibrium. They tend to be hypotonic for the first several years of life prior to the development of useful function. Mental retardation is almost invariable in this group. Until further studies are published, patients placed in this category should be considered to have a genetic disease.

The fourth category that is commonly used in the physiologic and motor classification is the *mixed group*. Patients in this category commonly have mild spasticity, dystonia, and/or athetoid movements. Ataxia may also be a component of the motoric dysfunction in patients placed in this group.

TABLE 17.1

Classification of Cerebral Palsy by Physiology and Anatomy

Physiology	Anatomy
Spasticity	Diplegia
Dyskinesia	Hemiplegia
• Choreoathetosis	
• Dystonia	
Ataxia	Quadriplegia
Mixed	Double hemiplegia

PEARLS & PERILS

Classification

- The original classification system for cerebral palsy is a descriptive one, based on anatomy and physiology of the impairment. This system affords a shorthand way of communicating the patient's deficits. It does not afford a prognosis or a treatment program.
- A recently validated system classifies the patients by their *function*. This affords a shorthand way of communicating the patients' functional deficits. A correlation exists between the function class and associated problems.

Anatomic grouping

Diplegia refers to involvement predominantly of the legs. *Quadriplegia* refers to dysfunction of all four extremities; in

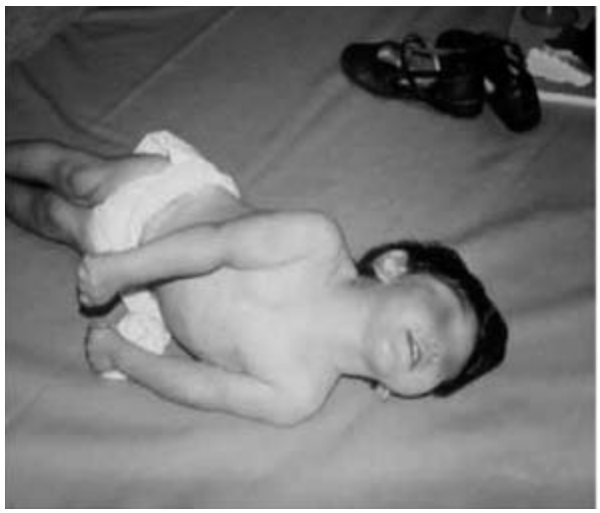

Fig. 17.1 This patient's arms and legs are extended and some twisting of the upper extremities is quite noticeable; an excellent example of dystonia.

some children one upper extremity might be less involved; the term triplegia then would be substituted. *Hemiplegia* refers to individuals with unilateral motor dysfunction; and in most children the upper extremity is more severely involved than the lower. Finally, an unusual situation may occur where the upper extremities are much more involved than the lowers; the term *double hemiplegia* is applied to this group of patients.

Functional classification

A functional classification now in general usage was first described by Palisano *et al*. in 1997. The following is a brief synopsis of the scale. Level 1 describes a child who is basically clumsy but otherwise has full mobility. The child in level 2 walks without assistive devices but has limitations on walking outdoors and in the community. The level 3 patient walks with assisted mobility devices and does have some limitations in walking outdoors. "Differences are seen in the degree of achievement of functional mobility. Children in level 3 need assistive mobility devices and frequently orthoses to walk; while children in level 2 do not require assistive mobility devices after age 4." Level 4 children have self-mobility that is severely limited even with the use of assistive technology. The level 5 children have no self-mobility even with assistive technology. Subsequent studies have found that this classification system also correlates with some of the associated problems (Beckung & Hagberg 2000). For example, the level 4 and 5 children correlate significantly with the presence of cognitive disabilities and epilepsy. Wood noted the stability of this system (Wood & Rosenbaum 2000). Once the child was classified into one of the five levels by age 2 years, prediction as to what the child could accomplish motorically was accurate (Table 17.2).

Epidemiology

Cerebral palsy is a common problem. The worldwide incidence of cerebral palsy is approximately 2–2.5 per 1000 live births (Hagberg *et al*. 2001). Each year about 10 000 babies born in the United States develop cerebral palsy (Boyle *et al*. 1996). Cerebral palsy occurs more commonly in children who are born very prematurely than at term. Data from Sweden on 241 children with cerebral palsy indicate that 36% were born at a gestational age (GA) of less than 28 weeks; 25% at 28–32 weeks GA; 2.5% at 32–38 weeks GA; and 28.5% at term (Hagberg *et al*. 2001). The types and severity of cerebral palsy are clinically well established. The same study reported that 33% of the cerebral palsy population was hemiplegic, 44% diplegic, and 6% quadriplegic.

Pathogenesis

Cerebral palsy is a syndrome consisting of motor deficits experienced by the patient of many etiologies. Therefore, the pathogenesis can only be discussed as it relates to the specific cause that can be identified in approximately 50% of the patients. Under some conditions, it is possible to establish a specific etiology of cerebral palsy, namely *genetic syndromes* (Fisher & Russman 1974; Hughes & Newton 1992), *congeni-*

TABLE 17.2

Functional Classification System

Level 1: Clumsy child; no assistive devices
Level 2: Walks independently but limited in outdoor activities
Level 3: Walks with assistive mobility devices
Level 4: Self-mobility severely limited even with assistive devices
Level 5: No self-mobility even with assistive devices

PEARLS & PERILS

Epidemiology

- Cerebral palsy as an outcome of difficult labor has not been clearly established.
- Most children who had low birth weight, breech presentation, or clinical depression at birth were perfectly normal 7 years later.
- Risk factors or causation are established in only 50% of patients with cerebral palsy
- A diagnosis of cerebral palsy is based on history and physical examination, not on the presence or absence of risk factors. The lack of a history of prematurity or "birth trauma" neither precludes nor implies the diagnosis of cerebral palsy.

tal malformations, and *in utero* or perinatal central nervous systems infections. In 1957 Kurland omitted congenital malformations as an etiology of cerebral palsy. Nelson and Ellenberg (1978) did not exclude malformations, but were careful to exclude progressive disorders. This latter position on the etiology of cerebral palsy was cited in the Practice Parameter: Diagnostic assessment of the child with cerebral palsy of the AAN and CNS (Ashwal *et al.* 2004). Nelson *et al.* (1998) found that a group of neonates later diagnosed with cerebral palsy had elevated blood levels of cytokines and coagulation factors in neonatal blood samples, suggesting an injury model for cerebral palsy. The discovery that specific gene defects are responsible for many developmental brain anomalies might warrant distinguishing these malformations from cerebral palsy, even though the manifestations are often quite similar. As pointed out by Stanley, the main contribution from the NCPP study is a very important negative finding, that cerebral palsy syndromes overall are not causally related to perinatal problems, particularly asphyxia. It may well be that developmental malformations of the fetal brain are responsible for the perinatal and postnatal problems that, heretofore, have been ascribed to poor management of the labor and delivery. Corroborating Freud's speculation of over 100 years ago, Stanley wrote: "*Difficult birth, in certain cases, is merely a symptom of deeper effects that influence the development of the fetus*" (Stanley 1994). A specific cause cannot be identified in over one-half of the patients. Although several risk factors for the development of cerebral palsy have been clearly identified, the majority of children born with known risk factors will *not* develop cerebral palsy (Table 17.3).

The major controversy regarding the etiology of cerebral palsy relates to perinatal events. Little argued that asphyxia and/or obstetric "factors" were definite causes of cerebral palsy. However, the Swedish and NCPP studies have shown only that these problems are risk factors. For example, only 20% of children with Apgar scores less than 3 at 5 minutes developed cerebral palsy in the NCPP (Nelson & Ellenberg 1981). Furthermore if the Apgar score at 5 minutes was more than 7, it was unlikely that obstetric "complication" caused the brain damage.

TABLE 17.3

Cerebral Palsy: Etiologic Groups

Obvious prenatal
- Simple inheritance
- Defined prenatal syndromes
- Unequivocal prenatal syndromes
- Cerebral malformations

Potential prenatal or prenatal
- Presence of one or more risk factors

Obvious postnatal

Unknown: none of the above

Risk factors correlated with prenatal and perinatal events

In many patients with cerebral palsy, only "risk factors" can be identified. A univariate analysis of risks associated with the future development of cerebral palsy identified separate *maternal, pregnancy, labor* and *delivery* characteristics (Nelson & Ellenberg 1985). Such *maternal* factors, as level of maternal education, marital status, parity, paternal age, pregnancy spacing, smoking history and intercourse frequency were *not* associated with an increased risk of the child developing cerebral palsy. Unexpectedly, a history of maternal diabetes, and the length of time to become pregnant, also was not predictive of future cerebral palsy. On the other hand, in this particular analysis, maternal mental retardation, epilepsy and hyperthyroidism prior to the pregnancy were significantly associated with the development of cerebral palsy in the child (Table 17.4).

Pregnancy problems, which were identified as relative risk factors associated with future cerebral palsy, included severe toxemia and incompetent cervix, when associated with premature birth. Third trimester bleeding, but not first or second trimester bleeding was also a significant factor. Kidney and bladder infections, radiation exposure and hyperemesis gravidarum were not associated with increased risk. In a more recent study of risk factors and pregnancy, Grether *et al.* emphasized the very high prevalence of cerebral palsy in twins compared to singletons (Grether *et al*.1992).

Risk factors identified during the *labor* and *delivery* periods included vaginal bleeding at the time of admission, and placental complications such as abruptio, premature rupture of the membranes, chorionitis, and breech presentation. However, many of these risk factors were significant only if a baby weighed less than 2500 g at birth. In addition, some

TABLE 17.4

Cerebral Palsy: Risk Factors

Prenatal
- Two or more previous abortions
- Maternal retardation
- Bleeding during pregnancy in births at term
- Pre-eclamptic signs
- Small-for-gestational age baby
- Placental infection
- Multiple births

Perinatal
- Asphyxia producing clinical encephalopathy
- Cerebral hemorrhage
- Placental ablation
- Hypoxia
- Hyperbilirubinemia
- Central nervous system infection

of the risk factors, such as oxytocin augmentation, cord prolapse, or breech delivery, were relevant only if they were associated with low Apgar scores.

Risk factors associated with type of cerebral palsy

The Swedish studies also correlated the anatomical and physiological abnormalities with prenatal and perinatal risk factors. Children with spastic diplegia were almost universally appropriate for gestational age; 55% were born preterm. Furthermore, there was a lower proportion of prenatal risk factors among this group of infants. The diplegic children born at term had a much more complex situation, having both prenatal and perinatal risk factors in a much higher frequency. These included toxemia, placental infarction, and evidence of intrauterine asphyxia, including meconium staining.

The dyskinetic syndromes are most likely to occur with perinatal risk factors, such as asphyxia and hyperbilirubinemia. Of these patients, 37%, in addition to having perinatal risk factors, also had prenatal risk factors present such as fetal deprivation (small for gestational age) (Brun & Kyllerman 1979; Kyllerman *et al*. 1982; Kyllerman 1982). Rosenbloom has suggested that a pattern of perinatal events in term babies may lead to dyskinetic cerebral palsy, a pattern that differs from that leading to spastic quadriplegia (Rosenbloom 1994). Based on an analysis of 17 patients with dyskinetic cerebral palsy 10 experienced severe fetal distress occurring late in labor; the birth asphyxia was severe but short-lived and the hypoxic-ischemic encephalopathy was only mild or moderate.

Diagnosis

Cerebral palsy is easily diagnosed in a child who is not developing motor skills, whose muscle tone is generally increased and who is not regressing. However, the child who is not developing normally and who has normal or decreased muscle tone presents a common diagnostic problem. Persistent primitive reflexes or the lack of development of the protective reflexes at the expected time are important findings on the neurological examination, suggesting corticospinal tract impairment (O'Shea *et al.* 1992). Moro reflex should be unobtainable after 6 months of age (Fig. 17.1). The asymmetric tonic neck response should never be obligatory when the patient is placed in the appropriate position; that is, the infant should "break" the tonic neck posture spontaneously after 15–30 seconds, and it should be unobtainable after 6 months of age. The side protective reflexes should be evident after 5 months of age and the parachute reflex is typically obtained after 10 months of age. Another important observation is the finding of hand preference. A child should not cross the midline when reaching for an object until after 1 year of age and should not show clear hand preference on examination until 18 to 24 months of age. The development of handedness prior to this time suggests a hemiplegia or a brachial plexus injury.

PEARLS & PERILS

Diagnosis

- Handedness should not develop before 18–24 months of age; look for dysfunction on the less used side.
- Poor head control, present at 3 months of age, should make one suspicious of cerebral palsy. The presence of risk factors should heighten the diagnostic concern.
- The most common diagnosis for the floppy baby is cerebral palsy. It is not uncommon for a floppy baby to develop a dyskinesia by or even after age 2 years.
- Cerebral palsy does not mean mental retardation. It is important to highlight this issue when discussing the diagnosis with the parents.

Evaluation of the patient with cerebral palsy

The information presented below is based on a recently published practice parameter (Ashwal *et al*. 2004).

Role of imaging

The evaluation of the child with cerebral palsy, once the diagnosis had been established, may start with an imaging study. In neonates, neuroimaging is frequently obtained when there is a history of complications during pregnancy, labor and delivery, when the infant is born very prematurely (<32 weeks), or when neurological symptoms or findings are present on neonatal examination. The value of and indications for obtaining neuroimaging in preterm and term infants has been published (Ment *et al.* 2002). If an imaging study has determined the etiology of cerebral palsy in a particular patient a second imaging study is obviously not necessary.

Approximately, 75% of CT scans are abnormal in children who have been diagnosed as having cerebral palsy (Table 17.5A). The yield from CT scans varies depending on the type of cerebral palsy (hemiplegic > ataxic > mixed > diplegic > quadriplegic > hypotonic > dyskinetic) with the percentage of abnormal CTs in those with dyskinetic cerebral palsy being much lower than in other forms of cerebral palsy (Table 17.5B). Further, in many patients, the timing of the insult could be determined (Table 17.5C). Some of the more common etiologies of *prenatal onset* include intrauterine infection, stroke, toxemia, and placental abruption. *Perinatal onset* includes hypoxic ischemic encephalopathy, kernicterus, and trauma. *Postnatal onse*t includes infection, stroke and trauma. Etiologies tend to be different in term

TABLE 17.5A

Computed Tomography in Children with Cerebral Palsy; Overall Yield of Finding an Abnormal CT Scan in Children with Cerebral Palsy

Reference	Age (years)	Type of cerebral palsy	% Abnormal
Wiklund *et al.* 1991	5–16	Hemiplegic	73
Wiklund *et al*. 1991	5–16	Hemiplegic	75
Miller & Cala 1989	6–35	Ataxic	62
Chen 1981	0.08–7	Mixed	84
Kolawale *et al.* 1989	1–10	Mixed	73
Taudorf & Melchior 1984	NA	Mixed	67
Schouman-Claeys *et al.*1989	0.6–15	Mixed	63
Cohen & Duffner 1981	0.67–10	Hemiplegic	87
Molteni *et al.* 1987	5–16	Hemiplegic	93

TABLE 17.5B

Percentage of Patients with an Abnormal CT Based on Type of Cerebral Palsy

Hemiplegic (n = 146)	89%	Quadriplegic (n = 111)	70%
Ataxic (n = 19)	88%	Hypotonic (n = 19)	73%
Mixed (n = 29)	79%	Dyskinetic (n = 14)	36%
Diplegic (n = 153)	75%		

TABLE 17.5C

Classification of Timing of Injury of Cerebral Palsy Based on CT Scan Abnormalities*

Reference	Type of cerebral palsy	% Prenatal	% Perinatal	% Postnatal	% Unclassifiable
Wiklund *et al.* 1991	Hemiplegic	44	39	0	17
Wiklund *et al*. 1991	Hemiplegic	64	82	0	7
Chen 1981	Mixed	33	54	13	0
Kolawale *et al.* 1989	Mixed	16	35	26	28
Taudorf & Melchior 1984	Mixed	11	74	15	0
Molteni *et al.* 1987	Hemiplegic	53	47	0	0
Total		**32**	**50**	**12**	**6**

and preterm babies and are discussed further in the section on MRI.

A CT scan in a child with cerebral palsy may on occasion detect conditions that are surgically treatable that might not be detected by neurological examination. One retrospective study reported that 22.5% of 120 patients had potentially treatable lesions (hydrocephalus, arteriovenous malformation, subdural hematomas and hygromas, and a vermian tumor) (Kolawole *et al*. 1989). The majority of other studies reported either no patients with potentially treatable lesions (Cohen & Duffner 1981; Molteni *et al.* 1987; Wiklund *et al*. 1991) or lower incidences of 5% (Chen 1981), 14% (Taudorf *et al*. 1984) and 17% (Miller & Cala 1989) (Table 17.5D). On occasion, CT (as well as MRI) may detect abnormalities that suggest a potentially treatable inborn error of metabolism (see section on metabolic testing).

MRI scans of children with cerebral palsy were abnormal in about 89% of patients (range 68–100%) (Table 17.6A) (Candy *et al.* 1993; Cioni *et al.* 1999; Hayakawa *et al.* 1996; Jaw *et al.* 1998; Krageloh-Mann *et al.* 1995; Okumura *et al.* 1997; Sugimoto *et al.* 1995; Truwit *et al.* 1992; Yamada *et al.* 1993; Yin *et al.* 2000; Yokochi *et al.* 1991b; Yokochi *et al.* 1991a). The yield on MRI (Table 17.6B) depends on the type of cerebral palsy that was present (dyskinetic >quadriplegic > hemiplegic > diplegic > ataxic) and is somewhat different than that reported using CT. Further, MRI may be helpful in determining whether the injury was prenatal, perinatal or postnatal in onset (Table 17.6C). Onset was thought to be prenatal in approximately 40%, perinatal in 35%, and postnatal in 4%. The yield from MRI also depends on whether the child with cerebral palsy was born prematurely, at term or whether cerebral palsy was due to an insult later in life. In most series, this is

TABLE 17.5D

Percentage of Patients with other Etiologies of Cerebral Palsy Based on CT and Clinical Data

Metabolic	4%	Brain malformation	7%
Genetic	2%	Treatable condition	5%

*Etiologies could not be determined in all patients in the studies listed in Table 17.5A and in some patients more than one category of etiology was given. Data from the studies listed in Table 17.5A.

due to the fact that MRI is more sensitive in detecting periventricular leukomalacia, other perinatally acquired lesions as well as subtle congenital anomalies of brain development. In summary, an MRI affords more complete information than CT without the added burden of radiation.

Metabolic testing

Metabolic disorders may on rare occasions masquerade as cerebral palsy. Six case series describe 30 children who ultimately developed what appeared to be dyskinetic cerebral palsy due to glutaric aciduria (type 1) (Haworth *et al.* 1991; Kyllerman *et al.* 1994; Baric *et al.* 1998; Hauser & Peters 1998; Hartley *et al.* 2001; Smith *et al.* 2001). These children typically develop normally until 5–10 months of age when they suffer an acute encephalopathy manifested by coma that is followed by dystonia, motor impairment and macrocephaly (in about 60%). Distinctive MRI and CT findings occur in half the patients and are manifested by frontal and temporal atrophy. Early diagnosis is important as glutaric aciduria is treatable; early intervention may prevent significant motor and cognitive impairment. Other metabolic disorders presenting with symptoms suggestive of cerebral palsy also have been reported in small case series and include Lesch-Nyhan syndrome (Mitchell & McInnes 1984), 3-methylglutaconic aciduria (Gibson *et al.* 1997; Straussberg *et al.* 1998; Pantaleoni *et al.* 2000), pyruvate dehydrogenase deficiency (Lissens *et al.* 1999), argininemia (Prasad *et al.* 1997; Willis *et al.* 2000) deficiency, succinic semialdehyde dehydrogenase deficiency (Gibson *et al.* 1997) and female carriers of ornithine transcarbamylase deficiency (Christodoulou *et al.* 1993). Other childhood neurologic disorders (e.g. dopa responsive dystonia, hereditary spastic paraplegia, ataxia telangiectasia) may initially be misdiagnosed as cerebral palsy because of the slow rate of progression of symptoms (Swaiman 1999). Other clinical or laboratory features of such conditions and observations that neurologic symptoms are progressive should suggest that the child does not have cerebral palsy and mandates the need for further evaluation.

TABLE 17.6A

Magnetic Resonance Imaging in Children with Cerebral Palsy

Reference	Age (years)	Type of cerebral palsy	% Abnormal
Krageloh-Mann *et al.* 1995	5–17	SQ	91
Yin *et al.* 2000	0.25–18	M	91
Candy *et al.* 1993	0.25–2.25	M	77
Okumara 1997, pt 2	1–19	M	78
Cioni *et al.* 1999	1–18.3	M	100
Jaw *et al.* 1998	0.33–13	M	95
Sugimoto *et al.* 1995	0.75–15	M	100
Hayakawa *et al.* 1996	0.5–6	SD	79
Truwit *et al.* 1992	0.08–41	M	93
Yamada *et al.* 1993	NA	M	100
Yokochi *et al.* 1991	NA	D	68

Mean % abnormal MRI 89%

TABLE 17.6B

Percentage of Patients with an Abnormal MRI Scan Based on the Type of Cerebral Palsy

Dyskinetic (n = 3)	100%	Diplegic (n = 99)	94%
Quadriplegic (n = 104)	98%	Ataxic (n = 8)	75%
Hemiplegic (n = 50)	96%		

TABLE 17.6C

Classification of Timing of Injury of Cerebral Palsy Based on MRI Scan Abnormalities*

Reference	Type of cerebral palsy	% Prenatal	% Perinatal	% Postnatal	% Unclassifiable
Krageloh-Mann *et al.* 1995	Spastic quadriplegic	14	39	0	46
Yin *et al.* 2000	Mixed	26	54	3	18
Cioni *et al.* 1999	Mixed	59	30	11	0
Jaw *et al.* 1998	Mixed	29	28	3	8
Sugimoto *et al.* 1995	Mixed	44	37	0	19
Subtotal		37	35	4	15

* Etiologies could not be determined in all patients in the studies listed in Table 16.6A and in some patients more than one category of etiology was given. In some studies there were no data provided as to a specific etiology.

Coagulopathy testing

Patients with hemiplegic cerebral palsy frequently have suffered a prenatal or perinatal cerebral infarction. Data from three CT studies listed in Table 17.5 (n = 196) found cerebrovascular occlusion, usually in the middle cerebral artery distribution, in 13% (Wiklund & Uvebrant 1991), 32% (Taudorf *et al.* 1984) and 37% (Cohen & Duffner 1981) of individuals. Children, in contrast with adults, often have a coagulopathy, congenital heart disease or an infectious process as the etiology of stroke (Lynch *et al.* 2001). Several studies have reported coagulation abnormalities as the etiology of neonatal cerebral infarction (Thorarensen *et al.* 1997; Harum *et al.* 1999; Kraus & Acheen 1999; Gunther *et al.* 2000; Kenet *et al.* 2000; Golomb *et al.* 2001; Okun *et al.* 2000; Mercuri *et al.* 2001). These have included factor V Leiden deficiency, the presence of anticardiolipin or antiphospholipid antibodies and protein C or S deficiency. The studies have also described the relation between neonatal cerebral infarction, coagulopathies and a later diagnosis of hemiplegic cerebral palsy. The question should be raised as to whether treatment is indicated even if a coagulopathy is identified. Further, if a coagulopathy is identified as possibly being causally related to the motor disability, are future siblings at risk? There are no data that answer these questions.

Associated problems (Table 17.7)

Epilepsy (Table 17.8)

Given the higher frequency of epilepsy in children with cerebral palsy, EEG may be considered during the initial evaluation (Zafeiriou *et al.* 1999). The utility of EEG for establishing an etiology in this population has not been prospectively investigated. Approximately, 43% (range 35–62%) of children with cerebral palsy develop epilepsy (Table 17.9) (Brun & Kyllerman 1979; von Wendt *et al.* 1985; Miller & Cala 1989; Murphy *et al.* 1993; Albright 1996; Hadjipanayis *et al.* 1997; Kaushik *et al.* 1997; Chambers *et al.* 1999; Cioni *et al.* 1999). One prospective study compared patients with cerebral palsy and epilepsy to those with epilepsy alone. Children with cerebral palsy had a higher incidence of epilepsy with onset within the first year of age (47% vs. 10%), history of neonatal seizures (19% vs. 3%), status epilepticus (16% vs. 1.7%), need for polytherapy (25% vs. 3%), and treatment with second-line antiepileptic drugs (31% vs. 6.7%). They also had a lower incidence of generalized seizures (28% vs. 59%) and of remaining seizure-free (37% vs. 90%) (Kwong *et al.* 1998). Factors associated with a seizure-free period of 1 year or more in epileptic children with cerebral palsy include normal intelligence, single seizure type, monotherapy, and spastic diplegia. Similar findings have been observed by other investigators in the studies listed in Table 17.8 and are summarized in the review by Wallace (Wallace 2001). Children with cerebral palsy who have abnormal neuroimaging studies are more likely to have epilepsy. The prevalence of epilepsy also varies depending on the type of cerebral palsy that is present. Data from the studies listed in Table 17.8 indicate that children with spastic quadriplegia (50–94%) or hemiplegia (30%) have a higher incidence of epilepsy than patients with diplegia or ataxic cerebral palsy (16–27%) (Co-

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Associated Problems

- Hemiplegic patients with cerebral palsy commonly have a smaller hand and somewhat smaller foot compared with the normal side. This is not the result of disuse but rather the result of the lack of a trophic factor.
- Such a hand not only will be small but also will have a sensory loss. One can unequivocally state that the hand will be a helping hand and but not good at skilled acts.
- Therapists may be unrealistically enthusiastic about making this hand "normal" with an aggressive program.
- Hemiplegic patients may have homonymous hemianopsia. Identification of this problem is important so that one can give advice regarding appropriate classroom seating.

TABLE 17.7

Magnetic Resonance Imaging Abnormalities in Children with Cerebral Palsy Based on Preterm, Term and Postnatal Onset of Insult

	Preterm	Term	Postnatal
Acquired lesions	261	178	22
Periventricular leukomalacia (PVL) with other areas of injury	227	45	—
Diffuse encephalopathy (cortical/subcortical atrophy/ventriculomegaly)	14	71	—
Focal ischemic/hemorrhagic (e.g. infarct porencephaly)	14	52	10
Multicystic encephalomalacia	3	10	—
Trauma (at birth or later)	0	0	4
Infection	3	0	8
Malformations*	48	55	0
Cortical dysplasia/polymicrogyria	8	18	—
Schizencephaly	6	11	—
Pachygyria/lissencephaly	5	9	—
Complex brain malformation	22	6	0
Agenesis/hypoplasia of the corpus callosum	3	3	—
Arachnoid cyst	1	0	—
Vermian/cerebellar hypoplasia	1	2	—
Hydrocephalus/holoprosencephaly/hydranencephaly	2	2	—
Miscellaneous/unknown	7	18	1
Delayed/abnormal myelination	1	9	—
Normal	3	21	6

Data from the following studies Yin *et al.* 2000; Okumara 1997, pt 2; Cioni *et al.* 1999; Sugimoto *et al.* 1995; Hayakawa *et al.* 1996; Krageloh-Mann *et al.* 1995; 1991; Candy *et al.* 1993; Jaw *et al.* 1998; Truwit *et al.* 1992. Abnormalities considered "insults" on neuroimaging were designated as Preterm (insult occurred before 38 weeks gestation whether infant born prematurely or at term); Term (insult occurred after full-term gestation in the perinatal period up to 1 month of age); or Postnatal (insult occurred after one month of age in infants born prematurely or at term). Malformations were categorized as Preterm if detected in infants born before 38 weeks gestation or Term if detected in infants born after a full-term pregnancy.

* The data in the malformations section of this table are separated into preterm, term and post-term as that is how they were reported in the original reports. It is believed, however, that these malformations occur prenatally.

TABLE 17.8

Associated Conditions in Children with Cerebral Palsy

Reference	% Mental retardation	%Visual defects	% Speech-language disorders	% Hearing impaired
Zafeiriou *et al.* 1999	40	39	54	15
Murphy *et al.* 1993	65	10	No data available	4
von Wendt *et al.*,1985	70	19	No data available	7
Kolawale *et al.* 1989	66	15	59	14
Total	**52**	**28**	**38**	**12**

hen & Duffner 1981). In patients with dyskinetic cerebral palsy, it may occasionally be difficult to differentiate partial complex seizures from dyskinetic movements.

Mental retardation

Cognitive and neuropsychological functions in children with cerebral palsy are commonly impaired (Miller 1998). In general, there is some, but no absolute, relation between the type of cerebral palsy and severity of cognitive impairment. Children with spastic quadriplegia have greater degrees of mental impairment than children with spastic hemiplegia. Motor deficits of children with spastic cerebral palsy appear to correlate with the severity of cognitive deficits in contrast to those children with dyskinetic CP where this relation is lacking (Fennell & Dikel 2001). Children with different forms of cerebral palsy may be difficult to assess because of the motor deficits and in some forms of cerebral palsy (e.g. spastic diplegia) the differences between performance and verbal intelligence test scores actually increase with age.

TABLE 17.9

Prevalence of Epilepsy in Children with Cerebral Palsy

References	Types of cerebral palsy	% Patients with epilepsy
Murphy *et al.* 1993	Mixed	46
von Wendt *et al.* 1985	Mixed	48
Miller & Cala 1989	Ataxic	59
Zafeiriou *et al.* 1999	Mixed	36
Hadjipanayis 1997	Mixed	42
Al-Sulaiman *et al.* 2001	Mixed	54
Chambers *et al.* 1999	Mixed	36
Bruck *et al.* 2001	Mixed	62
Cioni *et al.* 1999	Mixed	35
Kwong *et al.* 1998	Mixed	38
Kaushik *et al.* 1997	Mixed	56
Taudorf & Melchior1984	Mixed	35
Cohen & Duffner 1981	Hemiplegic	58
Total		**43**

Laterality of hemiplegia may also be a contributing factor – those children with right hemiplegia may be more likely to have impaired language function due to left hemisphere injury (Aram & Eisele 1994), although this remains controversial (Trauner *et al*. 1996). There is also a strong association between greater intellectual impairment in children with cerebral palsy and the presence of epilepsy, an abnormal EEG or an abnormal neuroimaging study (Wallace 2001).

Ophthalmologic impairments

Visual impairments and disorders of ocular motility are common (28%) in children with cerebral palsy (Table 17.7). There is an increased presence of strabismus, amblyopia, nystagmus, optic atrophy, and refractive errors (Schenk-Rootlieb *et al.* 1992; American Academy of Pediatrics Committee on Practice and Ambulatory Medicine 21 1996). Children whose cerebral palsy is due to periventricular leukomalacia are also more likely to have visual perceptual problems. Many of these difficulties should be detected if currently accepted guidelines for vision screening in children with cerebral palsy are employed (Hartmann *et al*. 2000).

Speech and language disorders

Because of bilateral corticobulbar dysfunction in many cerebral palsy syndromes, anarthric or dysarthric speech and other impairments related to oral-motor dysfunction are common. For example, articulation disorders and impaired speech intelligibility are present in 38% of children with cerebral palsy (Table 17.7) (Clarke & Hoops 1980; Love *et al*. 1980). Because their impaired mobility can cause limited interaction with individuals in the environment, children with cerebral palsy might not be able to develop the linguistic skills necessary to develop more complex speech patterns (Uvebrant & Carlsson 1994). Language (as opposed to speech) deficits in cerebral palsy go hand in hand with verbal intellectual limitations associated with mental retardation (Falkman *et al*. 2002). Oral-motor problems including feeding difficulties (Reilly *et al*. 1996; Sullivan *et al.* 2000), swallowing dysfunction (Clarke & Hoops 1980) and drooling (Blasco & Allaire 1992) may lead to potential serious impacts on nutrition and growth (Stallings *et al.* 1993), oral health (Pope & Curzon 1991), respiration (Shaw 1996), and self-esteem.

Hearing impairment

Hearing impairment occurs in approximately 12% of children with cerebral palsy (Table 17.7). This occurs more commonly if the etiology of cerebral palsy is related to very low birth weight, kernicterus, neonatal meningitis or severe hypoxic-ischemic insults. Children with cerebral palsy who have mental retardation or abnormal neuroimaging studies are at greater risk for hearing impairment. Of concern are recent studies from the Center for Disease Control that almost half the children found to have severe congenital hearing loss (with or without CP) in the greater Atlanta area were not recognized until almost age 3 years (Van Naarden *et al*. 1999). Established guidelines for neonatal audiometric screening have recently been published (2000).

Common health problems

There are few data regarding the occurrence of common health problems in children with cerebral palsy. For example, the frequency of pneumonia, urinary tract infections and otitis media is unknown. On the other hand, three

health problems have been studied in detail, namely drooling, nutrition and incontinence.

Drooling

This problem may be responsible for severe skin irritations, but of greater significance is its unpleasant cosmetic effect (Rapp 1980; Sochaniwskyj *et al.* 1986; Dunn *et al*. 1987). Most studies of drooling in cerebral palsy suggest that hypersalivation is not the cause of the problem but rather, oral motor dysfunction. Fluoroscopy studies show ineffective and inadequate swallowing mechanisms. It is not surprising then that anticholinergic medication, in addition to the unpleasant side affects, have not been effective. Many other programs have been tried over the years attempting to help the children with this dysfunction, but none has been universally successful. Surgical intervention, including reposition of the salivary ducts and dividing the cordi-tympani has sometimes been effective. However, the operation is not always successful and undesirable side effects can occur, such as increased difficulty in swallowing food. During the last 10 years, behavior modification programs to help the individual control drooling have been effective. Rapp (1980) developed a device which provided auditory cues when the child drooled excessively. These cues effectively helped the small children in the study group control their drooling up to 6 months after the auditory signal was taken away. Koheil has demonstrated that electromyography, biofeedback and behavior techniques were effective (Koheil *et al.* 1987). The EMG auditory feedback provided the signal to the patient that he/she was having difficulty controlling oral motor function. Dunn *et al*. (1987) in a single case study design demonstrated that a patient could be taught self-control procedures with nonvocal positive reinforcement techniques. The criteria for success in the three studies included: (1) a mental age of more than 2 or 3 years, despite the fact that chronological age was as great as age l6; (2) motivation to control drooling; and (3) an understanding by the patients that drooling was socially unacceptable. Finally, Suskind and Tilton have reported that botulinum toxin A injections can be effective (Suskind & Tilton 2002).

Nutrition

Poor nutrition also may be a major problem (Patrick *et al.* 1986; Shapiro *et al.* 1986; Waterman *et al.* 1992). Several early studies cited poor weight and height gain in children who were severely spastic or athetoid. This poor growth has been thought to be associated with oral motor dysfunction and/or pseudobulbar palsy. This raises several questions: how to provide adequate and appropriate nourishment; and, if nourishment is provided, will the malnourished cerebral palsy child gain weight and height? Finally, will the adequately nourished child be more "healthy?" Recent studies have shown that either tube feeding or gastrostomy feeding resulted in a significant increase in weight gain and, in some patients, a significant increase in height. Criteria for using this type of nutritional support have yet to be established. The adverse effects of poor nutrition on the natural course of disease of patients with cerebral palsy are poorly understood. For example, are these children more prone to infection and skin breakdown? Will improving the child's nutritional status minimize or prevent further pneumonia? Further studies are needed to answer these questions. The parental resistance to these benign, reversible procedures should not be allowed to stand unchallenged when the child will benefit.

Bladder dysfunction

A third health problem commonly encountered in patients with cerebral palsy is bladder dysfunction but not urinary tract infections. Unfortunately, the literature provides little information on the incidence of this problem. Nevertheless, in addition to one's clinical experience, the few published studies suggest that the problem is significant. In a recent review of 50 patients with cerebral palsy (both children and adults), referred to a urological service, 28% complained of enuresis, 26% complained of stress incontinence, 18% complained of urgency and 6% noted dribbling (McNeal *et al.* 1983). More than 36% of the patients had more than one symptom. However, only 4 of 45 patients who underwent cystometrogram were noted to have a neurogenic bladder. Are the bladder difficulties related to lack of sphincter control? Are the problems more prevalent in patients who are retarded? Is it a more frequent problem for children whose primary deficit is spasticity or dyskinesia? Future studies are also needed in this area. For the present, clinical awareness and surveillance should lead to recognition of problems of practical importance to the patient and family.

Constipation

Constipation is another problem that must be monitored by the physician. Presumably, this problem occurs as a result of the patient's inability to control the abdominal muscles that provide the propulsion for the stool. Symptomatic treatment must be provided.

Secondary sexual characteristics

Performing a survey of 207 patients with CP, Worley *et al.* have shown that those patients who are barely or non-ambulatory (GMCS 3, 4 or 5) begin puberty earlier but end later compared to the able-bodied population. In addition, menarche occurs later in girls with CP.

Treatment

General treatment principles

Prior to discussing specific treatment programs, some general principles should be stated.

1. Long-term treatment objectives must be defined to the extent possible, taking into consideration not only the patient's motor deficits, but also his associated problems including cognitive abilities, social skills, emotional status, vocational potential, and, most important, the availability of family support. Will the patient be able to accomplish his daily living needs? Will the patient be independent in all areas, or just some? Will the patient need public or private transportation to reach his place of employment? Will leisure activities be accessible? These questions should be considered as the treatment program is being developed. They will become more obvious and important as the patient becomes older.
2. The effects of the patient's growth and development on his problem, with and without the proposed treatment, should be evaluated.
3. Valid alternatives, which look at risk/benefit ratios and humane/ethical dilemmas, and which might include nontreatment, should be considered.
4. Because the manifestations of cerebral palsy vary from patient to patient, treatment programs must be individualized.

A team of knowledgeable individuals with different expertise best accomplishes the treatment of a child with cerebral palsy. A typical team includes a physician trained in the evaluation and treatment of developmentally disabled children. The diagnosis must be established; progressive disease must be considered and excluded, and, if possible, specific genetic syndromes identified. A knowledgeable orthopedist is another physician member of the team. Contracture, subluxed or dislocated hips, and scoliosis are the deformities that can interfere with function and comfort. Nonphysician members of the team usually include a physical therapist, occupational therapist, orthotist, speech/language pathologist and a clinical nurse specialist. Many programs have found that a psychologist, social worker and educator can play vital roles.

Treatment principles for the infancy and toddler ages

The diagnosis of cerebral palsy in most patients is established during the first 2 years of life. At that time, the patient should become involved in a physical or occupational therapy program or both. There are a variety of therapy programs, none of which have proved to be more efficacious than others. The complexity of motor relationships, the inconsistent correlation of pathology with function, the lack of correlation of therapy with functional outcomes and the lack of a careful analysis of the natural course of disease are explanations for this situation (Goldberg 1991). The first therapeutic programs developed included passive range of motion exercises (to prevent contracture) and bracing (to prevent the abnormal muscles from interfering with normal muscle function) (Weiss & Betts 1967). In the late 1950s and early 1960s, the Bobaths developed a program now known as neurodevelopmental treatment (NDT), which was aimed at inhibiting the primitive reflexes and facilitating normal movement by active patient participation (Bobath 1967). Variations of this form of therapy have been advocated during the past 15 years, although attempts to validate any one treatment program have been unsuccessful (Palmer *et al.* 1988; 1990). Early intervention programs which provide not only specific "hands-on" therapy but also psychologic support, are thought to be beneficial, although there is no evidence that they enhance the child's development (Binder & Eng 1989; Palmer *et al*. 1990). Even this concept has been questioned in a study of parent satisfaction with an infant stimulation program for cerebral palsy.

The psychological impact of rearing a disabled child can be devastating. This subject has been the focus of several studies. A study addressing the issue of psychological stress in mothers whose children are disabled concluded that the specific diagnosis did not cause as much stress as expected among mothers; however, the dependency of the disabled child on the mother for help in accomplishing activities of daily living was significantly correlated with maternal stress (Breslau *et al*. 1982). Specifically, the neurologically handicapped child, such as a child with cerebral palsy, who needed a great deal of care including feeding, toileting, dressing, and help with mobility, caused a great deal more distress to the mother

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Treatment

- None of the various occupational or physical therapy programs has ever been validated or clearly shown to be more efficacious than other comparable programs. Empirically, they seem to be extremely helpful, and clearly provide emotional benefit for patients and families.
- Early intervention programs to enhance motor and cognitive development in the physically handicapped population have not been shown to be beneficial, as opposed to early intervention programs for the environmentally deprived population (for example, Head Start). On the other hand, the need to foster compensatory abilities early on and to provide emotional support must be considered when one is developing a program.
- The goals of any specific treatment program must be carefully outlined. Orthopedic intervention is not necessarily intended to change function dramatically. Rather the goal of a specific procedure might be limited to better positioning.

in comparison with distress resulting from a child with an illness such as cystic fibrosis. A therapy program might be extremely helpful in these cases, not necessarily to stimulate development but rather to offer parents easier ways to work with their child.

Treatment principles for the school age and adolescence age groups

As the child with cerebral palsy approaches school age, the goals of the therapy programs begin to shift from enhancing motor development and minimizing contracture toward helping the child cope with the expectations of the classroom. Sitting properly and moving about the environment (including the use of a wheelchair) are gross motor needs that may require physical therapy (Nwaobi *et al.* 1983). Use of the small muscles for fine motor function such as writing, cutting, etc., may need to be enhanced. Most important is a therapy program to help the child communicate, either with speech or communication devices. Dressing, feeding, toileting, and other activities of daily living (ADLs) are important needs that should be incorporated into the educational "treatment" program. The occupational therapist is usually the person to work with the patient toward these ends.

Treatment options

The motor deficits can be analyzed in four distinctive ways: (1) loss of selective motor control and dependence on primitive reflex patterns for ambulation; (2) abnormal muscle tone that is strongly influenced by body posture and/or position and/or movement; (3) imbalance between muscle agonists and antagonists; and (4) impaired body balance mechanisms.

1 Loss of selective motor control and dependence on primitive reflex patterns for ambulation

A remedy does not exist that can significantly alter selective motor loss, such as lack of control of lower extremity muscle. Physical and occupational therapy programs can provide help. The primary goals of a physical therapy (PT) program are to minimize the impairment, reduce the disability and optimize function[3]. Various schools of therapy promote programs that superficially vary greatly, but nevertheless have certain common principles, including development of sequence learning, normalization of tone, training of normal movement patterns, inhibition of abnormal patterns, and prevention of deformity.

2 Abnormal muscle tone that is strongly influenced by body posture and/or position and/or movement

Selective dorsal rhizotomy

Selective dorsal rhizotomy (SDR) involves the cutting of approximately 50% of the dorsal roots, thereby decreasing the muscle tone in the lower extremities (Abbott 1996). As a result of the decrease in the muscle tone, discomfort or pain will be alleviated, and sitting posture and/or gait will improve. The ideal candidate is a child who has normal or near normal strength in the lower extremities, who has not developed fixed contractures and whose alteration of tone will lead to the desired improvements in function.

The first of three randomized trials comparing SDR with physical therapy (PT) was published in 1997 (Wright *et al.* 1998). A significant decrease in muscle tone 1 year later in those patients who received the operation compared to the PT group was found. Further, the surgical group showed significant improvement in motor skills as measured by the gross motor function measure scale (Steinbok *et al.* 1997). McLaughlin *et al.* (1998) found similar significant changes in muscle tone in patients who underwent SDR. However, they did not find significant improvement in function using the same scale. They noted that the majority of their patients had a higher score on the GMFM preoperatively compared to those in the Steinbok study and suggested that the scale is not very sensitive at the high end. Wright *et al.* also noted significant tone reduction occurred in the SDR group compared to the PT group 1 year later. Improved gait velocity and stride length were also noted in the rhizotomy group compared to the PT group. The GMFM showed that there was a modest increase in function, statistically but not necessarily clinically significant, compared to the control group.

Botulinum toxin

Botulinum toxin A (BTX-A) is a neurotoxin produced by the bacterium clostridium. The toxin exerts its effect by inhibiting the release of acetylcholine from the presynaptic site at the muscle-nerve junction. The unit of measurement for BTX-A is the mouse unit (U), a unit not of weight but of bioactivity or potency. One unit of the BTX-A is equivalent to the amount of toxin needed to kill 50% (LD50) of a group of 18–20 g female Swiss Webster mice. The LD50 for monkeys given BTX-A intravenously is 40 units per kilogram (Cosgrove & Graham 1994). The lethal dose in humans on the other hand is not known. Extrapolating from these data, a 70 kg human would require at least 3000 U parentally to be lethal.

BTX-A, when injected into the muscles of spastic mice will normalize the tone and allow the muscle to lengthen with growth of the limbs (Cosgrove & Graham 1994). This experimental observation has led to the use of BTX-A in cerebral palsy (Russman *et al.* 1997). A combination of muscle weakening and strengthening of the agonist muscle minimizes or prevents contracture development with bone growth. This type of intervention is used when a limited number of muscles are causing deformities such as spasticity of the gastrocnemius muscle causing a toe-heel gait or hamstring spasticity being responsible for a crouch gait. Recovery of the muscle tone occurs because of the sprouting of the nerve

terminals, a process which peaks at approximately 60 days (Cosgrove *et al*. 1994).

Intrathecal baclofen infusion (ITB)
Baclofen, a GABA agonist, administered intrathecally via an implanted pump (ITB) has been helpful to patients whose muscle tone is more generalized and, whose muscle tone is interfering with function (Albright 1996). As baclofen does not cross the blood-brain barrier very effectively, large doses must be used PO to achieve success compared to administering baclofen intrathecally. Invariably, the patient on PO medication becomes lethargic. The candidates for this intervention can be divided into two groups. Group 1 is ambulatory patients whose gait is adversely affected by the muscle tone and who have some underlying muscle weakness. SDR in these patients is contraindicated as the procedure will cause muscle weakness, possibly, causing an ambulatory patient to become non-ambulatory. A second group of patients are those whose generalized tone interferes with activities such as hygiene, transferring from a chair to a bed or just maintaining a safe upright position.

Oral medications
The use of oral medication for the management of abnormal tone has been disappointing. For spasticity, dantrolene, baclofen and diazepam have been used. Tinizide, a new antispasmodic, has been shown to be efficacious in some patients with spinal cord injury and multiple sclerosis. There are no studies of this medication in the treatment of cerebral palsy. Medications for the dyskinesias, including dystonia, athetosis, and hemiballismus have been equally disappointing (Pranzatelli 1996).

Other treatment modalities
Transcutaneous electrical stimulation as advocated by Pape *et al.* consists of a low level electric stimulus to the nonspastic antagonist muscles for prolonged periods of time, while the patient is sleeping (Pape *et al.* 1993). The theory is that this treatment will strengthen the stimulated muscles that in turn will overcome the effect of the spastic muscles, thereby improving the patient's function. Unfortunately, research is lacking supporting the theoretical basis of this treatment. Most of the information as to success of this type of intervention is anecdotal.

3 Imbalance between muscle agonists and antagonists

Static contracture of muscle related to spasticity is a common problem for which surgical lengthening of the musculotendinous unit is frequently performed. Fixed muscle contractures are almost never seen in patients with pure dyskinesias, but when they do occur, surgical intervention is considered, but with extreme caution.

Rang *et al.* and Bleck have argued cogently that the overall result is much better if all contracted muscles are lengthened simultaneously rather than staging the procedures (Rang 1986; Bleck 1987). Not only does accomplishing all surgery during the course of a single procedure lessen morbidity, but by simultaneously balancing all major lower extremity joints, much better function is possible. In many centers for cerebral palsy, gait analysis is felt to be necessary for objective pre- and postoperative evaluations (Gage 1994). Gait analysis is a method by which the walking pattern of an individual is examined in detail. It is based on the gait cycle, which is the basic unit of walking.

4 Impaired body balance mechanisms

The child with cerebral palsy invariably has abnormalities of balance to some degree. In spastic diplegia, posterior balance is affected most severely. A child with only disturbances in posterior equilibrium is usually able to walk without the use of external aids. If anterior balance is also affected, crutches are necessary for ambulation. Children with deficiencies in lateral equilibrium usually require a walker or, if the lateral equilibrium reactions are severely deficient, may be unable to walk independently. The deficiencies in equilibrium are related to an irreparable neurological lesion and are lifelong.

Prevention

Low birth weight babies account for the greatest number of patients with cerebral palsy. In a review of intraventricular hemorrhage and the use of phenobarbital to prevent this phenomenon, Kuban *et al.* noted that the incidence of cerebral palsy in those mothers who were toxemic and had received magnesium sulfate was less than a comparable group (Kuban *et al.* 1992). O'Shea found a decreased risk of subarachnoid hemorrhage and intraventricular hemorrhage in these babies whose mothers had multiple gestations, were pre-

PEARLS & PERILS

Evaluation of the Patient after a Diagnosis Has Been Made Based on History and Physical Examination

- Obtain MRI (rather than a CT scan) when the etiology is not obvious.
- Metabolic and genetic testing is not indicated unless atypical features are present such as dysmorphic findings on PE or the history suggests intermittent changes such as dyskinetic movements.
- Consider testing for a coagulopathy if the child has a hemiplegia. However, it is very unclear as whether the presence of positive findings will alter the management of the patient or change the advice about the risk for future children.

eclamptic, received tocolytic agents and received steroids (O'Shea *et al*. 1992). Finally, Nelson found that only 7.1% of mothers receiving magnesium sulfate gave birth to babies who developed cerebral palsy as opposed to 30% who did not receive $MgSO_4$ (Nelson & Grether 1995). A recent controlled trial was prematurely stopped as the treated group experienced complications; the complete data have not yet been published (Mittendorf *et al*. 2003). An Australian study, also recently completed, suggested that the use of magnesium sulfate immediately prior to delivery of a premature baby did decrease the combined mortality and cerebral palsy rate in the treated group, but not at a statistically significant level (Crowther *et al.* 2003).

Prognosis

When the diagnosis of cerebral palsy is first established in a nonambulator, the first question asked is "Will my child walk?" Criteria for predicting independent walking have been developed (Bleck 1975). If, by the age of 1 year, the patient still has persistent primitive reflexes and the protective reflexes have not developed, it is unlikely that the child will ever ambulate independently. Further, if the child has severe dyskinesias, or falls into the dysequilibrium category, ambulation will not be achieved. Even though cerebral palsy is a result of a nonprogressive central nervous system lesion, the child who is a marginal ambulator, upon entering the early teens, may lose walking ability because of contractures, excess weight gain, or lack of motivation. Those involved with the care of cerebral palsy patients must be alert to these potential problems and take early preventive measures.

Because cerebral palsy is commonly associated with mental retardation, parents also express concerns about the child's cognitive development. Data from the analyses of large series help address this issue. The quadriplegic patient who has epilepsy, almost certainly will be, at best, educable mentally retarded. Of patients with dysequilibrium syndrome 90% are also retarded. CT and MRI studies also offer prognostic insights into cognitive development. Lesion size, degree of motor disability and electroencephalogram abnormalities, in one study were found to correlate with cognitive impairment. However, location of the lesion was not predictive (Cohen & Duffner 1981).

In most patients, a prognosis about intellectual development must be deferred pending the development of language because this skill is correlated with intellectual development. Therefore, in the questionable situations, a prognosis cannot and should not be rendered until after age 2 years. Furthermore, in the athetoid patient who might have a severe dysarthria, a prognosis about intelligence should be postponed until school age is attained. An examiner experienced with the severely disabled dyskinetic population should perform the evaluation, as the patient may be a poor examinee because of the motor disability and the scores might thus be misleading.

As the child matures, changes in muscle tone and function may occur, which might raise concerns about the diagnosis. For example, the hypotonic infant and toddler commonly develop spasticity or athetoid movement. Not only may the muscle tone change, but the disability may lessen or disappear entirely. An analysis of the data from the NCPP showed that 118 of 229 children diagnosed as having mild cerebral palsy at age 1 showed no motor disability at age 7. However, as a group, they had a higher incidence of learning difficulties and afebrile seizures compared to the general population. Obviously, even the child who improves over time is at risk for the associated problems (Nelson & Ellenberg 1982).

Finally, the examiner must be able to discuss issues of lifestyle with the parents. Communication is the most important skill required by a human being. Without this ability, even with a normal intellect, the child will have difficulty making his wants known, limiting his ability to participate in family activities, peer activities, etc. However, the technical advances being made, and expected to be made in the future allow a more positive outlook for even the most severely disabled patient with cerebral palsy.

Prognosis

- On reaching the early teens, marginal ambulators may stop walking because of contractures, excessive weight gain, or lack of motivation. This does not necessarily mean that the patient has a progressive disease.
- Quadriplegic patients with epilepsy at best are educable mentally retarded.
- Muscle tone in some patients will change over the years. Hypotonic patients may eventually become ataxic or might develop dyskinesias. Hypotonic boys should always have a uric acid test to rule out Lesch–Nyhan disease.
- Some children with the diagnosis of cerebral palsy at age 1 year will not have significant motor disabilities at age 7 years. However, such children have a higher incidence of learning disabilities.
- Communication is much more important than ambulation or even having self-help skills.
- Do not think that all patients with cerebral palsy who cannot speak are retarded. This specifically applies to the patient with choreoathetosis.
- A change for the worse in muscle tone or functional status does not necessarily mean that the patient has a progressive disease.

PEARLS & PERILS

Prognosis about vocation

The goal of any treatment program is to maximize the child's strengths and minimize the weaknesses. This obviously in-

volves an intensive treatment program that has already been discussed. Education is also critically important for the individual with cerebral palsy. The educational program must be geared not only to develop academic skills, but also to assure that the patient will be as optimally and rewardingly employed as feasible.

Studies regarding vocational status of individuals with cerebral palsy, in the 1950s and 1960s, have indicated that employability is related to cognitive skills, self-care, independency, severity of the physical disability, educational level attained, and mobility in the community. As pointed out by O'Grady *et al.* the studies heretofore have been retrospective (O'Grady *et al.* 1985). Ninety-seven students with cerebral palsy in the San Francisco, California area, between the ages of 7 and l6, were evaluated in the 1960s and 1970s and predictions were made as to their future employability. In l983, 60 of the 76 individuals over age l8 were contacted. At the time of the survey, only l7 were employed, although 39 had been employed at some time. Employment was related to the severity of the disability and the cognitive skills of the patients. A positive correlation was found between employment and mildness of cerebral palsy; that is, an individual with normal or near normal intelligence and minimal physical disability was more likely to be employed. Further, unemployment was correlated with those individuals who had severe physical disabilities and/or were retarded. An accurate prediction for patients with cerebral palsy who were in the middle range of intelligence, severity of handicap and self-help abilities, was quite unreliable. For those individuals who did better than predicted, family support and personal determination were felt to be paramount in their ability to attain their specific status. Further, the development of technology helped at least one individual who was predicted to be unemployable, but was working as an office computer assistant. Other positive factors identified in the present investigation as being important to vocational status, were an integrated education and a community-based assessment program.

One has to conclude from this recent study, as well as those in the past, that employability is not related solely to the individual's disability, but rather to other factors including family support, educational programs, technology, and community-based programs.

Conclusions and summary

Cerebral palsy is a term used to describe a patient who has a nonprogressive brain lesion leading to a motoric deficit. That the motor disability may change over the years does not obviate the diagnosis. Associated problems including seizures, mental retardation, language disorder, speech deficits, as well as a strabismus, must be evaluated and treated appropriately. There are many causes of cerebral palsy, including genetic diseases and embryological abnormalities. Most often, a specific cause cannot be identified. However, risk factors can be identified in about 30% of cases; risk factors alert the clinician to anticipate the presence of cerebral palsy in a patient; they should be considered separate from causation.

Cerebral palsy is an acceptable term as long as it is used appropriately and as long as the issues associated with this term are carefully explained to the parents. Cerebral palsy ranges in severity from minimal limitations, requiring no treatment, to total care and intensive treatment. It is those who require "total care" whom the public commonly associates with the term cerebral palsy. Consequently, the diagno-

KEY CLINICAL QUESTIONS

1. The diagnosis of cerebral palsy is established by:
   1. The finding of an abnormal MRI scan of the brain
   2. A history of hypoxic-ischemic encephalopathy in the neonatal period
   3. A history of a motor deficit that is not worsening and increased reflexes and/or clonus on examination.
   4. The presence of spasticity or dystonia on examination
   5. All the above
   Answer: 3

2. The evaluation of a child who has been diagnosed with cerebral palsy and whose past history does not suggest an obvious cause such as IVH, encephalitis, and meningitis should consist of one of the following:
   1. An MRI
   2. Coagulation evaluation if the child has hemiplegia
   3. Metabolic testing including urine for organic acids
   4. EEG
   5. All of the above
   Answer: 1

3. The use of botulinum toxin A medication is indicated for those children who have:
   1. Spasticity
   2. Dystonia
   3. Hemiballismus
   4. All of the above
   5. None of the above
   Answer: 4

4. Surgical intervention in children with cerebral palsy should take place when:
   1. As soon as fixed contractures develop
   2. Only when the child reaches adolescence
   3. Only when the contractures cause a dysfunction
   4. Preferably after the age of six
   5. None of the above
   Answer: 4

5. Which of the problems occur in children with cerebral palsy as frequently as able-bodied children?
   1. Strabismus
   2. Seizures
   3. Urinary tract infections
   4. Severe learning deficits
   Answer: 3

sis must be carefully articulated to the parents, emphasizing the various degrees of impairment. If one anticipates a treatment program including physical therapy and potential orthopedic intervention, the term is appropriate and should be used.

Annotated bibliography

Nelson KB, Ellenberg JH: Children who "outgrew" cerebral palsy. Pediatrics 69:529–536, 1982.

This article is still the classic. Children diagnosed as having cerebral palsy may improve from the age 1 to age 7 so that the child's motor skills are not a major problem and rehabilitation programs for the motor disability are unnecessary

Abbott R: Sensory rhizotomy for the treatment of childhood spasticity. J Child Neurol 11(Suppl 1):S36–S42, 1996.

Albright AL: Intrathecal baclofen in cerebral palsy movement disorders. J Child Neurol 11(Suppl 1):S29–S35, 1996.

Russman BS, Tilton A, Gormley ME, Jr: Cerebral palsy: a rational approach to a treatment protocol, and the role of botulinum toxin in treatment. Muscle Nerve Suppl 6:S181–S193, 1997.

CONSIDER CONSULTATION WHEN...

- The diagnosis of cerebral palsy is in question.
- The child *has* the hypotonic form of cerebral palsy.
- The etiology of the child's motor deficit *is* unclear.
- The patient is losing motor skills.
- There is a family history of similar problems.

The above three articles provide information about the current use of tone management protocols for the child with cerebral palsy whose abnormal muscle tone is interfering with function or quality of life.

Ashwal S, Russman BS, Blasco PA et al.: Practice Parameter: Diagnostic Assessment of the Child with Cerebral Palsy. Neurology 62:851–863, 2004.

A committee of child neurologists and developmental pediatricians produced this article. The recommendations for diagnostic evaluation of the child with cerebral palsy are based on a review of the evidence from articles published in peer-reviewed journals.

CHAPTER 18

Disorders of Motor Execution II: Higher-order Motor Deficits

Ruthmary K. Deuel, MD and Amy C. Rauchway, DO

OUTLINE

Clumsiness
Dyspraxia
Material-specific dyspraxias
Conclusion

Disorders of motor execution that accompany paralysis and spasticity may be categorized as disorders of primary motility. This chapter describes different higher-order motor disorders manifest by clumsiness, and/or inadequate performance of sequential motor acts. Children's motor development and performance may be severely handicapped by such deficits. The true incidence of such higher-order motor deficits (a term currently used to cover all of them is Developmental Coordination Disorder [DCD], ICD-9 315.4) is not known, but estimates range from 2% to 12% of first graders in regular schools (Gubbay 1975; Iloeje 1987; Nichols 1987; McHale & Cermak 1992; Dewey & Wilson 2002). Thus disorders of cerebral function that result only in clumsiness and dyspraxia, without paralysis or spasticity, are common and probably similar in incidence to specific learning disorders with which they are often associated (Johnson *et al.* 1981; Nichols 1987; Deuel 1992).

Higher-order motor deficits were first clearly described about 100 years ago in adult patients with acquired brain damage (Liepmann 1900). They were not recognized in children until the 1920s (Orton 1925), most likely due to the fact that no obvious alteration in strength, tone, coordination, or sensation accompanies them (Liepmann 1900; 1908; DeRenzi *et al.* 1968; 1980; Geschwind & Damasio 1985). In children higher-order motor execution deficits have long been defined as "failure to learn or perform voluntary motor activities with an age-appropriate efficiency, despite adequate strength, sensation, attention and volition" (David *et al.* 1981). This general definition, of course, may be made more specific in relation to the three major types of higher-order motor deficit: clumsiness, motor dyspraxia, and material-specific dyspraxia.

In the pediatric literature, even at present, clumsiness and dyspraxia are often called "a soft sign" (Deuel & Robinson 1987), and then the "soft sign" is used only as a diagnostic marker for more commonly recognized neuropsychiatric disorders of childhood, such as hyperactivity or attention-deficit/hyperactivity disorder (ADHD). Even well-evaluated movement assessment batteries for children (Croce 2001) are not constructed to distinguish among the three types of higher-order motor deficits. Although literature firmly supports a high incidence of disorders of higher-order motor execution among groups of children with cognitive and attention disorders (Pyfer & Castelman 1972; Denckla & Rudel 1978), there is absolutely no support for the view that disorders of motor execution are inevitably linked to them in individual children (Nichols 1987; Deuel & Doar 1992). When attention and cognitive disorders are found in conjunction with higher-order motor deficits, it is fitting for the physician to consider if the motor deficits are actually primary (leading to the major therapeutic effort being directed toward the motor deficits), whether the two are "comorbidities" (leading to major treatment efforts for both), or whether the neuropsychiatric disorder is primary, as in Asperger syndrome (Green *et al.* 2002; Schmitz *et al.* 2003), again leading to appropriate treatment emphasis.

Detecting higher-order execution deficits is difficult for the physician, as the chief complaint usually suggests a neuropsychiatric disorder. In the present illness there may be no mention of motor difficulties. Nonetheless, a careful developmental history reveals very delayed or even nonfulfilled milestones for various gross and/or fine motor acts throughout preschool years. A history of chronic fine motor delays is reassuring that the problem is not acquired. In addition to the chief complaint being nonrevealing, a basic neurological exam will not show clumsiness, apraxia, and material specific dyspraxia without items deliberately aimed at detecting them. Higher-order motor deficits are, in fact, most apparent during naturalistic action (Buxbaum *et al.* 1995), and are best termed "dynamic signs," since they appear

during motion. To examine for them, one should employ age-appropriate sequences of motions performed under the examiner's surveillance. These will establish on an objective basis whether or not a higher-order motor deficit is present (Table 18.1) in the school-age and adolescent child.

When motor deficits appear to be of recent onset or progressive, they may be proclaiming significant medication side effects, collagen vascular disorders, or other potentially treatable and/or progressive diseases, such as metachromatic leukodystrophy, subacute sclerosing panencephalitis (Jabbour 1969; Percy *et al.* 1977), Rett syndrome (Hagberg *et al.* 1983). In addition, cerebellar lesions may lead to motor execution deficits. Sydenham chorea, dystonia musculorum deformans, and kinesigenic dystonia are among entities that may need to be considered in the differential diagnostic process. While pure DCD early gained a reputation for independence from intracranial pathology, recent increases in sensitivity of available measures have altered this rule. Investigation of etiology by magnetic resonance imaging (MRI), particularly if a progressive disorder is suspected, is clearly warranted. In general, recent literature supports judicious use of sensitive neuroimaging and electroencephalographic investigations in children with motor execution deficits (Menkes 2000).

Beyond the issue of etiology, the major reason to define higher-order motor deficits is their propensity to cause long-term severe educational and social handicaps (Gubbay 1975; 1985; Knuckey & Gubbay 1983; Hollander *et al*. 1996; Segal *et al.* 2002). This happens through various intermediary mechanisms, starting with the effects on self-esteem of being always behind peers in motor performance.

When a higher-order deficit is found and is chronically handicapping, long-term remedial management is in order. Such individualized management is often very helpful in both restoring functional ability and self-esteem. Even in children with cerebral palsy and other disorders of primary motility, who, as often happens, suffer additionally from higher-order motor dysfunction (Crothers & Paine 1959; Frei 1986), analyzing all motor deficits with the goal of determining the specific handicapping potential of each deficit for that individual child is recommended. The separate headings: (1) clumsiness, (2) dyspraxia and (3) material-specific dyspraxias (notably, dysgraphia) allow management to be optimally directed.

TABLE 18.1

Neurologic Evaluation

History
Gross motor milestones: walked independently (10–15 months), climbed stairs by self (14–24 months), rode big wheel or trike (2–3 years), rode bicycle (4–6 years) Fine motor milestones: held cup (10–14 months), drew (3–4 years), buttons and snaps (3–4½ years), prints name (4½–6 years), tie shoes (4½–6 years)
Direct examination (see Chapter 4 Appendix, items N86–N158)
Gaits: walking, running, skipping, tandem, hopping on one foot, climbing stairs Upper extremity: finger-tapping, wrist-turning, button-pressing, finger–nose–finger, copying, drawing, writing Dyspraxia: imitation of nonsense gestures, pantomime to command, use of actual objects
Tests with age-standardized normative values
Purdue Peg Board Kaufman ABC hand movements Spatial memory PANESS (Denckla, 1985)

Clumsiness

A child with clumsiness, suffers from slowness and imprecision in completion of very simple (single-phase) acts, such as flexing a finger or rotating the wrist and forearm. In the past this developmental motor disability has been considered together with pure dyspraxia (Ford 1960; Gubbay 1975; Iloeje 1987) but is separable from it on empirical grounds (David *et al.* 1981; Poeck 1986; Deuel 1992).The main point of differentiating clumsiness from pure dyspraxia is that speed and dexterity are affected in clumsiness (Table 18.2). The deficits observed in the purely clumsy child fulfill the criteria of Liepmann's (1908) limb-kinetic apraxia or Kleist's (1934) melokinetic apraxia. These authors described a decrement in dexterity and speed of movements without strength or tone changes in adult stroke victims. The purely clumsy child similarly exhibits slow and inaccurate fine and/or gross motor performance in the face of an otherwise normal neurologic examination. Fortunately, items such as finger tapping and wrist supination and pronation are part of the standard examination, so direct recognition of clumsiness is more likely than recognition of pure motor dyspraxia (described below). Even so, if direct resistive strength of finger muscles is not also tested, the slowness may be misinterpreted as weakness. The neurologic examination (see Chapter 4) also enables differentiation of clumsiness, not only from weakness and spasticity, but also from synkinesis, movement disorders elicited by motor acts, and tremor. Each brings its own differential diagnosis, prognosis, and treatment. Synkinesis is unwilled activity (involuntary movement) of voluntary musculature that occurs during the course of a voluntary action. It is directly elicited by production of the voluntary target action (Rasmussen 1993). Examples include involuntary opening of the eyes when a child is told to open her mouth, or involuntary opening of the mouth when she is commanded to open her eyes very wide. Synkinesis is readily evaluated in a neurologic exami-

FEATURES

Table 18.2 Clumsiness

Discriminating feature

1. Slow completion of single-phase movements of single joints, in the absence of weakness, spasticity, or spontaneous adventitious movements

Consistent features

1. Finger or foot tapping, or both, too slow for age
2. Outcome of movement sequences improved when there are no time constraints

Variable features

1. Association with dyspraxia
2. Association with adventitious movements
3. May affect facial, pedal, or axial motion separately

PEARLS & PERILS

Clumsiness

- Slow, fine finger movements due to clumsiness are sometimes mistaken for distal weakness. A direct test of flexor and extensor finger strength will determine the correct designation.
- Clumsiness is a primary cause of school failure in the early grades, preventing adequate academic achievement because mechanical demands are heavy and intellectual ones are light.
- Clumsiness is very conducive to low self-esteem, starting very early in development. This early secondary low self-esteem mediates depression, continued failure, and thus failure in areas that have no motor requirements whatsoever.
- Some clumsy individuals can improve their performance with guidance from a specific modality of sensory input. For example, the musically gifted clumsy child may be a superb performer on the flute even though she cannot tie her shoes. It is important to evaluate a range of motor performances.
- Clumsiness is not a soft sign of cognitive or attention disorders, although it is statistically associated with both (Denckla & Rudel 1978; Nichols 1987; Dewey *et al.* 2002). In fact some believe that it is one of several possible causes of ADHD.
- Often a simple explanation to parents and teachers of the mechanical difficulties at the root of the child's slow and labored performances will change these authorities' attitudes and demands to a great extent, allowing a marked increase in the child's self-esteem and improved performance through improved motivation.

nation. An item that directly elicits upper extremity synkinesis is the Fog test (Fog & Fog 1963), which requires the child to walk on the sides of the feet, either the insides or outsides of the sole. When the child performs it, especially if a relatively narrow base is demanded, the arms and hands may enter distorted postures (Wolff *et al.* 1983), that approximate hemiparetic ones.

Mirror movements are the best-known form of synkinesis. These are synkineses that occur in groups of muscles directly homologous to the groups that are in voluntary play. During the performance of the finger-tapping test a mirror movement commonly occurs: the hand that has not been commanded to tap nevertheless carries out the very same tapping activity, which may persist even in the face of a command for it to stop. The occurrence of mirror movements in the nondominant hand when the dominant hand is performing is an abnormality in persons older than 6 years of age. It has been confirmed that the amount of effort required for the voluntary (commanded) activity predicates mirror synkinesis in normal children (Todor & Lazarus 1986). Thus when searching for true excess mirror synkinesis, it is best to avoid tasks that require strenuous effort. A patient suffering from extreme mirror movements produces them in simple, nonstrenuous, everyday unimanual activities, such as turning a door handle. The incidence of mirror movements is much less (2%) than that of higher-order motor deficits in general (Nichols 1987). Clumsy children very often exhibit mirror movements. The above-mentioned finding concerning interaction between degree of exertion and occurrence of mirror movements may explain their occurrence in clumsy children, who have to exert a large amount of effort to accomplish simple motor acts. Developmentally determined mirror movements diminish with increasing age (Wolff *et al.* 1983). For persistent and handicapping mirror movements, an effective treatment is not known, but it may be helpful to deliberately engage the hand not involved in the voluntary action with grasping or pressing a surface. Some children spontaneously use this maneuver.

Tremor (involuntary oscillations of a body part occurring at rest or during willed action) has several types. Intention tremor, when the oscillation increases as the limb in motion nears its target, is known as a sign of cerebellar disease. To test for it, use the finger-to-nose and the heel-to-shin test of the neurologic examination and observe for it during the tandem gait test and during writing, drawing, and picking up small objects. In every child with intention tremor, particularly if signs of ataxia are present, a lesion of the cerebellum or its brainstem connections must be considered. Action tremor, on the other hand, occurs throughout the limb movement but not when the limb is at rest. Action tremor, often benign in etiology (for example, benign familial tremor), may severely restrict fine motor performance.

To help a clumsy child, the limits and influence of that particular child's motor disability must first be defined. Most pediatric occupational therapy facilities are able to quantify, using age normed tests, clumsiness in young children for whom the current major effective remedy is a combination

of "bypass" and practice. However, self-esteem usually remains an issue despite therapy, and caretakers need to take an active role in alleviating the child's performance anxieties and poor self-image. The reduction of mechanical impediments to speedy production in required activities (a so-called by-pass method) is often used (e.g. Velcro flap shoes instead of laced shoes, zippers instead of buttons, snapped rather than buckled belts). While practice improves the child's performance of a given act, stress may lead to disintegration of the performance. Thus under stress (as when dressing for school) certain amounts of help may be granted, but when the child is in a more relaxed situation (as when undressing for bed), this additional help can be withdrawn. It is important to realize that purely clumsy (as opposed to other types of DCD) children's performance problem is simply a mechanical one in that the "motor program" is appropriate to the goal of the action, and only speed and precision of execution is deficient.

As for prognosis, severe clumsiness is unlikely to be fully resolved by maturity (Knuckey & Gubbay 1983; Hollander *et al.* 1996). However, enough dexterity to allow survival in a society of people who are more adroit is usually achieved. A general rule is that if the child can learn to overcome or go around mechanical blocks and thus avoid the deficit in self-esteem created by the performance deficit, clumsiness will not be a severe handicap in the adult life of a normally intelligent individual (Ford 1960).

Dyspraxia

Dyspraxia (called apraxia when acquired in adulthood) is defined as the inability to perform developmentally appropriate sequences of voluntary movements in the face of preserved power, coordination, dexterity, sensation, and cooperation. Individual fine and gross movements are often dexterous and well aimed (Table 18.3). However, depending on the type of activity required, an incorrect sequence of individual movements is produced, sometimes with additions of unrequired movements (parapraxes) (Poeck 1986) or with the spatial requirements of the sequence violated, or both. Thus the final product of what looks like a quick, dexterous complex movement may be completely ineffectual. A common example is rapid manipulation of shoelaces without a tie.

The characteristic failure in the elaboration of a complex voluntary act, without observed clumsiness or slowness, may be the reason why motor dyspraxia is generally unrecognized as a source of defective actions; a motor deficit is seldom suspected, even by experienced professionals. Because primary motility (strength, coordination, and dexterity) is preserved, a standard neurologic examination does not reveal the dyspraxic deficit. Although neurodevelopmental examinations for soft signs do contain items that are affected by dyspraxia, dyspraxia *per se*, not contaminated by clumsiness, is not a recognized soft sign. Thus an unrecognized dyspraxic motor deficit may lead the child to be labeled as lazy, oppositional, or unintelligent, with adverse effects on self-esteem, motivation, and conduct. Any of a wide array of school and behavioral problems may be the presenting complaint for the dyspraxic child. However, if a detailed account of motor development is obtained, the history will indicate a motor abnormality. Dyspraxic children are usually delayed in dressing and grooming themselves independently and have specific problems with buttoning, snapping, zippering, donning coats and boots, tying shoes, and manipulating combs, toothbrushes, and scissors. They are often unwilling even to attempt coloring, carpentry, sewing, and cooking. This may happen despite the fact that gross motor (sitting, walking, climbing stairs, and playing soccer, for example) milestones were normal.

FEATURES

Table 18.3 Dyspraxia

Discriminating feature

1. Inability to perform developmentally appropriate sequences of voluntary movements in the face of preserved volition, power, speed and coordination for single motions, and sensation

Consistent features

1. Abnormal outcome of rapidly performed movement sequences
2. Ability to choose the correct sequence when alternatives are modeled
3. Extra or inappropriate movements (parapraxis)

Variable features

1. Association with clumsiness
2. May affect manual, pedal, axial, facial, or oro-buccal motions separately, or occasionally, all of these

The etiologies of dyspraxia are diverse. Adults with apraxia after stroke usually have damage to cerebral gray matter. It may follow a stroke in childhood (Crothers & Paine 1959), and it may be one of the first signs of a degenerative disease. Although dyspraxia is said to occur in mental retardation, perhaps if developmental quotient of praxic ability could be reliably determined, it would be commensurate with the intelligence quotient (IQ) in most mentally retarded children, as it is in normal children (Deuel & Doar 1992). Dyspraxia is also frequent in frank cerebral palsy (Frei 1986) as an additional deficit. In most dyspraxia that is associated with learning and attention problems, the etiology is obscure. It seems likely that involvement of the association cortex in some fashion underlies such functional deficits (Deuel 1977), but direct evidence is not available. Functional imaging studies that could elucidate these facets have yet to be carried out, and those studies that have recently addressed physiological aspects of motor abnormalities (Johnston *et al.* 2002;

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Dyspraxia

- The best screening test for dyspraxia is an accurate, detailed history of motor development, followed by observation of age-appropriate motor sequences.
- On a general-purpose neurologic examination of school-aged children, the item most prone to be disturbed in manual dyspraxia is the finger-to-nose test (for the child it is a new, nonsense motor sequence).
- To ascertain dyspraxia definitively, a standard manual dyspraxia battery may readily be administered in conjunction with the neurologic examination. Elements of such a battery are presented in Chapter 4 Appendix items N115–N149.
- Facial dyspraxia is often seen in the developmental language disorder called verbal apraxia or dilapidated speech (Aram & Horwitz 1983), and oral-buccal dyspraxia is a constant finding. The finding of facial dyspraxia can help differentiate this diagnostic entity from other speech and language disorders, and point the way to appropriate therapy.
- Parents and teachers generally do not recognize a "motor" deficit in the motor dyspraxic child, but, as with the clumsy child, complain of child's laziness, sloppiness, or avoidance of tasks.
- Dyspraxia is not systematically ascertained on the general-purpose neurologic examination, nor is it tested specifically in most extended or neurodevelopmental examinations designed to detect neurologic soft signs.
- The secondary developmental effects of dyspraxia, diminished self-esteem and avoidance of motor sequencing tasks, may be much more handicapping than the motor deficit *per se*. The secondary effects may remain long after the child has developed effectual praxis.
- Speech pathologists may understand the term dyspraxia to refer only to dyspraxia of speech.

Estil *et al*. 2002; Wilson *et al.* 2002), have involved the lumped "Developmental Coordination Disorder," without separating dyspraxia from pure clumsiness. Because morphologic pathology is not found in the vast majority of children with either dyspraxia or clumsiness, variations in information processing at the neuronal system interaction level, related to genetic and epigenetic factors, may be the cause. The KE family presents with marked oromotor dyspraxia, severe impairment of linguistic and grammatical skills, and abnormalities in the basal ganglia on MRI, that have been attributed to a point mutation in the FOXP2 gene (Lai *et al.* 2001).

To test for dyspraxia it is best to conduct a complete neurologic examination that includes several types of patient-performed tasks, including pantomiming of actions, imitating actions of the examiner, and using actual familiar objects (DeRenzi *et al.* 1980; Chapter 4 this volume, Appendix items N115–N149). Such tasks should demand of the child age-appropriate complex voluntary motor activity, and be separated as to whether they demand pantomime, imitation, or use of actual objects skills. Possible items for pantomime testing in younger children are asking the child to blow a kiss or wave goodbye. For older children items from the adult apraxia examination are valid (e.g. pantomime pouring water from a pitcher into a glass, batting a baseball, or brushing teeth). The child should also be able to recognize any act he was unable to perform from among three examiner-performed actions. Choosing the correct one demonstrates the child's recognition of the act and understanding of the command. Effective completion of a complex act by a dyspraxic child, unlike completion by a clumsy child, does not improve with extended periods of time allowed for completion. This facet of the dyspraxic's performance can help differentiate clumsiness from dyspraxia, although some children demonstrate both difficulties.

There are no psychometric-style tests for dyspraxia. However, the Kaufman ABC (Kaufman & Kaufman 1983) test has a hand-movement copying subtest that does at least test sequential manual abilities and has normative standards from 2½ to 12½ years. Chapter 4, items N115–N149 does provide tests aimed at separating the three types of dyspraxia. Gubbay (1975) has standardized a motor performance battery but it fails to provide any means of differentiating apraxia from clumsiness and adventitious movements, as do most later developed tests, such as the Movement Assessment Battery for Children (MABC) (Croce 2001).

The management of dyspraxia depends on its handicapping significance for, and the age of, the child displaying it. Simple recognition of the apraxic deficit, and the counseling of the child and the parents that it is due to a specific motor problem (and not carelessness, laziness, or other voluntary oppositional personality traits) may be very helpful in removing an unnecessary stigma from the child. If the dyspraxia is idiopathic or the result of static brain damage, further management should include a combination of practice of the required motor sequences and bypass of the complex motor acts that are causing trouble. Dyspraxia is most likely to be handicapping and obvious when the child is learning a new complex motor sequence. One 10-year-old child was introduced to throwing darts when at a social gathering. At each attempt she threw the dart backward, with incremental embarrassment to her parents. The incident caused them to seek medical consultation for mental retardation in their child, whose full scale (WISC-R) IQ was 110. Apraxic children, placed in unfamiliar situations that require unfamiliar acts, are often not able to devise new or effective motor sequences.

Such embarrassing motor inefficiencies cannot be completely avoided by dyspraxic children, but learning to use conscious strategies, such as verbal self-cuing, can help, particularly in the older child. The child can develop a system of conscious self-questioning: "How are the other kids in line ahead of me doing this?" "Which hand comes first, which

part of the object is the front/the left/the right?" Such questions may help the older apraxic child consciously control motor sequencing. A nondyspraxic child, of course, seldom needs such explicit cognitive aids. The child should be made aware of situations in which the apraxic deficit will surface. She should be encouraged to understand that the problem is motor output, not intelligence. This understanding can shore up self-esteem which, in turn, empowers her to seek innovative ways to fulfill academic requirements. She should be helped to avoid situations with excessive motor demands. Practice of a given motor sequence is sometimes very useful, just as with clumsiness, although obviously every motor sequence to be encountered cannot be practiced and the amount of practice needed to overcome dyspraxia makes prioritization imperative.

Because it has rarely been evaluated separately from clumsiness and synkinesis, both the incidence of pure idiopathic dyspraxia and the prognosis are unclear. In most cases it seems to be developmental, in that the ability to carry out effective complex motor sequencing improves with age. Idiopathic dyspraxia does occur alone. In a group of 30 school-aged children given a quantitative apraxia battery and finger-tapping and wrist-turning tests, there was no correlation between finger-tapping speed (always affected in clumsiness) and apraxia scores (Deuel & Doar 1992).

Material-specific dyspraxias

Material-specific dyspraxias are the most circumscribed higher-order motor deficits. They cannot be detected unless the specific material with which there is difficulty is presented during testing. The most commonly recognized material-specific dyspraxia is linguistic (or dyslexic) dysgraphia. In linguistic dysgraphia the child cannot orally spell words correctly, but may be able to draw quite well, presenting a true material-specific (verbal material) dysgraphia. When affected children make written letters and words very poorly, spell incorrectly in both written and oral attempts, and truncate written assignments but read fluently and with good comprehension, they are clearly different from dyslexics (see Chapter 20), who have the written language disorder described, plus an inability to read. Far from 100% of children with dysgraphia have severe dyslexia, whereas some form of dysgraphia does appear in 100% of severely dyslexic children (Deuel 1981). The material specificity of the disorder is certainly best exemplified by the dyslexic child with dysgraphia, because many such dyslexic children have excellent fine and gross motor abilities when tested on other material than written expression of letters, words, and sentences. An example is seen in Fig. 18.1, in which a writing sample may be compared with the same child's drawing of a band. Motor execution deteriorates not only from drawing to writing but also as words become more difficult to spell.

Clumsy children may also be called dysgraphic, but in them the defect is not material specific, because oral spelling is normal, and they show other evidence of clumsiness when they draw or perform other fine motor activities. Written productions are sparse in both types of dysgraphia.

To evaluate dysgraphia a pertinent history is important and a review of written schoolwork is helpful. One should observe production of written words, sentences, or paragraphs, depending on the subject's educational status. Copying of a grade-appropriate sample should also be evaluated. To determine if spelling deficits are related to writing,

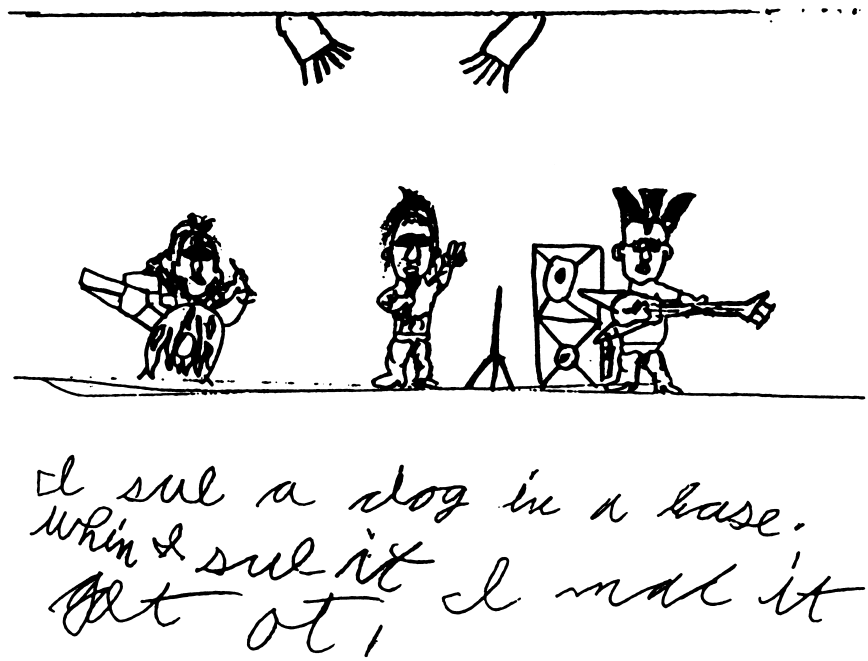

Fig. 18.1 A cartoon (produced in about 5 minutes) after the request to "draw me a picture and write a paragraph." The text says, "I saw a dog in a case. When I saw it, I made it get out." This paragraph required about 7 minutes to compose and write out. The writer was a 12-year-old sixth grade student with a performance IQ of 112. (Adapted with permission from Deuel R; Developmental dysgraphia and motor skills disorders. J Child Neurol 10 (Suppl 1):S6–S8, 1995.)

PEARLS & PERILS

Dysgraphia

- Highly abbreviated handwritten output or downright refusal to complete written assignments in the verbally advanced or normal child suggests isolated dysgraphia as a cause.
- In dysgraphia scores on individual IQ tests, such as the Wechsler Intelligence Scale for Children, are generally normal on all subtests except the coding subtest.
- Neat but very slow writing characterizes dysgraphic children. Slow output leads to paucity of written output.
- The first-grade child who writes letters backward should not be declared dyslexic or dysgraphic.
- It is important to test writing speed in the child whose school performance is under consideration.
- It is important to test for oral spelling in a child who always fails written spelling. Otherwise, an incorrect attribution to a linguistically based abnormality rather than to a simple motor abnormality or to a spatial disorder may be made.

as in the clumsy child with dysgraphia, the child should be asked to spell words aloud. When giving these tasks it is important to remember that letter reversals are common in normal young children and do not *per se* indicate dyslexia. Psychologists often employ the Test of Written Language (TOWL-3; Hammill & Larson 1996), which has age-appropriate norms to determine if there is an abnormality and its extent.

Constructional dyspraxia is the second kind of material-specific dyspraxia. Poor spatial intuition, great difficulty drawing and constructing three dimensional models are its hallmarks. Some children with this disorder may also present poor social and organization skills, i.e. the right hemisphere deficit syndrome (Voeller 1995). Constructional dyspraxia can be differentiated from clumsiness and from dysgraphia by normal oral spelling, and drawing more severely disordered than writing. Testing for constructional dyspraxia should include drawing age-appropriate shapes and figures in addition to writing and spelling exercises for dysgraphia. More formal tests include the Bender Gestalt test (Bender 1946; Lacks 1999) and the Benton test of visual memory (Benton 1974).

The management of material-specific dyspraxias is various. Dysgraphia can be severely handicapping scholastically, and its treatment with bypass methodologies (for example, dictation of essays) is well known to most educators. Word processors with spell-check are very helpful, presumably because the motor demands of keyboarding are less than that of handwriting.

KEY CLINICAL QUESTIONS

- A 7-year-old girl with known Trisomy 21 is brought by her mother who believes the girl has been misplaced in a class for the severe-moderately retarded. On history, fine motor skills were markedly delayed, while gross motor and language skills were more modestly delayed. On exam she is attentive and talkative, has mild hypotonia, excellent strength, no adventitious movements, very slow finger tapping, and after rapidly orally spelling it for you, labors slowly to print the four letters of her first name. What further testing would you request to substantiate your diagnosis of clumsiness? What remedial modalities will you recommend? Comment: a Wisc-III IQ test showed Verbal IQ of 78 and Performance IQ of 51. Occupational therapists provided adaptive equipment and training in self-help skills, thus enabling the child to maintain her self-esteem and make good progress in a program for the mildly retarded.
- A 12-year-old sixth grade star soccer goalie was seen after he was barred from sports because of failing grades in history, English, and social studies. He commented that he missed his older sister, his longtime "homework monitor," who had just started college in a distant city. His entire past medical history (except onset of speech at about 2½ years) was normal, as was his physical and neurological exam and his drawing, but not writing sample (see Fig. 18.1). What specific disorder of motor execution can you designate? What further diagnostic evaluation would you do? What remedial measures would you recommend? Comment: This child should be given quantitative specific tests of cognition that do not involve spoken language, as well as standard individual academic achievement tests, and the TOWL (see text). Management may include bypass methodology, such as teaching him to take cryptic class notes, word processing (with spell-check) written assignments, and some tutoring. He should be allowed to return to his soccer team as soon as these remedial measures are in place.
- An 8-year-old third grader comes because "She's stopped paying attention to what she is doing." Past medical and developmental history is normal, but in the past few weeks her mother has noted uncharacteristic slow motor activities. She appears very eager to please, and on neurological exam has mild hypotonia and a slow, ataxic tandem gait with dysmetria and a marked end-excursion tremor of the dominant right hand. What are your differential diagnostic thoughts? What specific test would you request? Comment: Since you have found unequivocal signs of right cerebellar dysfunction in a child whose personality is prompting her futile efforts to halt them, a high-resolution MRI with attention to the posterior fossa is first in order. All three common forms of cerebellar tumor are suspect.

Conclusion

Higher-order motor deficits are an important source of school failure and low self-esteem. This source is often completely unsuspected before the child encounters an informed clinician. This chapter can only briefly discuss the modes of presentation of such disorders, their differential diagnoses, and ways to make a positive diagnosis, as well as outlining principles of remediation for the specific subtypes. The clinician's awareness of these issues remains most valuable to the patient.

CONSIDER CONSULTATION WHEN...

- A child has a significantly unusual walking or running gait.
- A child is consistently the last to finish a race.
- A child exhibits significant fine or gross motor deficits on physical therapy, occupational therapy or psychoeducational testing.

Annotated bibliography

Deuel RK, Doar BP: Developmental manual dyspraxia: a lesson in mind and brain. J Child Neurol 7:(S1): 99–103, 1992.

A study of 164 school children 5–12 years of age given an apraxia battery and WISC-R IQ tests. Twenty-four of the children had dyspraxia according to their battery performance. Within this subgroup there was no correlation between WISC full scale IQ and severity of dyspraxia. In contrast there was a positive correlation between motor performance on the apraxia battery and full scale IQ in the entire 164-member group, again suggesting that specific cognitive and motor dysfunctions are best segregated and quantified before treatment is recommended.

Gubbay SS: Clumsiness. In: Fredriks JAM, editor: Handbook of clinical neurology, vol 46, Neurobehavioral disorders. Amsterdam, 1985, Elsevier North Holland, pp. 159–167.

This chapter includes a great deal about the general dilemma of a child with higher-order motor deficits. However, in common with much more recent writings, it fails to differentiate the various forms of these motor execution disorders.

Leiguarda RC, Marsden CD: Limb apraxias: higher-order disorders of sensorimotor integration. Brain 126:860–879, 2000.

A thoughtful analysis of brain functional and anatomic studies in human adults with the three classic forms of apraxia, correlated with results from monkey neurophysiological studies that raises the notion that a conceptual system (failure of which would lead to ideational apraxia) and a production system (failure of which would lead to ideo-motor and limb-kinetic apraxia) may be separable entities. This analysis depends on the relatively recent concept of multiple parallel-distributed pathways being used in concert to effect action.

Liepmann H: Drei Aufsatze aus dem Apraxiegebiet. Berlin, 1908, Karger.

This is a thoughtful synoptic text that reviews the general concept of apraxia as a higher-order motor execution deficit. It describes and coherently classifies forms of apraxia commonly seen after focal cerebral lesions in adults. It presents tests to differentiate the various types. It describes parapraxis (extra movements sometimes inhibitory to task completion). It outlines a very modern concept: there are many brain areas that initiate movement depending upon the type and purpose of the action.

Nichols PL: Minimal brain dysfunction and soft signs: the Collaborative Perinatal Project. In: Tupper DE, editor: Soft neurological signs. New York, 1987, Grune & Stratton, pp. 179–199.

A statistical evaluation of the Collaborative Perinatal Project outcome concerning soft signs in a large cohort of children. It is especially pertinent to motor execution deficits in relation to other cortical function deficits. The 30 000 subjects all received a standard battery of tests, including a Wechsler Intelligence Scale for Children and a neurologic examination at age 7 years. They had all been followed since birth.

CHAPTER 19

Disorders of Cognitive Function in the Preschooler

Ruth Nass, MD and Gail Ross, PhD

OUTLINE

Developmental language disorders
Autistic spectrum disorders
Developmental coordination disorders
Visuospatial disabilities
Attention deficit hyperactivity disorder
Variations in temperament and cognitive style

Developmental language disorders

General discussion

A developmental language disorder (DLD) is diagnosed when a child with normal intelligence and hearing fails to develop language in an age-appropriate fashion (Table 19.1). Most children have good receptive language by age 2 years, along with a 50 to 100-word (or more) vocabulary and some two-word phrases. Lack of well-developed expressive language by age 3 years is definitely abnormal. However, the large degree of individual variability in the rate of language acquisition (Bishop & Leonard 2000; Toppleberg & Shapiro 2000; Verhoeven & van Balkom 2003) makes it difficult at times to distinguish DLD from initial idiosyncratic delay with eventual catch-up and normal language. For example, in a group of approximately l000 ultimately normal children, first word acquisition occurred anywhere from age 6 to 30 months and phrase acquisition anywhere from l0 to 44 months (Morley 1965). This variability also accounts, at least in part, for the wide range (1–25%) in the reported prevalence of DLD in preschool children. Erring on the side of overdiagnosis in the young child and initiating therapy is probably better than underdiagnosis.

Risk factors for DLD include low birth weight or prematurity, parental mental retardation, and a family history of developmental language disorders (National Collaborative Perinatal Project, Lassman *et al.* 1980). Increased monozygotic versus dizygotic twin concordance rates indicate that heredity, not just shared environment, is the cause of familial clustering (Bartlett *et al.* 2002). A number of gene loci have been implicated including: 13q 16q and 19q (SLI Consortium 2002). In the three generation KE family half the members are affected with a severe speech and language disorder that is transmitted as an autosomal dominant monogenic trait – the FOXP2 forkhead-domain gene (Watkins *et al.* 2002a; Vargha-Khadem *et al.* 2005). Notably, however, a recent screening of 270 4-year-olds with DLD was negative for the FOXP2 mutation (Meaburn *et al.* 2002). Whether frequent episodes of otitis media increase the risk of a DLD is debated (Shriberg *et al.* 2000).

Diagnosis

Table 19.2 lists additional warning signs that suggest DLD during the first 3 years. However, it is worth noting that a DLD diagnosis at age 2 years may not be reliable. In one recent study only about 40% of children retained the diagnosis at ages 3 and 4 years (Dale *et al.* 2003). In another study only one-quarter of children diagnosed with a DLD as preschoolers still had a DLD at school age; more than half of the original cohort turned out to have IQs too low to diagnose DLD. Ten per cent were normal (Webster *et al.* 2004). Another basis for diagnosis is a large discrepancy between nonverbal intelligence and language capabilities (Klee *et al.* 2000; Aram

FEATURES

Table 19.1 Developmental Language Disorders

Discriminating feature

1. Language deficit

Consistent feature

1. Problems with comprehension or production

Variable features

1. Mental retardation
2. Social problems
3. Pragmatics difficulty

et al. 1992). Various discrepancy criteria have been used to identify children with developmental language disorders. In one study children clinically designated as having a developmental language disorder were identified only 40–60% of the time, using variations of the Stanford Binet IQ test – Test of Language Development discrepancy score. A nonverbal IQ – specific language test performance discrepancy criteria of 1 standard deviation (i.e. Wechsler Performance IQ versus the Peabody Picture Vocabulary Test, Token Test, Rapid Automatized Naming, Sentences repetition subtest of the Comprehensive Evaluation of Language Function identified 34% of very low birth weight 7-year-olds and 45% of controls as having a developmental language disorder. A two standard deviation discrepancy yielded 14 and 19% frequency in the two groups, respectively (Aram *et al.* 1992). However, both under and over diagnosis occur with the best currently available criteria.

TABLE 19.2

Warning Signs of a Developmental Language Disorder

Limitations in expressive language
Has feeding problems related to sucking, swallowing, and chewing
Fails to vocalize to social stimuli and fails to vocalize two syllables at 8 months
Produces few or no creative utterances of three words or more by age 3
Limitations in vocabulary
Has small repertoire of words understood or used and acquires new words slowly or with difficulty
Limitations in comprehending language
Relies too much on contextual cues to understand language
Limitations in social interaction
Rarely interacts socially, except to have needs met
Limitations in play
Has not developed symbolic, imaginative play by age 3
Does not play interactively with peers
Limitations in learning speech
Expressive speech contains numerous articulation errors or is unintelligible to unfamiliar listeners
Limitations in using strategies for language learning
Uses unusual or inappropriate strategies for age level, e.g. overuses imitation (echolalia), does not imitate verbalizations of others (dyspraxia), does not use questions for learning ("why" questions)
Limitations in attention for language activities
Shows little interest in book reading, talking, or communicating with peers

Source: Modified with permission from Nelson NW: *Childhood language disorders in context: infancy through adolescence.* New York, 1993, Macmillan; Hall N: Developmental language disorders. *Semin Pediatr Neurol* 4:77–85, 1997.

Subtypes of developmental language disorders

Depending on subtype, DLDs vary in their characteristic features, etiology, prognosis, and treatment response (Table 19.3). The subtypes listed focus on psycholinguistic features and are named for the areas that are most problematic (Table 19.4) (Rapin 1996).

Articulation and expressive fluency disorders

Pure articulation disorders

Articulatory skills improve with age and, as with language development, the normal range is considerable (Morley 1965). Most children (70%) speak intelligibly by age 2 years. Unintelligible speech is the exception at age 3 years (15%). However, almost 50% of children at age 4 years still have articulation difficulties. A common problem is defective use of "th" or "r." At kindergarten entry, one-third of children still have minor to mild articulation defects, but speech is unintelligible in less than 5%.

Stuttering and cluttering

Stuttering is a disorder in the rhythms of speech. The speaker knows what to say, but is unable to say it because of an involuntary, repetitive prolongation or cessation of a sound. Some degree of dysfluency is common as language skills evolve during the preschool years, particularly as mean length of utterance (MLU) reaches 6–8 words between ages 3 and 4 years. However, stuttering, in contrast to developmental dysfluency, is probably a linguistic disorder (errors occur at grammatically important points in the sentence), as well as a motor planning problem (Logan 2003). Stuttering is often a genetic trait. Although the cause of developmental stuttering is unknown, the main theories are anomalous dominance and abnormalities of interhemispheric connections (Foundas *et al*. 2001). Stuttering occurs more frequently in children with other DLDs and with mental retardation (Gordon 2002). Cluttering, by contrast, as seen in Fragile X syndrome, is characterized by incomplete sentences and short outbursts of two- to three-word phrases, along with echolalia, palilalia (compulsive repetition reiterated with increasing rapidity and decreasing volume), perseveration, poor articulation, and stuttering.

Phonological programming disorder

Children with the phonological programming disorder have fluent speech, and MLU approaches normal. Despite initially poor intelligibility, serviceable speech is expected. Language comprehension is relatively preserved. Most such children show delayed rather than deviant phonology, and improve 1 and 7 years after their preschool diagnosis. It is debatable whether this disorder is a severe articulation problem or a mild form of verbal dyspraxia (Shriberg 1994). The fact that patients with the phonological programming

TABLE 19.3

Subtypes of Developmental Language Disorders

	Verbal auditory agnosia	Phonological syntactic	Verbal dyspraxia	Phonological programming	Semantic pragmatic	Lexical syntactic
Comprehension – receptive						
Phonology	↓	↓				
Syntax	↓↓	↓				
Semantics	↓↓	?			↓↓	↓
Production – expressive						
Semantics (lexical)	↓↓	↓			↓↓	Nl or ↓
Syntax	↓↓	↓	?	?		↓
Phonology	↓↓	↓	↓	↓		
Fluency	↓↓	↓	Nl or ↓	Nl or ↓	Nl or ↓ or ↓	↓
Pragmatics	Nl or ↓	Nl or ↓			↓↓	↓

Nl = normal. Source: modified from Rapin I: *Preschool children with inadequate communication*. London, 1996, MacKeith Press.

TABLE 19.4

Glossary of Linguistic Terms

Functors	The small words of the language like prepositions, conjunctions, etc. These are also called closed class words because they are limited in number.
Lexicon	The words in a language, the dictionary of word meanings.
Mean length of utterance	Number of morphemes per utterance.
Morpheme	The smallest meaningful unit in a language occurring either in a word or as a word. A compound word like *compounding* is made up of three morphemes, com*pound*ing. Prefixes, suffixes and inflected endings like*ed, *s, and *ly are also morphemes.
Phoneme	A distinct sound unit in a language. In English there are 46: 9 vowels and 37 consonants.
Phonology	The rules a speaker follows when combining speech sounds.
Pragmatics	The communicative intent of speech rather than its content, e.g. asking a question at the right time and in the right way.
Prosody	The melody of language, the tone of voice used to ask questions, for example, or show emotion.
Semantics	The meaning of words, their definition.
Syntax	The grammar of a language, the acceptable relationship between words in a sentence.

disorder have more difficulty learning manual signs than controls supports an association with dyspraxia (Bradford & Dodd 1994; Bishop 2002a). A preremediation paired associate learning task may help select the best remediation method for each child because some are better with symbols and some with signs (Pearce *et al*. 1987). An adult aphasia equivalent does not exist.

Verbal dyspraxia

The speech of children with verbal dyspraxia (Nevo *et al*. 2001), also called dilapidated speech (Critchley 1970; Ferry *et al*. 1975), is extremely dysfluent. Utterances are short and laboriously produced. Phonology is impaired and includes inconsistent omissions, substitutions, and distortions of speech sounds. Syntactic skills are difficult to assess in the face of dysfluency. Language comprehension is relatively preserved. Many require speech and language therapy for prolonged periods. Children with verbal dyspraxia who do not develop intelligible speech by age 6 years are unlikely to acquire it later. The frequency with which nonverbal praxis deficits – buccal-lingual dyspraxia (e.g. positioning muscles of articulation) and generalized dyspraxia or clumsiness – coexist with verbal dyspraxia is unknown (Bishop 2002). The presence of a more diffuse disorder of praxis has significant therapeutic implications because children with verbal dyspraxia may depend on signing and writing skills for communication (Shriberg *et al*. 1997). Although often accompanied by more neurological symptoms, verbal dyspraxia most resembles the adult aphasia called aphemia.

Disorders of receptive and expressive language

Phonological syntactic syndrome

Phonological syntactic syndrome (also called mixed receptive expressive disorder, expressive disorder, and nonspecific formulation-repetition deficit) is probably the most common DLD (Wilson & Risucci 1986; Korkman & Hakkinen-Rihu 1994). The phonological disturbances consist of omissions, substitutions, and distortions of consonants

and consonant clusters in all word positions. The production of unpredictable and unrecognizable sounds makes speech impossible to understand. The syntactic impairment consists of a lack of functors and an absence of appropriate inflected endings. Grammatical forms are atypical not just delayed. Whereas a normal young child may say "baby cry" or "a baby crying," children with phonological syntactic syndrome produce deviant constructions, such as "the baby is cry" (Van der Lely 1997; Bishop *et al*. 2000). Telegraphic speech is common. The presence or absence of difficulties in other language areas is variable. Overall, comprehension is relatively, although not wholly, spared. Semantic skills tend to be intact. Repetition, pragmatics, and prosody may be normal. Autistic children with this DLD subtype produce a significant amount of jargon.

Neurological dysfunction is especially frequent in this developmental language disorder subtype. Feeding problems due to sucking, swallowing, and chewing difficulties are common, and drooling is often persistent. The neurological examination may reveal signs of pseudobulbar palsy, oromotor apraxia, hypertonia and incoordination. This DLD most resembles Broca's aphasia in adults.

Verbal auditory agnosia

Despite intact hearing, meaningful language is not understood by children with verbal auditory agnosia (VAA) (also called generalized low performance and global dysfunction). VAA may occur on a developmental basis, and as an acquired disorder, the Landau–Kleffner syndrome (Tuchman 1997; Galanopoulou *et al*. 2002). VAA is common in low functioning children with autism. VAA best supports the theory that DLDs result from difficulty with processing basic sensory information entering the nervous system in rapid succession (Bishop *et al*. 1999; Tallal & Benasich 2002).

The outcome from the developmental form of VAA is generally poor. The outcome from the acquired disorder is somewhat better with approximately one-third of patients having a good outcome. VAA is seen in adults with acquired bitemporal lesions.

Higher-order language disorders

Semantic pragmatic syndrome

Children with the semantic pragmatic syndrome (also called repetition strength and comprehension deficit, language without cognition, and cocktail party syndrome in children with hydrocephalus usually with accompanying meningomyelocoeles) are fluent speakers, even verbose. Vocabulary is often large and somewhat formal. Parents are often encouraged by the child's sizable vocabulary only to find later that the verbosity did not indicate superior cognitive skills. Many children have trouble with meaningful conversation and informative exchange of ideas. They talk to talk. Pragmatic skills are lacking. Children with semantic pragmatic syndrome often show deficits in prosody; their speech has a monotonous, mechanical, or sing-song quality. They cannot convey the additional pragmatic intentions that prosody affords, such as speaking with the proper emotion or indicating by tone of voice that they are asking a question. Comprehension may be impaired. Phonological and syntactic skills are generally intact (Rapin 1996). Semantic pragmatic syndrome is often seen in higher-functioning autistic children (Bishop 2002b; Bishop & Norbury 2002).

Repetition strength in the setting of fluent speech with impaired comprehension characterizes the adult aphasia syndrome of transcortical sensory aphasia. Difficulties with prosody and pragmatics suggest right hemisphere dysfunction.

Lexical syntactic syndrome

The lexical syntactic syndrome is relatively common, occurring in approximately 15% of children with DLD (Wolfus *et al.* 1980). Speech is generally dysfluent, even to the point of stuttering, because of word-finding difficulties and poor syntactic skills, with many hesitancies and false starts. Both literal and semantic paraphasias are common. Syntax is immature, not deviant. Phonology is spared, and therefore speech is intelligible. Repetition is generally better than spontaneous speech. In conversation, idiom use is better than spontaneous speech. Pragmatics may be impaired, particularly when this syndrome occurs in autistic children. Comprehension is generally acceptable, although comprehension that requires processing highly complex syntactic utterances may be deficient.

No clear counterpart for the lexical syntactic syndrome exists among the acquired aphasias of adulthood, despite overlap with anomic aphasia, conduction aphasia, and transcortical aphasia.

Outcome of developmental language disorders

The occurrence of a DLD, even when it appears to resolve, may affect later social emotional adjustment, educational achievement, and vocational choices. Short and long-term behavioral, social-emotional and psychiatric problems are associated with early language problems (Irwin *et al*. 2002; Jerome *et al*. 2002; Brownlie *et al*. 2004; Clegg *et al*. 2005). In school-age children with speech and language problems, the frequency of attention deficit hyperactivity disorder (ADHD) ranges from 30% to 49%, and the frequency of behavioral and emotional problems ranges from 10% to 22% to 50% (Toppleberg & Shapiro 2000; Beitchman *et al*. 2001). The biggest differentiating factor between those with and without a psychiatric diagnosis is the degree of language deficit. In the National Collaborative Perinatal Project (Lassman *et al*. 1980) children with receptive and expressive language problems at age 3 years were at significantly increased risk for one of the three study defined "minimal brain dysfunction"

syndromes – hyperkinesis, soft signs, learning disabilities – at age 7 years (Nichols & Chen 1981). In preschool children with DLD, nonverbal intelligence is the best single predictor of overall long-term outcome and severity of language problems is the best predictor of later language skills. Preschool language skills are the best single predictor of later reading ability and disability (Snowling *et al*. 2000). Even children with good receptive skills who speak late may be at risk for continuing subtle language difficulties and later reading and language-based academic difficulties (Rescorla 2002), including writing (Bishop & Clarkson 2003). Thus, both screening and follow-up studies of children with DLD are important. Persisting, although often subtle, language problems in adolescence and beyond have been reported in as many as 90% (Conti-Ramsden *et al*. 2001; Rescorla 2002). Communication problems, again often subtle, may continue into adult life in 50–70% (Young *et al*. 2002).

Workup

The workup of the child with a developmental language disorder must include an assessment of hearing and an assessment for overall level of cognitive functioning. An electroencephalogram (EEG), including a sleep record, may be useful in children with isolated language delay to exclude subclinical seizures (Tuchman 1997). Overnight sleep recordings increase the yield considerably. Major risk factors for epilepsy and epileptiform EEGs are mental retardation, cerebral palsy, language regression, and the verbal auditory agnosia language disorder subtype.

Perisylvian abnormalities associated with language disorders have been reported, particularly in verbal dyspraxia and the phonological syntactic syndromes. Complete opercular agenesis has been reported in association with suprabulbar palsy (Worster–Drought syndrome). Polymicrogyria has also been reported in the perisylvian region. Patients with the most extensive disease have the greatest language impairments, while those with posterior parietal polymicrogyria have milder symptoms (Nevo *et al.* 2001; Alarcon *et al.* 2002; Guerreiro *et al.* 2002). Semantic pragmatic syndrome has been reported in patients with agenesis of the corpus callosum and with hydrocephalus, which supports a possible localization in the subcortex and its connections or a disconnection effect. Some children and adults with DLD (as well as relatives of DLD probands) do not have the typical planum temporale and frontal cortex asymmetry patterns (De Fosse *et al.* 2004; Herbert *et al*. 2005). The absence of the typical planum asymmetry may be the result of aberrant neurogenesis, which leads to reduced cell development in the perisylvian regions or atypical patterns of cell death (Semrud-Clikeman 1997; Herbert *et al.* 2005). Callosal size may be decreased in some children with DLD (Preis *et al.* 2000). An extra sulcus in the inferior frontal gyrus was statistically associated with a history of DLD (Clark & Plante 1998) in a group of 41 neurologically normal adults. In one recent series one-third of 35 children with DLD had nonspecific MRI abnormalities including ventricular enlargement (5), central volume loss (3), and white matter abnormalities (4) (Trauner *et al.* 2000). Rare reports document right hemisphere abnormalities in the DLD child suggestive of a right hemisphere contribution to language acquisition (Plante *et al.* 2001). In the KE family (see above) the caudate nucleus and inferior frontal gyrus are reduced in size bilaterally, while the left frontal opercular region (pars triangularis and anterior insular cortex) and the putamen bilaterally have a greater volume of gray matter (Watkins *et al.* 2002b; Vargha-Khadem *et al.* 2005). Recent functional imaging show more posterior and more

Developmental Language Disorders

PEARLS & PERILS

- If in any doubt, assess hearing. Missing a hearing loss is missing a potentially treatable cause of DLD.
- In spite of individual variability, failure to develop normal expressive language skills by age 3 years is pathologic.
- Between 18 months and 3 years, those children with both expressive and receptive delays are more likely to ultimately be diagnosed with a developmental language disorder than those with only expressive delays, who may catch up. Erring on the side of overdiagnosis in the young child with transient institution of unecessary therapy is better than underdiagnosis.
- An EEG is a useful screening procedure in children with DLDs, because treatment of an underlying paroxysmal disorder may improve language function.
- Failure to develop intelligible speech by age 6 years is a poor prognosis sign in verbal dyspraxia.
- DLDs often diminish, but the basic deficit affects language-related academic skills, particularly reading. Suggesting to the parents that they are merely an element of immaturity is generally inaccurate.
- Regression of articulation skills during stress and excitement is common during the preschool years. Artiulation in the office may be less adept than is actually the case.
- Beware of the child whose conversation is fluent but lacking in content. His parents may be the most resistant to accepting the diagnosis of DLD.
- The child with developmental language problems is at risk for emotional difficulties and should be monitored for possible intervention.
- The child who appears to "talk to talk" rather than to communicate and whose head is large ought to be assessed for hydrocephalus, in view of the frequency of the cocktail party syndrome in this disorder.
- Later reading problems are common in the child with a DLD. Expectant assessment should be performed if there is any hint of reading readiness difficulties.

bilateral activation in the family members with the FOXP2 gene mutation (Liegeois *et al.* 2003). An insufficient dosage of critical forkhead transcription factors during embryogenesis may lead to maldevelopment of brain speech and language regions of the brain (Lai *et al.* 2001). Metabolic imaging suggests abnormalities in the left temporal region and may vary by DLD subtype. Some children with DLD may be right hemisphere language dominant (Bernat & Altman 2003). Despite these research results there is no reason to image the typical DLD child in clinical practice, unless focal abnormalities are suspected from the history, e.g. a nonfamilial, early declaring left hander or on examination.

Treatment

Whether intensive early therapy changes the long-term outcome to an appreciable degree remains to be determined (Forrest 2002). Treatment of language disordered preschool children varies according to the kind of language impairment as well as its degree of severity. Children with a moderate to severe language impairment, who suffer associated social, cognitive and behavioral difficulties are best treated in a therapeutic nursery. Mildly impaired children can often do well in a regular nursery program combined with individual speech-language therapy. Play materials are used by the speech-language therapist with the preschool child in a directive way. Every activity becomes a language activity in that the child's actions are given words by the therapist. Play activities are also a helpful way to engage children with severe expressive difficulties. Pleasurable activities involving the mouth such as blowing bubbles or initiating mouth movements and sounds as well as nonvocal imitative games such as hand clapping have been found to foster language acquisition. Formal language work typically begins at the phonologic level involving repetition of sounds and sound sequences to encourage fluency. Treatment of receptive disorders often necessitates the use of visual modalities such as signs and gesture. Less severe disorders of comprehension are addressed through practiced structuring of conversations with the child. Developmental language disordered children with severe comprehension deficits rarely progress in treatment as well as children with primary expressive disorders.

Another tact for language remediation is driven by different theoretical frameworks (Dunn 1997). One approach involves identifying specific linguistic deficits (e.g. problems with morphology) and targeting them for remediation. Another involves identifying specific DLD subtypes and addressing them in remediation. This approach means, for example, that a child's level of comprehension is taken into account in selecting a strategy for improving language production. A third approach aims to detect a core cognitive processing deficit to be targeted for intervention. A fourth approach emphasizes the neuropsychological profile. In contrast to the other approaches, which are deficit centered, the neuropsychological approach defines and uses children's strengths to remediate their weaknesses; it also takes into account the child's temperament and neurodevelopmental status to determine his learning styles and develop optimal methods for remediating targeted deficits. To date no formal study has compared the efficacy of these approaches.

CONSIDER CONSULTATION WHEN…

- Table 19.2 warning signs are present a consultation with a speech and language pathologist is indicated.

Autistic spectrum disorders

General discussion

The triad of impaired sociability, impaired verbal and nonverbal communication skills, and restricted activities and interests, all of early onset, are diagnostic of the autistic spectrum disorders (ASD) (Rapin 1996; 2002) (Table 19.5, Fig. 19.1). The presence or absence of social disabilities distinguishes developmental language disorders (DLD) from ASD. IQ, language and social normalcy distinguish nonautistic mental retardation (NAMR) from DLD and ASD (Fig. 19.2). The range of disabilities seen among children in the autistic spectrum is considerable (Constantino *et al*. 2004). Asperger's syndrome (Table 19.6) represents the high-functioning end of the ASDs (Klin *et al.* 2001; Gillberg 2002; Frith 2004). Paralinguistic rather than linguistic problems are characteristic (Bishop 2002b). The frequency of ASD ranges from 0.4 to 70.0 per 10 000 children, depending on how the disorder is defined (Gillberg & Coleman 2000; Honda *et al.* 2005) (Table 19.7). The reported increase in incidence of the ASDs most likely reflects an increasing awareness of the different possible manifestations of the disorder (Wing & Potter 2002; Fombonne & Tidmarsh 2003), rather than a true increase in the incidence of ASDs.

A hereditary basis is probable in many cases because of (1) a high concordance in monozygotic twins (90%), (2) an approximately 5% increased risk for dizygotic twins and siblings, (3) a broader autistic phenotype in the families of probands (Piven & Palmer 1999), and (4) an association with several genetic disorders (Spencer 2001). The dramatically diminished risk in relatives who share 50% versus 100% of their DNA is most consistent with an oligogenic inheritance pattern, where more than 2 and as many as 100 genetic variants may contribute to susceptibility to developing autism. Each gene may make a different contribution to the disorder, with gene A more important for the development of repetitive stereotyped behaviors and gene B more important for language acquisition (Alarcon *et al.* 2002; Veenstra-Vanderweele & Cook 2003). Chromosomal abnormalities have been

TABLE 19.5

Criteria for Diagnosis of Autism

Six items or more from 1, 2, and 3, with at least 2 from 1, and one each from 2 and 3.

Impairment in social interaction

- Impaired use of nonverbal behaviors (eye gaze, facial expression)
- Poor peer relationships
- Impaired sharing of enjoyment, interests or achievements with others
- Lack of social or emotional reciprocity

Impaired communication

- Delayed language
- Impaired ability to sustain conversation
- Repetitive or idiosyncratic language
- Impaired pretend play

Restricted range of behaviors or interests

- Encompassing preoccupation
- Inflexible adherence to routines
- Stereotyped motor mannerisms
- Preoccupation with parts of objects
- Onset prior to age 3 years

Modified from *Diagnostic and statistical manual of mental disorders*, 4th edn. Text Revised Washington DC, 2000, American Psychiatric Association.

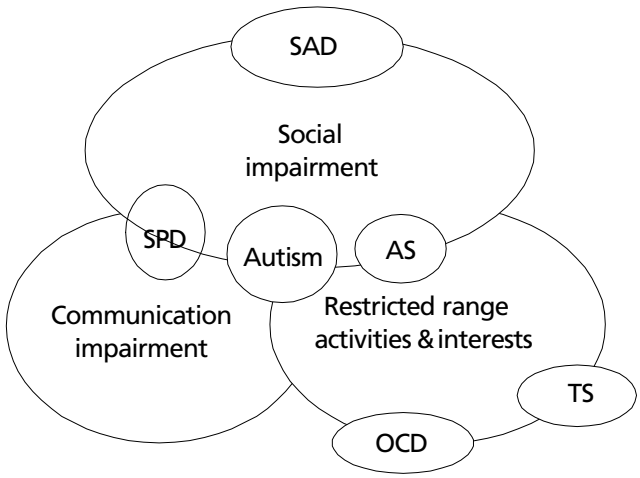

Fig. 19.1 Venn. TS =Tourette syndrome; OCD = obsessive-compulsive disorder; AS = Asperger syndrome; SAD = social anxiety disorder; SPD = semantic pragmatic disorder. This Venn diagram shows the overlap of all three symptom areas in autism, of two areas in AS, and of disorders involving a single symptom often reported in ASD families. Modified from Nass & Leventhal 2004.

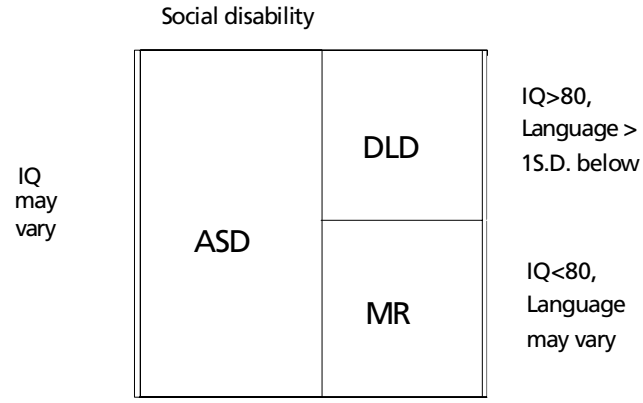

Fig. 19.2 Nosology. The presence or absence of social disabilities distinguishes developmental language disorders (DLD) from ASD. IQ, language and social normalcy distinguish nonautistic mental retardation (NAMR) from DLD and ASD.

TABLE 19.6

Asperger's Syndrome

Qualitative impairment in social interaction, manifested by at least two of the following:

- Impairment in use of nonverbal behaviors to regulate social interaction
- Failure to develop peer relationships
- Lack of spontaneous seeking to share enjoyments and interests
- Lack of social or emotional reciprocity

Restricted repetitive and stereotyped behavior, interests and activities, manifested by at least one of the following:

- Encompassing preoccupation
- Inflexible adherence to nonfunctional routines
- Stereotyped and repetitive motor mannerisms
- Persistent preoccupation with parts of objects

Disturbance causes significant impairment in functioning.
No clinically significant language delay.
No clinically significant cognitive deficit.

Modified from *Diagnostic and statistical manual of mental disorders*, 4th edn. Text Revised Washington, DC, 2000, American Psychiatric Association.

reported on chromosomes 2q37, 7q, 22q13, and 13q, among others. Both Fragile X and the Rett syndrome mutation can present with an autistic spectrum phenotype. However, the most common currently known specific genetic cause of autism appears to be a maternally inherited duplication of chromosome 15q11–13 (diagnosed by FISH), accounting for 1–3% of cases (Veenstra-Vanderweele & Cook 2003).

FEATURES

Table 19.7 Autistic Spectrum Disorders

Discriminating features

1. Sociability deficit
2. Language disability
3. Need for sameness

Consistent features

1. Play impairment
2. Stereotypic behaviors

Variable feature

1. Mental ability

Diagnosis

The three key features of the autistic spectrum disorders – language and communication impairments, social deficits, and rigidity – are highlighted in Fig. 19.1, a Venn diagram, which also indicates overlapping disorders (DSM–IV TR, APA 2000; Nass & Leventhal 2004). A number of different assessment tools, including parent questionnaires, parent interviews and direct assessments are available for use in the office by specialists in pediatric neurology, psychiatry, neurodevelopmental disabilities, and psychology (Lord & Risi 1998; de Bildt *et al.* 2004) (Tables 19.8–19.10). The Autism Diagnostic Observation Scale (ADOS) and the Autism Diagnostic Interview (ADI) are generally considered the gold standard for diagnosis, particularly for research studies, but are not usually necessary for making a clinical diagnosis.

Specific clinical features

Intelligence and Cognition

The presence of language and social deficits defines ASD, not the IQ level (Fig. 19.2). While 70–85% of children with ASD are mentally retarded, some have average or even superior intellectual ability. IQ is a key predictor of long-term outcome in autism, especially when the IQ is less than 50 (Stevens *et al.* 2000). Those with low IQ generally fare poorly. When Asperger's syndrome is included as an autism spectrum disorder, the rate of mental retardation in ASD drops considerably.

Some consider the core cognitive deficit of ASD to be an inability to grasp other people's thoughts; a failure to develop a theory of mind (Baron-Cohen *et al.* 2001). "Mindblindness" manifests differently at different stages of development (see Table 19.11). Others have suggested that the metacognitive basis of autism is an abnormality of executive functioning – the ability to problem solve, shift sets, and plan to reach a goal (Ozonoff *et al.* 2004). A third theory postulates the underlying basis as a failure of central coherence, the capacity to integrate information and see the gestalt (Volkmar & Pauls 2003; Frith 2003).

TABLE 19.8

Autism Checklist for Children under 3 Years

1. Does your child enjoy being swung, bounced on your knee, etc?
2. Does your child take an interest in other children?
3. Does your child like climbing on things such as up stairs?
4. Does your child enjoy playing peek-a-boo/hide-and-seek?
5. Does your child ever pretend, for example, to make a cup of tea using a toy cup and teapot, or pretend other things?
6. Does your child ever use his index finger to point, to ask for something?
7. Can your child play properly with small toys (e.g. cars or bricks) without just mouthing, fiddling, or dropping them?
8. Does your child ever bring objects over to you (parent), to show you something?
9. Does your child look you in the eye for more than a second or two?
10. Does your child ever seem oversensitive to sound, e.g. plugging his ears?
11. Does your child smile in response to face or your smile?
12. Does your child imitate you? For example, when you make a face will your child imitate it?
13. Does your child respond to her name when you call?
14. If you point at a toy across the room, does your child look at it?
15. Does your child walk?
16. Does your child look at things you are looking at?
17. Does your child make unusual finger movements near his face?
18. Does your child try and attract your attention to her own activity?
19. Have you ever wondered if your child is deaf?
20. Does your child understand what people say?
21. Does your child sometimes stare at nothing or wander with no purpose?
22. Does your child look at your face to check your reaction when faced with something unfamiliar?

Modified from Robins *et al.* 2001.

Language

Verbal and noverbal communication difficulties are a cardinal feature of ASD. The extent of the language deficit generally parallels IQ. In lower functioning ASD children, language, if present, is echolalic; repetitive and stereotyped phrases are common. Some children fail to process language and despite normal hearing can appear deaf (verbal auditory agnosia). Phonological syntactic and lexi-

TABLE 19.9

Things to Do in the Office to Assess for Autistic Spectrum Disorders in the Young Child

During the appointment, has the child made eye contact with you?	Yes	No
Get child's attention, then point across the room at an interesting object and say "Oh look! There's a [name a toy]!" Watch child's face. Does the child look across to see what you are pointing at?	Yes[1]	No
Get the child's attention, then give child a miniature toy cup and teapot and say "Can you make a cup of tea?" Does the child pretend to pour out tea, drink it, etc?	Yes[2]	No
Say to the child "Where's the light?" or "Show me the light." Does the child point with the index finger at the light?	Yes[3]	No
Can the child build a tower of bricks? (If so, how many?) (Number of bricks …)	Yes	No

Modified from Baron-Cohen *et al.* 1992. 1. To record yes on this item, ensure the child has not simply looked at your hand, but has actually looked at the object you are pointing at. 2. If you can elicit an example of pretending in some other game, score a yes on this item. 3. Repeat this with "Where's the teddy?" or some other unreachable object, if child does not understand the word "light." To record yes on this item, the child must have looked up at your face around the time of pointing.

PEARLS & PERILS

Autistic Spectrum Disorders

- Social deficits, rather than language deficits, may be key to defining the autistic spectrum disorders.
- If there is no language by age 5–6 years, language development is unlikely and the probable outcome is poor.
- Some children with autism may have subtle seizures and may benefit from anticonvulsants. If in any doubt, obtain an EEG. Video EEG monitoring is superior to routine monitoring.
- Fragile X syndrome is one of the most common known causes of autism. Obtain Fragile X DNA. The Rett mutation can also manifest in an atypical form as an ASD. A FISH for a maternal deletion of 15q11–13 and studies looking for subtelomeric deletions may be appropriate in families planning for more children to help to make a prenatal diagnosis on future siblings.
- Look for extrapyramidal signs in autistic children as a reflection of dopaminergic dysfunction.
- The child with an ASD mistakenly thought to have ADHD may become worse on stimulants, but he may also improve.
- Children with autism may respond to SSRIs, but higher doses may cause significant agitation or aggressiveness
- Early diagnosis is possible and important. Early and intensive intervention may make a significant difference.
- Although intellectual level is not a defining characteristic of the ASDs, it is an important predictor of long-term outcome.
- Look carefully at peer relations and language prosody and pragmatics in the child with attention and overfocus issues, he may actually have Asperger's syndrome and not ADHD.
- Tuberous sclerosis is a common cause of autism. A careful examination of the skin is mandatory in all children with ASDs.

cal syntactic language disorders are also seen in relatively low functioning and relatively higher functioning ASD children, respectively. The highest functioning children often have semantic and pragmatic deficits (Bishop & Norbury 2002). They talk too much; in essence they talk to talk. Such children are often extremely literal and concrete. Prosody is frequently impaired as evidenced by mechanical, excessively rapid, monotonic, high pitched or poorly modulated speech. Yet other children have the phonologic syntactic syndrome. Language skills at age 5–6 years are predictive of long-term prognosis. Children with conversational language will do significantly better than children who have little or no language (Rapin 1996; 2002).

Abnormalities of play are part of the autistic child's communication disorder. The range of early play includes repetitive stereotypic and indiscriminate sensory use of objects (mouthing, rubbing, etc.), purely functional object use and imitation, mechanical play with puzzles and the like, limited interactive play with adults like running, catching, and tickling games, and activities involving their circumscribed areas of interest (e.g. board games, computers, electronic games, or high-level word and number tasks). These activities may provide pleasure. Pretend play involving, for example, simple role taking is often rudimentary even in higher functioning children (Waterhouse *et al.* 1996).

Social skills

Social dysfunction is a hallmark of the ASDs. The aloof child most resembles the popular notion of autism. These children do not follow their parents around, run to greet them, or seek their comfort. They tend to have low intelligence, poor verbal and nonverbal communication skills, and little symbolic play. Passive children are generally somewhat higher functioning overall. They do not make social approaches, but will accept them when made by others. They engage in some pretend play and join in games, but take a passive role, e.g. the baby in the game of mothers and fathers. Children

TABLE 19.10

Clinical Instruments for the Diagnosis of Autistic Spectrum Disorders in Preschool Children

Measure	Special features
Checklist for Autism in Toddlers (CHAT) (Baron-Cohen *et al.* 1992; Robins *et al.* 2001)	Screening measure; administered in the office; intended for early diagnosis at 18–36 months (Charman *et al.* 2002)
Social Communication Questionnaire (SCQ) (Lord)	A good parent questionnaire screen for ASD that correlates with the Autism Diagnostic Interview results. Normed for children 4 years and over with a mental age over 2 years. Has lifetime and current versions; the latter can be used to monitor progress and/or medication.
Childhood Autism Rating Scale (CARS) (Schopler *et al.* 1988)	Combines parent report and direct observation; useful for clinicians in the office; provides a measure of severity, but may be less helpful with children with milder forms of ASDs
Autism Behavior Checklist (ABC) (Krug *et al.* 1980)	Questionnaire completed by parent or teacher; intended for children above age 3 years; more useful for low functioning children to distinguish them from MR children.
Gilliam Autism Rating Scale 2001	Completed by parents of low functioning children. Good screening tool for office use. Derived from the DSM.
Gilliam Asperger's Disorder Scale 2001	Completed by parents of high functioning children. Good screening tool for office use.
Social Responsiveness Scale (Constantino 2005)	Completed by parents or teachers for children over 4 years. Picks up mild disorders.
Vineland Adaptive Behavior Scales (Sparrow *et al.* 1984)	Primarily for low functioning children; scores based on parent interviews; provides separate scales for communication, socialization, daily living skills, and motor skills (Szatmari *et al.* 2002).
Child Behavior Checklist (Achenbach & Rescorla 2002)	A behavior checklist for parents and caregivers of children 1½–5 years. Although not designed to diagnose ASD, older ASD children score high on the scales measuring attention problems, social problems and thought problems and low on the scale for somatic complaints (Boelte *et al.* 1999).
The Early Childhood Inventory-4. (Gadow *et al.* 2001)	This scale assesses for a number of diagnoses including PDD and ADHD in preschoolers.
ADI-R (Lord & Risi 1998)	Semi-structured parent interview that is used primarily for children 3–5 years of age; in-depth assessment administered by trained professional.
ADOS (Lord & Risi 1998)	In-depth, standardized assessment instrument to be administered by trained professional; primarily a research tool, but can also be used clinically to diagnose and evaluate social, communicative, and play behaviors in verbal and nonverbal children, adolescents and adults.

TABLE 19.11

Theory of Mind

Theory of Mind (TOM): Stages of Development	
14–18 months	Joint attention: adult and child look at a toy together Protodeclarative pointing: child calls adult's attention to object he wants
18–24 months	Symbolic play
2–3 years	Beginnings of primitive TOM: seeing leads to knowing Understanding desire, pretending, intention to joke
3–4 years	First-order TOM: knowing what another person is thinking, understand that another person may not know what you know (false beliefs); seeing leads to knowing, e.g. looking up and away means thinking, knows someone's choice by eye gaze direction
4–5 years	Advanced first-order TOM: counterfactual reasoning enhanced by pretense, e.g. a pretend preparation for counterfactual syllogism task

Modified from Baron Cohen *et al.* 2001; Nass & Leventhal, in press.

who are interactive but odd make spontaneous social approaches to others, but do it in a peculiar way. They tend to talk at other people and their persistence may become annoying. Pragmatic language skills are impaired. For example, conversations are often started with a question. Many persons on the autistic spectrum are relatively unaware of their social ineptitude except to the extent that others tease them (Waterhouse *et al.* 1996). However, some are quite self-conscious. Several books written by high functioning people with ASD highlight the different levels of awareness and concern (Grandin 1995; Willey 1999). Some people with Asperger's syndrome have dubbed other people "neurotypicals."

Recent research has focused on the autistic child's lack of interest in the human face, manifest both in atypical ways of scanning it in social situations and by differences in the brain areas involved in the perception of facial emotion. The face is at the epicenter of social cognition. Difficulties in the domain of social cognition are considered by some the crucial feature of the ASD (Haxby *et al.* 2002; Volkmar & Pauls 2003; Wang *et al.* 2004; Gross *et al.* 2004).

Restricted range of behaviors, interests, and activities

A restricted range of behaviors, interests, and activities is the third cardinal feature of autism. In lower functioning children, repetitive, stereotyped behaviors consist of activities like twirling, rocking, flapping, licking, and opening and closing doors. Abnormal sensory reactivity is common in ASD children (Rogers *et al.* 2003) and may underlie some of the self-stimulatory stereotypies. Overlap and comorbidity with tic disorders and obsessive-compulsive disorders are seen in higher functioning children (Gillberg & Coleman 2000; Nass & Leventhal 2004) (see Fig. 19.1). Many of these children have great difficulties with transitions. Often they don't attend to others because they are in their own world. But, they can also have difficulty transitioning because they are over-focused on something. Some individuals with exceptional artistic, musical or mathematical talents, as well as idiot savants, may meet criteria for a diagnosis of an ASD or Asperger disorder. Some of these children grow up to be single minded, perhaps peculiar, nonsocial chess or mathematics geniuses.

Natural history and outcome

Considering autism as a spectrum disorder, it is not surprising that the natural history of autism shows great variability. The diagnosis is often suspected by 18 months (Baron-Cohen *et al.* 1992; Johnson *et al.* 1992; Robins *et al.* 2001). Review of videotapes of first birthday parities have been reliably used to diagnose ASD in hindsight. About one-third of autistic children regress between the ages of 1 and 3 years and are at highest risk for poor outcome (Rapin 1996; Rogers 2004; Lord *et al.* 2004). Scholastic success is best predicted by overall intelligence and by language facility at the time they enter elementary school. Some autistic toddlers and preschoolers improve greatly by school age, but may still seem socially odd and have peculiarities of language prosody and pragmatics. In one study. children diagnosed with Asperger's syndrome had better social skills and fewer autistic symptoms 2 years after study enrollment as preschoolers than the children with the diagnosis of autism. The differences in outcome could not be explained by initial differences in IQ and language abilities. Children with autism who made significant language gains did better than those who did not (Szatmari *et al.* 2000). Many ASD children have tics (Baron-Cohen *et al.* 1999). Nonverbal learning disabilities, ADHD, or obsessive-compulsive disorder may become the more accurate middle-school-age diagnosis (Klin *et al.* 2001). During adolescence about one-third improve and one-third deteriorate (Gillberg & Coleman 2000). Onset of seizures or mood disorders, especially depression, usually underlie adolescent decline. About two-thirds of adults have limited independence and almost one-half require institutionalization. Fair to good adult outcomes are reported in 15–30%, but only about 5% become competitively employed, lead independent lives, marry and raise families. Psychiatric problems are common even in this group. As our view of this disorder as a spectrum evolves, the percentage with better outcomes will probably increase. Some odd adults, including family members who share phenotypic characteristics with an autistic proband, may go undiagnosed in childhood and adolescence, and even function in the mainstream. Indeed, the broader autistic phenotype seen in families of an autistic proband exemplifies this (Piven & Palmer 1999). Some adults with ASD are highly productive and original in their work. Bartok, the composer, and Wittgenstein, the philosopher, are believed by some to have had ASD (Gillberg 2002).

Evaluation and etiology

The standard neurological examination is generally normal. The skin must be carefully examined for evidence of tuberous sclerosis, the most common diagnosable disease associated with autism (Bolton 2004). The extent of metabolic and genetic workup depends on the clinical suspicions and the relevance to family counseling (Filipek *et al.* 2000). Many medical disorders can produce an ASD phenotype (Table 19.12).

Formal audiological assessment is required to exclude a hearing impairment. An electroencephalogram (EEG), including a sleep record or overnight video-EEG monitoring, may be appropriate to exclude subclinical seizures, especially when language comprehension is impaired or developmental regression has occurred (McVicar & Shinnar 2004). Mild-to-severe epilepsy, partial and generalized, occurs in

TABLE 19.12

Causes of Autism

- Prenatal
  - 1 and 2 trimester bleeding
  - "Suboptimality" of pregnancy
  - Congenital infection
- Perinatal
  - Hyperbilirubinemia
  - Hypoglycemia
  - Respiratory distress
- Congenital
  - Unilateral cerebellar hypoplasia
  - Hydrocephalus
  - Microcephaly
  - Moebius syndrome
- Metabolic
  - Addison's disease
  - Adenylosuccinate lyase deficiency
  - Adrenoleukodystrophy
  - Celiac disease
  - Histidinemia
  - Hurler's syndrome
  - Hyperthyroidism
  - Hyperuricosuria
  - Hypothyroidism
  - Lactic acidosis
  - Lipidosis
  - Mucopolysaccharidosis
  - Peroxisomal disorders
  - Phenylketonuria
- Syndromes
  - Angelman
  - Anorexia nervosa
  - CHARGE association
  - Cohen syndrome
  - Cornelia de Lange
  - Dandy Walker syndrome
  - De Lange syndrome
  - Duchenne muscular dystrophy
  - Ehlers Danlos
  - Goldenhar
  - Goldenhar syndrome
  - Hypomelanosis of Ito
  - Joubert
  - Kleine Levin
  - Lujan-Fryns
  - Mobius
  - Neurofibromatosis
  - Noonan
  - Oculocutaneous albinism
  - Rett complex
  - Smith Magenis
  - Steinert myotonic dystrophy
  - Tuberous sclerosis
  - Velocardio facial syndrome
  - Williams syndrome

TABLE 19.12 (Continued)

- Chromosomal
  - Trisomy 21
  - 18q-, XYY, XXX
  - Fragile X
  - Marker chromosome syndrome
  - Sex chromosome abnormalities
- Epilepsy
  - Infantile spasms
  - Landau-Kleffner variant
- Vascular
- Infection
  - Meningitis
  - Herpes encephalitis
  - Congenital Infections: rubella, herpes, CMV, toxoplasmosis
- Trauma
- Toxins
  - Fetal alcohol syndrome,
  - Fetal cocaine syndrome
  - Fetal thalidomide
  - Lead encephalopathy

Modified from Gillberg & Coleman 2000.

up to one-third of patients with autism by early adulthood. Infancy (infantile spasms) and puberty are particularly vulnerable periods. Those who are retarded are at higher risk, but epilepsy occurs in high-functioning children as well. Epileptiform abnormalities on EEG and early epilepsy occur more frequently in children who show early regression and more severe language problems (Tuchman 1997; Galanopoulou *et al.* 2002). Studies using magnetoencephalography suggest that diffuse epileptiform activity is frequent in children with autistic regression (Lewine *et al.* 1999).

Three major forms of neuropathology have been reported in autism (Rumsey & Ernst 2000): (1) decreased development of forebrain limbic system structures (e.g. cingulate, hippocampus, amygdala), substrates for memory and emotion; (2) a decreased number of Purkinje cells in the cerebellum; and (3) age-related differences in cell size and number in cerebellar and brainstem nuclei, suggestive of a dynamic developmental process. Structural abnormalities reported in autism based on imaging studies include increased brain volume (especially males), increased ventricular volume, increased white matter volume, atypical asymmetry patterns in temporal and frontal lobes, hypoplastic corpus callosum, hypoplastic cerebellum (vermian lobules VI and VII), hyperplastic cerebellum (10%), hypoplastic parietal lobes, and abnormalities in right cingulate gyrus, hippocampus, and amygdala (Hendren *et al.* 2000; Tsatsanis *et al.* 2003; De Fosse *et al.* 2004; Herbert *et al.* 2005). Recent imaging findings suggest that there may be differential effects driving white matter to be larger and cerebral cortex and hippocampus-amygdala to be relatively smaller (Herbert *et*

KEY CLINICAL QUESTIONS

- Is the child's language normal, including his prosody and pragmatics?
- Is the child socially engaged in the usual circumstances?
- Is the child over-focused and very poor at transitions?

al. 2003). However, brain imaging is generally unproductive in routine clinical practice. However, a recent meta-analysis of imaging in children with developmental delay, including autism, does demonstrate that MRI may show abnormalities in one-third, especially when the neurological examination is abnormal (Shevell *et al.* 2003).

Most metabolic imaging studies reveal hypometabolism in frontal and temporal regions (Rumsey & Ernst 2000). Recent functional imaging studies suggest abnormalities of the cerebellum (Allen *et al.* 2004) as well as all along the pathway responsible for processing emotional faces (Wang *et al.* 2004) and performing theory of mind tasks (Gallagher *et al.* 2000) – fusiform face area, superior temporal sulcus, amygdala, cingulate, and ventral medial frontal lobe. Altered perfusion in the right medial temporal lobe has been found in association with an obsessive desire for sameness (Ohnishi *et al.* 2000). Positron emission tomography (PET) studies suggest abnormalities of both serotonergic and dopaminergic function (Garreau 1998).

Treatment

Early intervention offers the best opportunity for mitigating the developmental abnormalities in ASD and related developmental disorders. In many states, children under 3 years of age with developmental delay are eligible for state-financed early intervention programs. Toddlers and preschool children with a diagnosis of ASD should receive special education services in a therapeutic nursery or in a home-based behavioral modification program. Several university centers throughout the USA (i.e. TEACCH, University of North Carolina or Young Autism Program, UCLA) have programs specifically for ASD children (Handleman & Harris 2001). Treatment of Asperger's syndrome often focuses around the

CONSIDER CONSULTATION WHEN...

- Aggressiveness, anxiety or mood changes dramatically. A psychiatric consultation is indicated.
- The child is significantly disrupting family life and is dangerous to himself or others.
- There are new prolonged lapses or episodes of staring, in which case video-EEG monitoring may be appropriate.

TABLE 19.13

Medications for Autism

Hyperactivity and inattention	Psychostimulants (methylphenidate; amphetamine); clonidine (Catapres), guanfacine (Tenex), atomoxetine (Strattera)
Obsessive-compulsive behaviors	Tricyclics – Clomipramine (Anafranil); SSRI – fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox); atypical neuroleptics – risperidone (Risperdal), olanzapine (Zyprexa), ziprasidone (Geodon), aripiprazole (Abilify)
Mood and mood stabilizers	SSRIs, bupropion (Wellbutrin), velafexen (Effexor), valproate (Depakote), carabamazipine (Tegretol), gabapentin (Neurontin), topiramide (Topamax), lamotrigine (Lamictal)
Aggressive and impulsive behaviors	Mood stabilizers – carbamazepine (Tegretol), oxcarbazepine (Trileptal), divalproex sodium (Depakote), gabapenten (Neurontin), topiramide (Topamax), lithium; clonidine; beta blockers – propranolol (Inderal); anxiolytics – buspirone (Buspar)
Tics/stereotypies	Clonidine, clonazepam (Klonipin), pimizide (Orap), haloperidol (Haldol), risperidone, baclofan (Liorisol)
Self-mutilation	Naloxone (Narcan), propranolol, fluoxetine, clomipramine, lithium
Psychosis	Neuroleptics: haloperidol decanoate (Haldol), risperidone (Risperdal), chlorpromazine (Thorazine), olanzapine (Zyprexa), ziprasidone (Geodon), quetiapine (Seroquel), aripiprazole (Abilify), clozapine (Clozaril)
Seizures	Divalproex sodium (Depakote); adrenocorticotropic hormone (ACTH)
Sleep problems	Clonidine (Catapres), melatonin, antihistamines

Modified from Gilman J, Tuchman R: Autism and associated behavioral disorders: Pharmacologic intervention. *Annals of Psychopharmacology* 29:47–56, 1995; Martin A, Patzer D, Volkmar F: Psychopharmacologic treatment of higher functioning PDD. In: Klin A, Volkmar F, Sparrow S, editors: Asperger syndrome. New York, 2000, Guilford Press, pp. 210–228; Towbin 2003; McDougle et al. 2002; Tuchman 2004)

use of social groups (Klin *et al.* 2001; Kransny *et al.* 2003). Medication treatment may be necessary and can be useful (Table 19.13).

Developmental coordination disorders

Diagnosis

A developmental coordination disorder (DCD) is defined by motor coordination difficulties which are markedly inappropriate for age and IQ and which cause significant interference with academic achievement or activities of daily living (APA 2000) (Table 19.14). The reported frequency in various studies and age groups ranges from 1 to 10%; the frequency tends to drop as children get older (Hadders-Algra 2002). In one recent large population study of 7-year-old children, moderate coordination disturbances occurred in 9% and severe disturbances in 5% (Kadesjö & Gillberg 1999). There is a clear male preponderance. DCD is associated with ADHD symptoms about half the time (Landgren *et al.* 2000). Children with DCD also have high rates of oppositional defiant disorder, which is generally a comorbidity of the ADHD. Asperger's syndrome has been reported in children with isolated DCD and in those with both DCD and ADHD (Kadesjö & Gillberg 1999). DCD alone and in combination with ADHD shows a strong correlation with developmental language disorders, school difficulties and later reading problems (Denckla *et al.* 1985; Gillberg & Gillberg 1989; Landgren *et al.* 1998). DCD also co-occurs relatively frequently with visuoperceptual problems. Gillberg (2003) has described a disorder of attention, motor coordination and perceptual problems (DAMP) occurring in as many as 1–2% in a severe form and 3–6% in milder versions among preschool and early elementary school age children.

Low socioeconomic class, familial motor clumsiness, prenatal factors particularly maternal smoking during pregnancy and neonatal problems (10% with complicated neonatal courses and 7% with normal neonatal courses) (Hadders-Algra 2002) appear to be risk factors for DCD and DAMP (Landgren *et al.* 1998). In the National Collaborative Perinatal Project (Nichols & Chen 1981) familial retardation and mental illness were risk factors for DCD and DAMP, as were a number of pregnancy complications and chorioamnionitis.

Several discrete types of developmental coordination disorders occur and more than one may occur in the same child (Macnab *et al.* 2001): clumsiness, dyspraxia, dysgraphia, adventitious movements, and anomalous dominance or handedness. Clumsiness is defined as a slowness and/or inefficiency in performing elementary fine motor and sometimes gross motor movements (Gubbay 1980). Clumsiness is more common in children with learning disabilities, and for this reason, the combination was inappropriately termed minimal brain dysfunction for many years. Children with developmental dyspraxia have difficulty with motor learning and motor execution. Dyspraxia can be a generalized deficit or a material-specific deficit. It can occur alone, in association with clumsiness, and/or in combination with other learning disabilities. Ideomotor and ideational dyspraxia both occur in children (Deuel 1995). Dysgraphia (difficulty with writing) can be a primary disturbance, a manifestation of clumsiness or dyspraxia, or be secondary to dyslexia occurring as a manifestation of a higher-order cognitive disorder. Adventitious movements (i.e. synkinesis, chorea, tremor, and tic) may occur normally on a developmental basis and are designated developmental soft signs when they persist beyond the age when they ought normally to cease (Table 19.15). With regard to handedness (manual dominance), most ultimately right-handed children declare handedness after 1 year of age and before age 5 years. Strong dominance when established before age 1 year should raise concern that handedness is pathological and indicates disturbed

FEATURES

Table 19.14 Developmental Coordination Disorders

Discriminating feature

1. Gross and/or fine motor difficulties

Consistent feature

1. None

Variable features

1. Hyperactivity
2. Neurologic soft signs
3. Visuomotor and spatial perception difficulties

PEARLS & PERILS

Developmental Coordination Disorders

- Children with DCD are at risk for behavioral problems, ADHD and ODD at school age.
- Children with DCD are at risk for a variety of learning difficulties.
- Children with DCD are at risk for social difficulties.
- Monitor the academic and emotional development of children with DCD.
- Classic dyspraxic syndromes occur in preschoolers, but it is necessary to look specifically for them.

KEY CLINICAL QUESTIONS

- Do your child's motor coordination difficulties interfere with academic achievement or activities of daily living?

TABLE 19.15

Natural History of Soft Signs

Neurological system affected	Soft sign	Age of appearance or disappearance (years)
Cranial nerves	Head does not move with eyes	6–7
	Sticks tongue out for 10 seconds	6–7
Motor	Toe and heel walk	3–4
	Heel and toe walks without associated movements	5–7
	Hop 10 times	5
	Hops indefinitely	7
	One-foot stand for 30 seconds	7
	No longer drifts up and down with pronated and supinated arms	3–4
	Rigid tripod	4–5
	Dynamic tripod	5–7
	Choreiform movements	7–10
	Athetoid movements	2–4
Cerebellar	Tandem gait	6
	No overflow during rapid alternating movements	7–8
Sensory	Stereoagnosis, graphesthesia	6
	No longer extinguishes on double simultaneous stimulation	8

use of the other hand. The percentage of right-handed children, and probably the strength of handedness, increases through age 5 years. Eventually, more than 90% of children are right-handed. Most right-handed people are strongly, right-handed, while most left-handed people are ambidextrous. Dexterity in left-handed and right-handed people is equal. However, the frequency of learning disabilities is greater in left-handed than right-handed people, and the frequency of left-handed people is greater among the learning disabled.

Evaluation and etiology

Developmental coordination disorders because of their heterogeneity can only be fully evaluated using a battery that taps the gamut of motor skills. In one study (Geuze *et al.* 2001) about 75% of children who were judged to have DCD by a team of specialists (rehabilitation doctor, occupational therapist, and physical therapist), performed below the 15th percentile on a comprehensive motor battery. The remaining 25% had handwriting problems or low muscle tone issues not measured by the particular battery used. Adventitious movements are generally assessed separately. Synkinesia is best elicited by finger tapping, finger sequencing, and stressed gait testing. Choreiform movements are best elicited by having the child stand with eyes closed, tongue out and pronated arms extended with fingers spread (see Chapter 4).

Some investigators suggest that children with developmental coordination disorders have difficulty internally representing the visuospatial coordinates of intended movements. Such a deficit implicates parietal lobe dysfunction in DCD since it is involved in processing feed-forward information from downstream motor areas by comparing it with local visuospatial representations that specify the coordinates of the prospective actions (Wilson *et al.* 2002).

CONSIDER CONSULTATION WHEN...

- The child's pencil grip or handwriting is delayed, when the child is frustrated by his graphomotor difficulties, then a consultation with an occupational therapist is indicated.
- Motor coordination difficulties are markedly inappropriate for age and IQ and cause significant interference with academic achievement or activities of daily living.

Treatment

Children with significant DCD may benefit from process-oriented occupational therapy, motor imagery intervention, and perceptual motor training (Wilson *et al.* 2002). Computers can facilitate output for those with poor graphomotor skills. Sometimes children with DCD require a scribe in the classroom.

Visuospatial disabilities

Diagnosis

Visuospatial disabilities (VSD) involving perceptual, organizational, memory, imagery and/or motor functions occur in

KEY CLINICAL QUESTIONS

- Can the child draw a person with the age appropriate number of body parts?
- Can the child draw spontaneously, and on request, age appropriate shapes?

isolation and in the context of nonverbal learning disabilities when children reach school age (Table 19.16). Spatial difficulties are usually apparent on traditional IQ testing as a large discrepancy between the verbal and performance IQ subtest scores, which occurs because several performance IQ subtests measure visual spatial and perceptual processing. Although the literature on visuomotor and spatial disabilities in the preschool age child is rather scanty, the importance of visuomotor and spatial skills to future academic achievement is attested to by the predictive power of visuomotor tasks (Koppitz 1963; Beery & Buktenica 2003), which require the child to copy geometric shapes, for academic achievement in reading and math throughout the elementary grades (Weeks & Ewer-Jones 1992). Data from the National Collaborative Perinatal Project (NCPP) (Nichols & Chen 1981) document that a low score on a block sort task (which required matching blocks by color, size and shape) or a poor copy of a circle (about 5%) at age 4 years increased the risk of hyperactivity and abnormal neurological signs at age 7 years. By contrast, hyperactivity and abnormal neurological signs, as well as learning disabilities, were infrequent in high scoring block sorters. Children who could not copy a cross (about 30%) were at increased risk for both learning disabilities and neurologic soft signs. The 25% of the cohort failing a maze task were at increased risk for all three syndromes. By contrast, only about 10% of the 4-year-olds were able to copy a square (mostly girls) and those children were at *decreased* risk for all three syndromes.

Visuospatial Disabilities

- Preschoolers who are even mildly delayed in visuoperceptual development are at risk for later learning disabilities.
- Preschoolers who are even mildly delayed in visuoperceptual development are at risk for hyperactivity and neurologic soft signs. Some of these children will merit a diagnosis of Gillberg's disorder of attention, motor and perception (DAMP).
- Difficulties in visuomotor integration are relatively common in the preterm child and may stem from perinatal white matter injury.
- Children who show perceptual delays are at increased risk for hyperactivity and neurologic soft sign syndromes. Do not dub it maturational too quickly.
- Preterms and other children with early spatial deficits need to be monitored for nonverbal learning issues when they reach school age.

PEARLS & PERILS

Evaluation and etiology

Difficulties in the visuospatial domain that are suggested by a large verbal performance IQ discrepancy can be corroborated by specific neuropsychological measures of design copy and memory, picture memory and mental rotation ability. Visuospatial abilities are easily assessed in the office by the simply administered "draw a person test" and drawing shapes to request or copying them.

Right hemisphere dysfunction as the etiology of visuospatial and motor deficits in the preschooler is suggested by the documentation of, for example, difficulties creating spatial arrays during toy play and poor copying and drawing skills in preschoolers with congenital right brain strokes (Stiles 2001: Nass & Trauner 2004) (Fig. 19.3). Despite normal gross motor functioning and intelligence, premature children are more likely to exhibit deficits in visuomotor functioning than full-term children (Fig. 19.4) during the preschool period (Klein *et al.* 1985). Like term infants in the NCPP (Nichols & Chen 1981), children born premature who perform less well on a standard figure copy task (Beery & Buktenica 2003) at 3–4 years old are more likely to have learning disabilities at school age (Ross *et al.* 1996). Theoretically, the white matter damage in preterms may affect the right hemisphere white matter more than the left (Olsen *et al.* 1998; Nosarti *et al.* 2002). Visuospatial difficulties are also hallmark deficits in such genetically divergent syndromes as Turners syndrome, Williams syndrome, velo-cardio-facial syndrome, and neurofibromatosis, each of which probably predominantly involves right hemisphere dysfunction (Howlin & Udwin 2002). Williams syndrome is perhaps the best studied by neuroimaging. Williams syndrome patients have relative preservation of cerebral gray matter volume and disproportionate reduction in cerebral white matter volume. However, within the cerebral gray matter tissue compart-

FEATURES

Table 19.16 Visuospatial Dysfunction

Discriminating feature

1. Visuomotor and spatial perception difficulties

Consistent feature

1. None

Variable features

1. Hyperactivity
2. Neurologic soft signs
3. Developmental coordination disorders

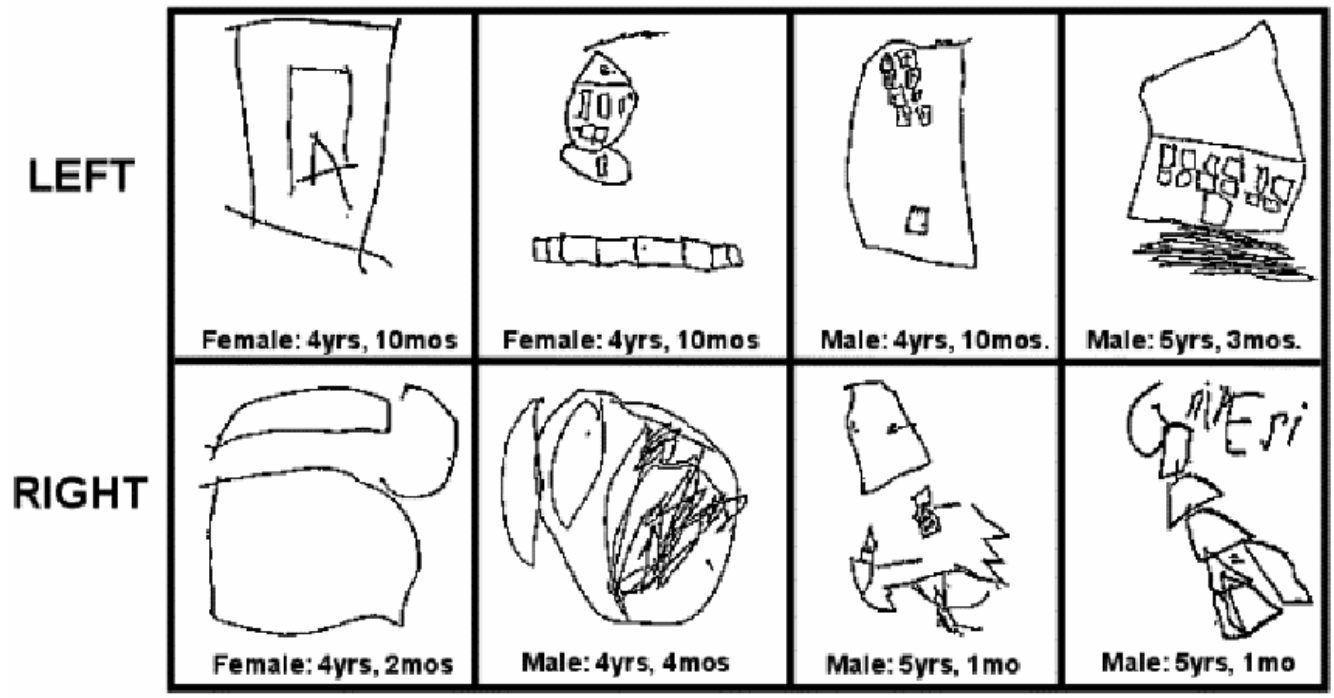

Fig. 19.3 Both the children with left and right hemisphere strokes draw houses less well than normal children their age. However, those with a right lesion do considerably less well. IQ and Gross motor skills were normal.

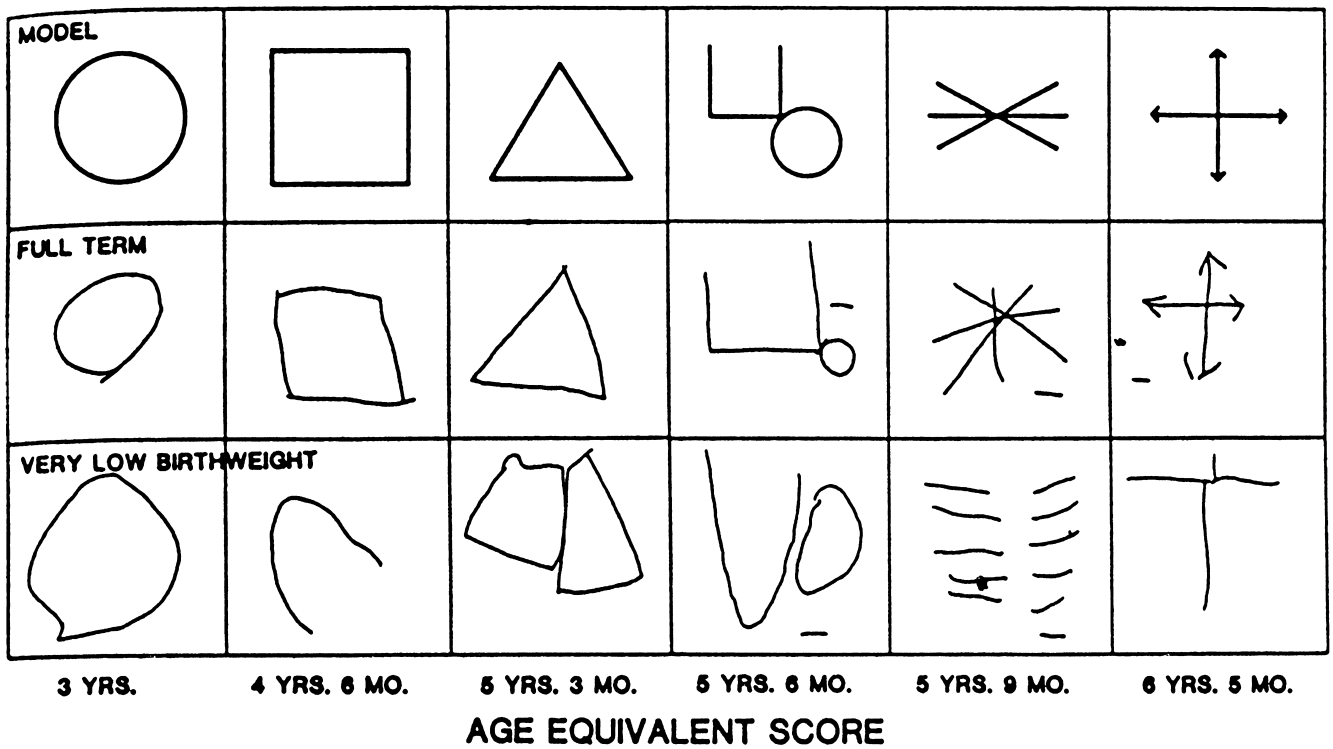

Fig. 19.4 These examples show the relative copy performance of a 5-year 9-month very low birth weight infant, in which IQ and Gross motor skills were normal, compared with a term control. (Klein N, *et al.* Preschool performance of children with normal intelligence who were low birth weight infants. *Pediatrics* 75:531–537, 1985.)

CONSIDER CONSULTATION WHEN…

- The child is notably delayed, especially if there are associated graphomotor difficulties and a failure to perform perceptual tasks age appropriately. A consultation with an occupational therapist should be sought.

ment, the right occipital lobe shows excess volume loss, a feature that could underlie the visuospatial difficulties (Reiss *et al.* 2000).

Treatment

Successful perceptual training programs for preschoolers identified as showing delays have been described (Tanguay 2001; 2003), although long-term follow-up studies documenting their effectiveness have not been reported. In general the treatment of visuospatial disabilities emphasizes the use of verbal strategies to navigate situations demanding visuospatial solutions. Visuospatial disabilities may seriously impair the child's perception of the world. Ordinarily simple tasks, like navigating the playground at school, become difficult. Visuospatial misperceptions may lead to serious social errors.

Attention deficit hyperactivity disorder

General discussion

ADHD is characterized as a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is generally observed in children of the same age. In about half the children with ADHD, onset occurs prior to 4 years of age (Palfrey *et al.* 1985; Connor 2002). The estimated frequency of ADHD in children between 2 and 5 years has varied widely from approximately 2–5% (Keenan *et al.* 1997; Bhatia *et al.* 1999) to 10% (Baumgaertel *et al.* 1995) to 18% (Pineda *et al.* 1999). Preschool males are significantly more likely than females to have ADHD (3:1) and as in older children boys are more likely to have the hyperactive impulsive form and girls the inattentive form (Earls 1980).

Because some degree of hyperactivity, impulsivity and inattention is common in preschool children (Palfrey *et al.* 1985) an accurate diagnosis of ADHD during the preschool period can be difficult. Furthermore, several studies suggest that ADHD symptoms are often transient, lasting only 3–6 months (Barkley 1998; Campbell 1990). For example, in one prospective study of 224 children followed from birth to kindergarten school entry, 41% of the preschoolers were found by parents, teachers or the researchers to have some attentional difficulties (Palfrey *et al.* 1985). In 5% the attentional issues were significant and persisted at least into elementary school; but an additional 8% had significant problems, which abated before school age. Another study found that even among those with severe and persistent enough symptoms to be diagnosed with ADHD, only one-half still met criteria for the diagnosis in elementary school. Therefore, a duration of symptoms of 12 months (rather than the 6 months suggested for school-age children) has been proposed as a more appropriate criterion for the diagnosis of ADHD in preschoolers (Barkley 1998). On the other hand a number of studies document a strong correlation between a diagnosis of ADHD during the preschool period and at school age (Richman *et al.* 1982; Campbell 1990; McGee *et al.* 1991). Preschool internalizing (anxiety and mood) and externalizing (hyperactivity and conduct) problems have also been found to be predictive of their DSM-IV counterparts 8 years later (Mesman & Koot 2001).

Diagnosis

Preschool children with ADHD are characteristically very hyperactive (Palfrey 1985; Kadesjö *et al.* 2001) (Table 19.17). Clinical observations of children diagnosed with ADHD demonstrate marked difficulties and/or difficulties in multiple domains of behavior (Kadesjö *et al.* 2001). Only 6% had no problems during clinical observation. Behavioral comorbidities are common in preschoolers with ADHD (Table 19.18). Young children with ADHD also tend to have high rates of language problems (Gadow *et al.* 2001) and developmental coordination disorder (Kadesjö & Gillberg 1998).

Parent and caregiver rating scales are the most accurate means of diagnosing ADHD during the preschool years (Routh *et al.* 1974; Behar 1977; Conners 1997; Achenbach & Rescorla 2000; Sprafkin *et al.* 2002). In one study, six DSM ADHD symptoms discriminated preschool children with ADHD from controls better than the remaining 12 items.

FEATURES

Table 19.17 Attention Deficit Hyperactivity Disorder

Discriminating features

1. No major psychopathology
2. Hyperactivity

Consistent features

1. Difficulty with sustained attention
2. Distractibility
3. Impulsivity

Variable features

1. Intense responsiveness to stimulation
2. Stimulus-seeking behaviors

TABLE 19.18

Attention Deficit Hyperactivity Disorder Comorbidities

	Cohort defined by	Overall comorbidity	ADHD	ODD	CD	Mood	Bipolar	Anxiety
Wilens *et al.* 2002a	ADHD	74% (79%)	100%	60% (60%)	23%	50%	26% (18%)	
Wiliens *et al.* 2002b	Referred for psychiatric evaluation	75%	86%	61% ODD and CD		43% depression		28%
Speltz *et al.* 1999	ODD		50%	100%	3%	10%		
Keenan & Wakschlag 2000	Referred for psychiatric evaluation	80%	60%	60%	42%			
Gadow *et al.* 2001	Referred for psychiatric evaluation		90/224	70/224		<10/224		<10/224

Percentage of children with school-age presentation with that comorbidity.

The symptoms were (1) difficulty sustaining attention, (2) easily distracted, (3) often "on the go," (4) runs/climbs about excessively, (5) does not follow through on instructions, and (6) difficulty remaining seated (Speltz *et al*. 1999). Impulsivity symptoms were not frequently endorsed, possibly because the examples and wording of the DSM applies more clearly to older children. However, scales designed specifically for preschoolers are favored over traditional DSM-based scales.

Questions more relevant to diagnosing ADHD in the preschooler are shown in Table 19.19. Cognitive test performance on structured measures that are very useful for corroborating the diagnosis in the older child are less helpful in discriminating between ADHD and normal preschool children. For example, preschoolers do not differ from controls on intelligence tests or on tests of attention and impulse control (Campbell *et al*. 1984) such as Matching Familiar Figures, Embedded Figures (Coates 1972) and Draw-A-Line Slowly (Maccoby & Hagen 1965).

Historically, allergies have been reported to occur more often in children with ADHD especially in the preschooler (Taylor 1991). Minor physical anomalies (e.g. hypertelorism, highly arched palate, low-set ears) may occur at a higher rate than in the general population (Waldrup *et al*. 1968). The neurological exam may reveal soft signs, but the findings are nonspecific.

Etiology and associated factors

ADHD has a significant genetic component, particularly among males, with one study indicating that 29% of parents and 21% of siblings of children with ADHD also had the disorder, in contrast with 4% and 6%, respectively of normal children (Biederman *et al*. 1992). Twin studies show hereditability rates ranging from 0.60 to 0.95 (Hudziak *et al*. 1998), indicating that ADHD is far more likely to be due to genetic than to environmental factors. Candidate genes include DAT (presynaptic dopamine transporter) and DRD4 (postsynaptic dopamine D4 receptor) (Swanson *et al*. 2000; Faraone *et al*. 2001). However, a number of nongenetic conditions may play a role in the etiology of ADHD including: perinatal factors, such as fetal alcohol syndrome, smoking during pregnancy, chorioamnionitis and prematurity; sequelae of early childhood illnesses, such as encephalitis and

TABLE 19.19

Characteristics of the Preschool Child with ADHD

Rushes through tasks paying little attention to details
Has difficulty paying attention to tasks or play activities
Does not seem to listen
Shifts from one activity to another
Has difficulties organizing activities
Avoids doing tasks that require mental effort
Loses things
Is easily distracted
Is forgetful
Fidgets or squirms
Has difficulty remaining seated
Runs about or climbs on things when asked not to
Has difficulty playing quietly
Is always on the go
Talks excessively
Blurts out answers before the question is complete
Has difficulty awaiting his turn
Interrupts people or disrupts group activities

0–3 scale, modified from Gadow KD, Sprafkin J: *Early childhood inventory-4 screening manual.* Stony Brook NY, 2000, Checkmate Plus.

meningitis; head trauma; and environmental factors, such as toxins, as well as psychosocial factors like lower social class and family discord (Nichols & Chen 1981; Nass 1995). Risk factors in the preschool child for hyperactivity at age 7 years found in the NCPP included hyperactivity and fine motor coordination problems.

ADHD is a neurobiological disorder predominantly reflecting dysfunction of the fronto-striatal and frontal cerebellar dopaminergic pathway. Norepinephrine levels or the balance between dopamine and norepinephrine likely plays a role as well. Structural and functional magnetic imaging studies have shown that the frontal cortex, striatum (caudate in particular), and cerebellar vermis are 5–10% smaller (Castellanos *et al.*1996) and blood flow/metabolism in the prefrontal cortex, striatum, and anterior cingulated is lower (Jensen 2000) in children with ADHD.

Abnormal morphology has also been noted in the frontal cortices, with reduced regional brain size localized mainly to inferior portions of dorsal prefrontal cortices bilaterally. Brain size was also reduced in anterior temporal cortices bilaterally. Prominent increases in grey matter were recorded in large portions of the posterior temporal and inferior parietal cortices bilaterally (Sowell *et al.* 2003).

Outcome

As discussed previously preschool ADHD may or may not persist into elementary school and beyond. Comorbid behavior problems often persist (Shelton 1998), as do language and perceptual motor difficulties (Kadesjö & Gillberg 1998). A number of studies indicate that both the presence of ADHD in the preschool period and its persistence into elementary school correlate with poor school achievement later (Nichols & Chen 1981; Palfrey *et al.* 1985; Campbell 1990; McGee *et al.* 1990; DuPaul *et al.* 2001).

Treatment

The preschool period presents parents with special problems in child management and is associated with high levels of parental stress and low confidence in parenting skills (Ross & Ross 1982). Early identification of children with ADHD and prompt intervention are important in minimizing the deleterious effects of this disorder on the child's later academic achievement, personal relationships with peers and family members, self-esteem, and behavior. Behavior management strategies are always indicated at home and nursery school as the first line of treatment for preschool aged children. Several investigators (Sonuga-Barke *et al.* 2001) have provided evidence that training parents in behavioral management skills can lead to modification of noncompliant behaviors in preschoolers. Behavior management techniques have also been shown to be effective in modifying behavior of preschoolers with ADHD in their classrooms (Barkley 1998).

PEARLS & PERILS

Attention Deficit Hyperactivity Disorder

- ADHD is a developmental disorder with onset prior to 7 years of age, but the peak onset actually occurs during the preschool period.
- ADHD in the preschool years is more likely to pose behavior management rather than learning difficulties.
- The critical time to detect and intervene for ADHD is during years three to four, when concerns about attention and manageability peak.
- Unusually high activity level is a hallmark of ADHD during the preschool period.
- A high behavioral comorbidity rate is a hallmark of ADHD during the preschool period.
- Parent and teacher behavior rating forms are best means of diagnosing ADHD in the preschool child. But, age-appropriate scales should be used.
- Parent training programs are effective interventions for preschool children with ADHD and are the first line of treatment
- Stimulant therapy should be considered when the child has not responded to behavior therapy, the family is unable to implement behavior therapy, or the child has severe symptoms of ADHD that are not sufficiently reduced through behavior therapy. Stimulants may have less efficacy and more side effects in the preschooler.
- A high percentage of children who will have ADHD at school age can be diagnosed during the preschool years.
- ADHD is most often an inherited disorder, particularly in boys.
- Complete disappearance of preschool ADHD symptoms does occur.
- IQ, academic and behavioral standing of ADHD children may lag throughout childhood.

Stimulant medications have been used, but only about 200 children have been entered in nine double-blind placebo-controlled studies looking at the effects of stimulants in the preschool child (see Connor 2002 for review). Eight of the nine studies found that stimulants reduced symptoms of ADHD in preschool children. Three groups reported improvements in all domains, including cognitive, social, and behavioral functioning; two, in behavioral functioning; and two in social interactions. However, one study found mixed results with a high rate of side effects in preschoolers; and another study failed to show significant treatment effects of stimulants or cognitive behavior therapy. One of the concerns of using stimulants with preschool children is the relatively high rate of side effects, as well as the dose-related rate of side effects including: sadness, nightmares, loss of appetite, drowsiness, and dulled affect (Firestone *et al.* 1998). However, it is notable that some behaviors thought to be side effects (e.g. insomnia, anxiety, and irritability) ac-

KEY CLINICAL QUESTIONS

- Does your child have difficulty sustaining attention?
- Is your child easily distracted?
- Is your child often "on the go"?
- Does your child run/climb about excessively?
- Does your child not follow through on instructions?
- Does your child have difficulty remaining seated?

CONSIDER CONSULTATION WHEN...

- ADHD is accompanied by significant oppositional behavior, anxiety, or mood issues. A consultation with a behavior modification expert would be indicated.

tually improve with medication in preschoolers (Firestone *et al.* 1998). While stimulants have been used successfully with ADHD preschoolers over 3 years old, results are based only on short-term usage. Alpha agonists like clonidine and guanfacine have also been used with some success in the preschool child, particularly in those with marked hyperactivity and conduct disorders. Overall, preschool children tend to have a less robust response to treatment and a higher side effect burden (Greenhill 1998;Wilens & Spencer 2000) perhaps because of their high rates of comorbidity – particularly mood and anxiety disorders – leading to more complex cases (Wilens *et al*. 2002).

Despite the lack of evidence regarding the safe and effective use of stimulants and clonidine in children under 3 years old, prevalence studies show that stimulant treatment for preschoolers increased approximately 3-fold during the early 1990s (Rappley 1998; Zito *et al.* 2000). Although children 2 years through 4 years old were treated at approximately one-tenth the rate of older groups, Zito *et al.* (2000) found that from 1991 to 1995, the prevalence in use of methylphenidate in one Midwestern Medicaid program increased from 6.9 to 20.8 per 1000 in 4-year-olds and from 1.1 to 3 per 1000 in 2-year-olds. Stimulants can be used but efficacy and side effects must be carefully monitored. Diagnosis accuracy is extremely important.

Variations in temperament and cognitive style

General discussion

Although not formally recognized as a disorder unless found in the extreme, individual variations in temperament and cognitive style have a significant effect on success during the preschool and school years. Individual differences in temperament (the how rather than the what of behavior) are present as early as the first few weeks of life and likely persist into adulthood (Guerin *et al.* 2003). Some aspects of temperament may be inborn (Bates & Wachs 1994; Kagan *et al.* 1997). Temperament can range from impulsive, with ADHD as the extreme, to the overfocused, with an ASD as the extreme. The withdrawn and fearful child is at one end of another temperament spectrum and the uninhibited and reckless one at the other. Certain temperament characteristics in preschoolers may be the harbingers of later social, emotional and behavioral disorders (Keogh 2002).

Diagnosis

Based on nine behavioral characteristics (activity level, rhythmicity, approach to new stimuli, adaptability, intensity, mood, persistence, distractibility, and threshold to stimulation) deemed to define an individual's temperament, four temperament clusters have been generated from large multiethnic studies using parent ratings (Thomas & Chess 1968) (Table 19.20). Almost one-fifth of the preschoolers were characterized as having difficult temperaments (irregularity of biological functions, withdrawal from novel stimuli, slowness to adapt, intense responses, and predominantly negative mood). There was a significant overlap between difficult temperament and ADHD in the preschool age group, in that both share the characteristics of low adaptability and negative mood. The temperament dimensions of persistence and distractibility may be useful in the early detection of impulsive children. A disproportionately large number of children with difficult temperament characteristics are eventually referred by teachers and physicians for problems in learning and behavior (Goldsmith *et al.* 1987). Nass and Koch (1987) found preschoolers with right brain injury were more difficult than their left lesion counterparts (Fig. 19.5), suggesting a neurologic basis for temperament differences, paralleling that found in adults with acquired pathology.

Another facet of temperament that has been described in the preschool child is the dimension of introversion/extroversion (shyness/fearlessness). This may parallel the "slow to warm up" subgroup (defined as withdrawal or slow

FEATURES

Table 19.20 Variation in Temperament and Cognitive Style

Discriminating feature

1. None

Consistent features

1. Overfocused/underfocused
2. Introverted/extroverted
3. Difficult, easy, slow to warm up, intermediate

Variable feature

1. None

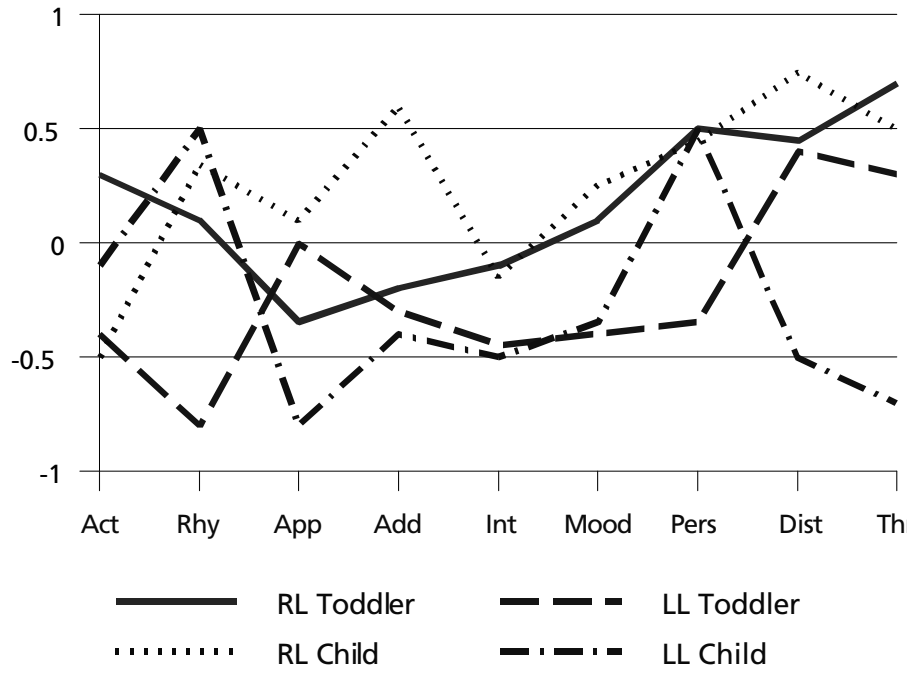

Fig. 19.5 Children with congenital right hemisphere strokes tend to have a more difficult temperament than those with left lesions, suggesting early right hemisphere dominance of emotion. From: Nass R, Koch D: Specialization for emotion: Temperament after congenital unilateral injury. In: Amir N, Rapin I, editors: *Pediatric Neurology: Behavior and Cognition of the Child with Brain Dysfunction*. Basel, 1991, Karger.

adaptability categories greater than 1 standard deviation from the mean) of Chess and Thomas (1996), which made up 15% of their original sample. Extremely shy and fearful children may be characterized by low temperament scores on adaptability, approach to new stimuli, and threshold to stimuli. Consistent with the view that there is a neurological basis for temperament differences, very shy versus very outgoing children differ in terms of degree of sympathetic tone, with the tone of the shy subgroup paralleling that seen in adults with right hemisphere dysfunction (Kagan *et al.* 1997). Preschool children who are very withdrawn and fearful may be more likely to develop anxiety disorders in later childhood (Klein & Last 1989; Carey & McDevitt 1994).

Workup/diagnosis

Parental questionnaires (Toddler Temperament Scale [ages 1–3 years]) and Behavioral Style Questionnaire [ages 3–7 years] are useful for documenting temperament characteristics in the preschool child (Carey & McDevitt 1994).

Treatment

Longitudinal studies have suggested that modifications in the expression of extremes in temperament and cognitive style may be affected by the environment. Goodness of fit (Chess & Thomas 1999), the relationship between a child's characteristics and the environmental demands and expectations, may either minimize or amplify inborn traits. For example, a stressed and demanding mother is much more likely to maintain or increase a difficult temperament style than is a responsive and calm parent (Carey & McDevitt 1994). Children who are at the extremes for shyness and fearfulness during the preschool period may improve over time if their mothers are successful in actively encouraging their children to be more sociable and to overcome their fears of new situations (Kagan *et al.* 1997). Optimal management of the difficult child may minimize the negative effect of preschool temperament on later behavior and academics.

PEARLS & PERILS

Variations in Temperament and Cognitive Style

- Both extremes of attentional style (impulsive to overfocused) put a child at risk for learning and behavioral difficulty.
- Cognitive style remains relatively stable throughout and is biologically based.
- Temperamental characteristics affect the child's acquisition of information and information processing.
- Temperament may be modified by the environment.
- Cognitive style may be modified by parents and teachers.
- The extreme of the overfocused style is the ASD child.
- The extreme of the impulsive child is the child with ADHD.
- A mismatch of parent and child temperament may lead to behavior problems in the child.
- Nonadaptive parenting can lead to an increase of extremes in cognitive style and temperament.

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CHAPTER 20

Learning Disabilities

Max Wiznitzer, MD and Debora L. Scheffel, PhD

OUTLINE

Definition
Epidemiology
Neurobiology
Evaluation
Treatment
Prognosis

Definition

Learning disabilities are disorders of higher cognitive function present from birth or early childhood, are neurologically based, and impact on the ability to learn or process information in one or more specific areas, rather than a global intellectual impairment. Individuals with learning disabilities may present to the child neurologist with a question of developmental delay, poor school performance, or behavioral problems. Also, in children who are already being followed for chromosomal/genetic disorders, consequences of prematurity, attention-deficit/hyperactivity disorder, traumatic brain injury or epilepsy, learning disabilities can later become evident.

This population of children has been described in the educational, psychologic, and medical communities by a number of terms, including developmentally learning disabled, minimal brain dysfunction syndrome, developmental aphasia, dysgraphia, dyscalculia, dyslexia, and perceptually handicapped. These terms diverge based on their relative orientation toward the etiology or behavioral manifestations of the disorder.

In 1963, the term Learning Disability was formally introduced. At that time this term referred to disorders in development of language, speech, reading, and associated communication skills needed for social interaction. This definition has been the source of debate and revision since its introduction. The federal definition is based on guidelines developed after passage of Public Law 94–142 (IDEA 97) and the operational definition from 1968:

A severe discrepancy between achievement and intellectual ability in one or more of these areas: (1) oral expression; (2) listening comprehension; (3) written expression; (4) basic reading skills; (5) reading comprehension; (6) mathematics calculation; or (7) mathematics reasoning. The child may not be identified as having a specific learning disability if the discrepancy between ability and achievement is primarily the result of: (1) a visual, hearing, or motor handicap; (2) mental retardation; (3) emotional disturbance; or (4) environmental, cultural, or economic disadvantage.

A consensus statement of the National Joint Committee on Learning Disabilities, composed of representatives from major professional organizations dealing with this subject, expanded the definition by adding length of occurrence and co-existence with other conditions, thereby defining learning disabilities as:

- Manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical abilities;
- Intrinsic to the individual, presumed to be caused by central nervous system dysfunction, and sometimes occurring for a person's entire life;
- Occurring, in some cases, concomitantly with other handicapping conditions (for example, sensory impairment, mental retardation, or serious emotional disturbance) or with extrinsic influences (such as cultural differences or insufficient or inappropriate instruction), but not resulting from those conditions or influences.

This legislative definition is primarily aimed at addressing societal needs by authorizing programs and mandating services. Definitions more operational in character are used for research purposes and, at the state level, for identification. Implementing the definition requires specifying how the diagnosis is made and determining the relationship between average intellectual competence and a learning disorder. Definitions for this purpose use any of at least four methods to arrive at a diagnosis: (1) deviation from grade level, (2) expectancy formulas, (3) simple standard score differences, and (4) standard regression analysis (Berninger & Abbott 1994). Based on deviation from grade level, a learning-disabled child might be identified by demonstrating achievement at a predetermined point below expected grade level. Expectancy formulas use IQ to adjust expected level of achievement based on potential ability; the difference between expected and observed achievement needed to define a learning disability is arbitrary. Using a standard score difference approach,

the age or grade-corrected standard score for achievement is subtracted from the IQ standard score; the cutoff criterion for amount of discrepancy is arbitrary. The regression discrepancy model takes into account measurement error, effects of regression toward the mean, and correlations between ability and achievement measures (Reynolds 1984).

The validity of any one of these assessment methods has been criticized. The result of this has been a movement toward changing the Individual for Education Act during the 2004 Reauthorization. The new law will probably recommend portfolio assessment, authentic observation, and comparison of daily performance in natural environments to determine eligibility of services. Exactly how this will be done and decisions made will be determined once the law is passed and regulations are written. In addition, some studies conclude that there is a spectrum of function, rather than a bimodal distribution, in skills such as reading, so that children at the lower end of the continuum will be identified as "learning disabled" with no clear cut-off between dyslexic and typically reading children (Beichtman *et al*. 1998; Fletcher *et al*. 1999; Levine 1999; Shaywitz & Shaywitz 1999; Gottesman & Kelly 2000). Incorporating this information and the new regulations into daily practice will be a challenge for special education providers in the next few years.

In addition to complex identification issues affecting the composition of the population as a whole, learning-disabled children comprise a heterogeneous group. Research has attempted to identify homogeneous subgroups within the larger population. All have core dysfunction in one or a combination of the following processes (Levine 1999; Gottesman & Kelly 2000):

1. Memory – Skills in this area are needed to follow directions, to retain information while solving problems, reading or transferring thoughts to paper (active working), to consistently study and remember information for tests (long-term consolidation), and to remember facts in a timely fashion (long-term retrieval). Dysfunction can be visual or auditory in nature.
2. Language – Difficulties can occur in expressive, receptive or processing skills and affect the various components of language: phonology (decoding and encoding the core sounds of language), syntax (the grammar and organization of sentences), semantics (meaning of vocabulary and sentences/communication) and pragmatics (the nonverbal communication and social aspects of language, e.g. gestures and facial expression). Dysfunction can be manifest as poor pronunciation and immature grammar, problems decoding written language, or difficulties following complex directions, retaining written language, detailing ideas in writing, distinguishing homonyms or learning sequences.
3. Visuospatial skills – Academic skills require the ability to discriminate shapes (which affects letter and number recognition), differentiate between foreground and background (to attend to relevant details), understand form constancy, and develop a sense of direction and right–left discrimination (for sports participation and daily organization). Difficulties in this area rarely cause a significant learning disability, but may aggravate other areas of dysfunction.
4. Temporal sequencing – These abilities address core skills such as correctly following multistep directions and the daily classroom schedule, learning to tell time and the understanding of serial order in writing, reading and mathematics. Deficiencies can affect learning the concept of mathematical computation, development of good organizational skills (including time management), following concepts in written language and performing in music class.
5. Higher order cognition – Thinking skills show a maturational process throughout the school years. This includes developments in concept acquisition (the grouping of ideas into defined categories with a gradual shift towards more abstract concepts), problem solving skills, the use of critical thinking and brainstorming, and an appreciation for rules in learning. Problems in this area can result in difficulties understanding the core rules of mathematics and the relationships in computational strategies, learning how to estimate or to formulate new ideas in writing, developing analytic skills, or recognizing patterns in learning (such as capitalization of proper names or countries).
6. Motor skills – Coordination of fine and gross motor skills is essential for adequate school performance. The child needs to master abilities ranging from dressing, cutting, and copying to appropriate pen/pencil grasp, letter formation (print and cursive), and speed of writing and computer keyboard use. Difficulties in this area can impact on a variety of core academic skills such as writing to performance in physical education, art and musical instrument use.
7. Social ability – Social skills are essential to navigate the daily life in schools. Individuals should be able to initiate and maintain social contacts, problem solve in challenging situations and terminate an interaction. Difficulties in this area can affect one's ability to request help, develop friendships and enjoy the school experience.

In addition to these areas, adequate attention is necessary. This is a skill that affects all areas of functioning. Dysfunction can be subtle and task specific (such as visual or auditory processing) or so significant that it meets criteria for attention deficit hyperactivity disorder (inattention, hyperactivity, impulsivity). While attentional dysfunction represents a behavioral rather than an academic deficiency, its impact can potentiate underlying learning disabilities or mimic a primary academic deficiency.

Each individual presents his/her own profile of strengths and weakness in these areas. Given the individuality of each case, it is often difficult to determine a specific etiology, intervention, or prognosis.

There are five main types of learning disabilities:

Dyslexia (reading disability)

It is estimated that, of all children with learning disabilities, 80% present with dyslexia, a reading disability (Table 20.1). Due to differences of opinion in how dyslexia is assessed and determined, dyslexia may be even more prevalent. (Shaywitz 2003, p. 29). Using the 2003 definition, the International Dyslexia Association defines dyslexia as:

> … a specific learning disability that is neurobiological in origin. It is characterized by difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities. These difficulties typically result from a deficit in the phonological component of language that is often unexpected in relation to other cognitive abilities and the provision of effective classroom instruction. Secondary consequences may include problems in reading comprehension and reduced reading experience that can impede growth of vocabulary and background knowledge.
>
> Lyon *et al*. 2003

In the past, attempts were made to differentiate dyslexia into subtypes, such as surface dyslexia (greater difficulty decoding irregular words), deep or phonologic dyslexia (difficulty reading regular words and nonwords), and dyseidetic dyslexia (difficulty recognizing letters and their meaning). Neurophysiologic and neuroimaging studies have supported the conclusion that dyslexia is primarily an inability to decode written language due to impairment in phonologic (or phonemic) awareness (knowledge that words can be broken down into smaller units of sound). Three areas of the brain are required to effectively read: the anterior region, temporo-parietal region, and the occipito-temporal region (Pugh *et al.* 2000). It is hypothesized that repeated reading of a word transfers it from the anterior area, through the parieto-temporal area and to the occipito-temporal area. As a reader becomes more sophisticated and experienced, the occipito-temporal area is relied on more heavily and the anterior area becomes less active. However, dyslexic readers increase their reliance on the anterior area as they mature. This limits the reader to attempting word analysis without the recall of word form and transfer of letters into sounds, thereby limiting fluency and impeding reading speed and comprehension (Pugh *et al*. 2000; Booth 2001; Lyon *et al*. 2003; Shaywitz 2003; Shaywitz & Shaywitz 2004).

A small number of individuals with dyslexia may have difficulties with the spatial skills needed for letter recognition or sequencing or with comprehension of written language due to inadequate sight vocabulary or recall of earlier text. These skills are localized in the occipito-temporal area.

The gap in reading skills increases as the nonimpaired reader becomes more adept in word recognition and automaticity. Because of these difficulties, affected individuals may actively avoid any task that requires sustained reading, leading to a further worsening in ability from lack of practice. Since school and life performance usually demands an adequate ability to read, this block in phonologic analysis interferes with the ability to understand the written text and limits learning and job opportunities.

FEATURES

Table 20.1 Reading Disorders (Dyslexia)

Discriminating features

1. At least average verbal or nonverbal intellectual potential
2. Significant discrepancy between intellectual potential and performance on measures of reading

Consistent features

1. Not a unitary disorder; heterogeneous population demonstrates a variety of levels of functioning in facets of reading performance
2. Deficient functioning in any one or combination of reading silently or orally, individual words in context; decoding, comprehension or rate

Variable features

1. Occur concomitantly with other handicapping conditions or extrinsic influences but are not primarily attributed to either
2. Deficient performance in skills representing either disrupted visual processes (for example, poor sight vocabulary, reversals), disrupted lexical or semantic access (for example, poor reading comprehension), disrupted phonemic processes (for example, poor decoding of multisyllabic words), or combinations thereof
3. Often occur concomitantly with oral language and written language disorders
4. Familial history of learning disorder
5. Indications of neurologic pathology

Dyscalculia (mathematics disability)

Mathematics skills appear to be innate. Elementary abilities, such as counting, one-to-one correspondence, quantities and volumes, are usually present by kindergarten age. Later milestones include writing three-digit numbers, addition and subtraction by age 8 years and aptitude in multiplication and division by age 10–12 years. Failure to achieve these milestones without more global cognitive impairment defines dyscalculia. Onset by age 6 years is manifested as problems with simple addition and basic math facts. In 10-year-olds, dysfunction includes difficulties with retrieval of learned information (such as multiplication tables and simple addition and subtraction), with manipulating money, and with following the appropriate sequence for calculation (Table 20.2).

Those with developmental disorders in math represent a heterogeneous group due to the complexity of process-

FEATURES

Table 20.2 Disorders of Mathematical Functioning (Dyscalculia)

Discriminating features

1. At least average verbal or nonverbal intellectual potential
2. Significant discrepancy between intellectual potential and performance on measures of mathematics achievement

Consistent features

1. Not a unitary disorder; heterogeneous population demonstrating a variety of levels of functioning in facets of mathematical performance
2. Deficient functioning in any one or combination of performing written and oral mathematic calculations or comprehension and application of mathematic concepts

Variable features

1. Occur concomitantly with other handicapping conditions or extrinsic influences but are not primarily attributed to either
2. Deficient performance in skills representing either language-based disorder (for example, poor comprehension of instructional vocabulary), disrupted visual-nonverbal processing (for example, inaccurate reading of operations signs), or a combination thereof
3. May be associated with poor eye-hand coordination, poor tactile form recognition, finger agnosia, cognitive inflexibility, gross motor incoordination, and poor socioemotional adjustment, if the disorders are nonlanguage-based.

ing necessary to reason mathematically or calculate (Geary 1993). A number of studies investigating subtypes of mathematical disabilities have suggested that at least three types may be identified: those with visual-perceptual deficits, those with linguistic deficits, including reading, and those with deficits in both areas (Spreen & Haaf 1986). Those with visual-perceptual deficits only exhibit visual-spatial orientation difficulties (e.g. right–left orientation problems), general psychomotor incoordination (e.g. problems characteristic of dysgraphia), and impaired tactile discrimination (e.g. finger agnosia). This pattern of abilities and deficits appears to be compatible with relatively deficient right hemisphere systems. Mechanical math errors associated with visual-perceptual deficits include difficulty aligning numbers for calculation or conceptualizing mathematical values related to relative size or distance, directionality (i.e. proceeding from right to left when the problem is arranged vertically and left to right when the problem is arranged horizontally), misreading of operational signs or numbers, inattention to the significance of sequence (e.g. 574/547), missing or adding a step in calculation of multistep problems, and graphomotor difficulties writing numbers. Those with linguistic deficits may present with both math and reading/spelling deficits. Features include difficulty understanding the words used to describe operations or word meanings in application problems, difficulty recalling the auditory equivalents of numerical symbols that affect oral problem solving and oral number fact drills, difficulty remembering steps in multi-step problems, and avoidance of problems that require reading printed words (Johnson & Myklebust 1967). These characteristics are representative of relatively deficient left hemisphere systems. Strang and Rourke (1985) have found that the majority of children who experience difficulties in arithmetic calculation have deficiencies in one or more linguistic abilities.

In addition to mathematical disorders due to visual-perceptual, linguistic, or mixed deficits, some posit a fourth subgroup differentiated by specific deficits in nonverbal symbolic representation and quantitative thinking (Johnson & Myklebust 1967; Geary 1993). Individuals with this subgroup evidencing disorders of nonverbal thinking may demonstrate inability to estimate calculation outcomes, count meaningfully (i.e. establish one-to-one correspondence), grasp the meaning of process signs, interpret graphs or maps, follow a sequence of logical steps toward problem solutions, monitor performance, shift set (as when two separate operations are required to solve a problem), and control impulsivity in problem solving strategies (Moses 1984; Pellegrino & Goldman 1987).

Researchers have traditionally devoted comparatively little attention to mathematical abilities of individuals with learning disabilities as compared with performance in other areas (Pellegrino & Goldman 1987). Carpenter's (1985) survey of elementary and secondary school learning disabilities teachers indicated that the average student with learning disorders spends one-third of his/her time in special education on instruction in mathematics. Comorbidity of reading and mathematics disabilities is well documented (Kulak 1993), such that many children diagnosed early as reading disabled will eventually display deficiencies in mathematics learning as well (Light & DeFries 1995).

Dysgraphia (writing disability)

The majority of individuals with learning disabilities have communicative difficulties in the acquisition and use of written language (Adelman & Vogel 1991). The written form of language is the most sophisticated and complex type of communication. It requires a level of abstraction not equaled in oral language since it is removed in time and space from its intended audience. Whereas oral speech is generally acquired spontaneously, the ability to communicate in writing is a result of conscious effort and explicit instruction. Writing requires the intention to communicate, formulation of the message, retrieval of auditory and corresponding graphic language symbols, sequencing of the content, and planning and execution of the graphomotor

sequences necessary for writing (Gaddes & Edgell 1994) (Table 20.3).

Problems with writing occur at several levels. Children with underlying motor difficulties (dyspraxia) can have problems with the mechanical aspects of putting words on paper with a writing instrument. An inability to adequately copy and, therefore, correctly make letter shapes and connections can also interfere with this motor component. Higher order language- and memory-based dysfunction can lead to problems recalling and writing appropriate names, adequately sequencing or remembering the core components of written paragraphs, attending to the mechanical or conceptual aspects of writing, overcoming inherent problems due to an underlying developmental language disorder or implementing abstraction skills. Difficulty with spelling is frequently associated with dyslexia or an underlying developmental language disorder (Hamstra-Bletz & Blote 1993; Gubbay & deKlerk 1995; Blondis 1999; Levine 1999; Basso & Marangolo 2000; Miozzo & De Bastiani 2002; Cotelli *et al*. 2003; Mather 2003).

Dysphasia (oral language disability)

Of all the problems experienced by children with disorders of higher cortical function, those with oral language impairments may be the most prevalent (Wiig & Semel 1984). It is estimated that 90% of youths classified as learning disabled have oral language disorders (Liberman *et al*. 1984; Vellutino 1991; Gough *et al*. 1992). Normal language acquisition requires that a child learn to hear and discriminate different phonemes, recognize the subtle auditory speech cues that occur in temporal sequence, master the motor skills of articulation and relate language ability to experiences needed to understand its meaning (Gaddes & Edgell 1994) (Table 20.4).

Developmental dysphasia includes disorders related to understanding and receiving linguistic information and using language for meaningful communication. Children with impaired receptive language may have deficits at different levels of language ability. Problems in aural processing may result in inconsistent or absent response to language, frustration, difficulty with attention and self-control, echolalic verbalizations, and/or inability to follow verbal directions. Difficulty with abstract concepts such as *before/after*, *few/many*, and *all/except* is characteristic. Because oral language is based on intentional meaning, perceiving the nuances of inferred meaning is often problematic. Understanding the significance of meta-linguistic elements, such as prosody, may also be impaired (Stark *et al*. 1991).

Most children with difficulty in understanding language also have expressive language disorders. Impaired expressive language and limited syntax may be present when

FEATURES

Table 20.3 Writing Disorders (Dysgraphia)

Discriminating features

1. At least average verbal or nonverbal intellectual potential
2. Significant discrepancy between intellectual potential and performance on measures of writing

Consistent features

1. Not a unitary disorder; demonstrating a variety of levels of functioning in facets of writing performance
2. Deficient functioning in any one or combination of motor control or planning affecting legibility, spelling, syntax and grammaticality, word retrieval, ideation, or formulation

Variable features

1. Occur concomitantly with other handicapping conditions or extrinsic influences but are not primarily attributed to either
2. Deficient performance in skills representing either disrupted visuomotor, auditory and verbal (for example, syntax or dysphonetic spelling errors), visual and verbal (for example, over-phoneticized spellings, capitalization omissions), or combined processing deficits
3. May occur concomitantly with reading and oral language disorders

FEATURES

Table 20.4 Language Disorders (Dysphasia)

Discriminating features

1. At least average verbal or nonverbal intellectual potential
2. Significant discrepancy between intellectual potential and performance on measures of oral language functioning

Consistent features

1. Not a unitary disorder; heterogeneous population demonstrates a variety of levels of functioning in facets of receptive and expressive language
2. Occur concomitantly with disorders in other verbal symbol systems such as reading, writing, and math applications
3. Deficient functioning in any one or combination of auditory discrimination, memory, comprehension, temporal sequencing, syntax, grammaticality, word retrieval, pragmatics, or formulation

Variable features

1. Occur concomitantly with other handicapping conditions or extrinsic influences but are not primarily attributed to either
2. Deficient performance in skills representing either a receptive, expressive, or global language disorder
3. Delayed language acquisition
4. Indications of neurologic pathology
5. Familial history of learning disorder

receptive understanding is limited. Children can have expressive disorders related to auditory-motor execution of speech; word retrieval; sequencing sounds in words, words in sentences, or sentences in text; analyzing oral language into component parts (i.e. words into sounds, syllables, or sentences into words); and/or syntax. Dysfunction can also involve higher-order skills in semantics; oral formulation and organization of ideas, and pragmatics (Vogel 1983; Johnston & Kamhi 1984; Curtiss & Tallal 1985; Leonard 1989). Deficient performance may be observed in finding the desired word to express an idea, naming the days of the week, counting in sequence, or naming items in a common category. Sound reversals or substitutions (e.g. *binglejells/jinglebells*) and generally poor oral fluency (owing to word retrieval difficulty or difficulty planning and organizing expression) often occur. Deficits in oral language development, such as sound discrimination, sequencing, and understanding of abstract linguistic concepts, often affect other language-related functions and limit general academic achievement. Oral reading performance, reading comprehension, spelling, written expression, and arithmetic reasoning may be affected (Kamhi & Catts 1989; Stanovich 1991).

Nonverbal learning disability

The syndrome of nonverbal learning disability (NLD or right hemisphere learning disability) has been conceptualized as the association of impairments in social/interpersonal skills, visuospatial and directionality abilities, fine and gross motor coordination, and academic dysfunction in reading comprehension, arithmetic and subjects requiring abstract and problem solving skills (Table 20.5). Manifestations include problems in social interaction, adjusting to unexpected transitions, activity level (increased or decreased), manipulation of objects (scissors, dressing), handwriting, concept formation, complex problem solving, reading comprehension, and arithmetic. As a result of these deficits, a child's social imperception may limit his/her social growth and significantly affect reasoning and adaptive behavior. Thus, nonverbal learning disabilities may have more profound negative effects than verbal disabilities since they distort fundamental life experience (Semrud-Clikeman & Hynd 1991; Badian 1996). In social situations, individuals with a nonverbal learning disability are unable to readily interpret novel information and, therefore, tend to respond in scripted, matter-of-fact verbal responses. Rote memorization of verbal information is a strength that often masks their difficulty understanding concepts (Matte & Bolaski 1998).

FEATURES

Table 20.5 Disorders of Nonverbal Functioning

Discriminating features

1. At least average verbal intellectual potential
2. Significant discrepancy between intellectual potential and performance on measures of nonverbal functioning

Consistent features

1. Not a unitary disorder, heterogeneous population demonstrating a variety of levels of functioning on nonverbal tasks
2. Occur concomitantly with relative proficiency in rote verbal capacities necessary for aspects of reading and spelling performance

Variable features

1. Occur concomitantly with other handicapping conditions or extrinsic influences but are not primarily attributable to either
2. Deficits in tactile perception, psychomotor coordination, and visuospatial and organizational functioning
3. Deficits in aspects of complex language functioning (that is, understanding inference and humor, figurative language, language pragmatics)
4. Deficits in social perception, judgment, and social interaction
5. Psychiatric complications including depression

Epidemiology

The prevalence of learning disabilities is about 10–20% and depends on the diagnostic criteria, assessment tools and population sample being used. For example, the United States Department of Education estimate of 5% only identifies the children receiving special education services and classified as having a learning disability.

Dyslexia is reported to be the most common learning disability, present in about 40–80% of those with the diagnosis of learning disability, and has a prevalence of 5–17%. While early studies suggested a male predominance, more recent research reports nearly equal male–female distribution. Dyscalculia occurs in about 3–6% of the population with either no gender or greater female predominance. Prevalence estimates range from 6 to 26% of those identified as learning disabled; Fletcher and Loveland (1986) estimated that 18% of their population evidenced specific deficits in mathematics, while McLeod and Armstrong (1982) reported 26% of their population experienced selective impairments in mathematics. Problems with written expression are estimated in 2–8% of school-aged children, more so in boys. Dyspraxia is reported in 5–15% of children (Beitchman *et al.* 1998; Shaywitz & Shaywitz 1999; Shelav *et al.* 2000; Shapiro 2001).

More than one learning disorder can occur in the same individual. Language-based disorders such as dyslexia, dysgraphia, and higher-order written language dysfunction can co-occur and may be preceded in the preschool years by a developmental language disorder. Dyslexia and dyscalculia can co-exist and result in worse performance in

testing compared to either disorder alone. The combination of dyscalculia, dysgraphia, finger anomia and right–left confusion has been labeled developmental Gerstman's syndrome, although no structural abnormality of the angular gyrus of the dominant parietal lobe is usually present, unlike in the acquired adult form. Co-occurrence of learning disability with attention deficit hyperactivity disorder has been categorized in the past as minimal brain dysfunction (ADHD, perceptual-motor problems and language-based learning disability) and, more recently, as dysfunction of attention, motor function and perception (DAMP) (Beitchman *et al.* 1998; Fletcher *et al*. 1999; Levine 1999; Blondis 1999; Shaywitz & Shaywitz 1999; Surresh & Sebastian 2000).

Neurobiology

Learning disabilities are clearly linked to various syndromes. Language-based learning disability is more prevalent than expected in disorders having an extra sex chromosome, such as 47,XXX, Klinefelter's syndrome and 47,XYY. Girls with Turner's syndrome can have dyscalculia, dysgraphia and social skills deficits. Learning disability is higher in prevalence in neurofibromatosis, Tourette syndrome, treated phenylketonuria (more so in mathematics), and Fragile X syndrome (with relative visuospatial and executive function weaknesses). Children with William syndrome have relative strengths in expressive language with atypical word choices on naming tasks and relative deficits in semantics and grammar that are masked by their good verbal memory. However, they have significant problems with visuospatial skills involving the ability to perceive parts and reconstruct items. Anatomically, they have relatively smaller occipital and posterior parietal areas in addition to microcephaly. Children with velocardiofacial syndrome have an average IQ of 70 (typical range 50–100) with emergence of a learning disability at or after second grade when educational demands shift to greater need for concept formation rather than rote memorization. They have relative deficits in visuospatial, perceptual motor, mathematics and nonverbal reasoning (problem solving, abstraction and planning) skills that persist through adulthood. Individuals with periventricular nodular heterotopia (PNH), a disorder of neuronal migration, have a discrepancy between reading skills and intelligence similar to that seen in patients with developmental dyslexia (Beitchman *et al.* 1998; Rivera *et al.* 2002; Molko *et al.* 2003; Bruandet *et al.* 2004; Chang *et al.* 2005).

Conditions occurring after birth that have a higher risk of learning disability include prematurity and low birth weight, meningitis and encephalitis, traumatic brain injury, stroke, lead poisoning, and pediatric epilepsy (Gaddes & Edgell 1994). Significant prematurity typically results in children with normal intelligence, learning disabilities and attention deficits. The degree and nature of cognitive dysfunction after central nervous system infection and head trauma is dependent on the severity of the initial condition and the localization of anatomic lesions/brain dysfunction. Stroke is associated with delays in language development, especially in the preschool years. Verbal IQ may be higher than performance IQ, with potential problems in attention, memory, and visuospatial skills (Nass 1997). Language-based learning disability is more common in those with concomitant epilepsy (Doose *et al*. 1996). Lead poisoning can be associated with executive function problems and language-based learning disability, reflecting the purported anatomic dysfunction in frontal lobes and deep gray nuclei (Finkelstein *et al.* 1998). Known environmental factors in at-risk populations include low socioeconomic status, limited exposure to educational opportunities and home-based language stimulation, and impaired nutritional status (Beitchman *et al.* 1998; Shaywitz & Shaywitz 1999; Grogorenko 2001; Shapiro 2001). In educational settings, the identification of a traumatic brain injury, epilepsy, or other physical causes of learning difficulties will often be labeled a physical disability rather than a learning disability.

Despite the large number of potential causative conditions, the most likely reasons for learning disabilities are familial and genetic predispositions. Dyslexia is the most studied learning disability. Twin studies have shown a higher concordance rate for dyslexia in identical compared to dizygotic twins. Studies have consistently shown the familial patterns in dyslexia. If a family member has a reading disability, there is a higher than expected probability that other relatives will also have reading problems. This risk increases in proportion to the nearness of the relationship (i.e. higher for a sibling than a cousin). The mode of transmission is uncertain, although polygenic or dominant inheritance is most likely. Linkages to loci on chromosomes 1, 2, 3, 6, 13, 15 and 18 have been established, some suggesting an association with specific components of the reading process (phonological, awareness, automatic reading, memory). A candidate gene, DYX1C1, on chromosome 15 has been reported. How this genetic predisposition interacts with potential environmental factors is still inadequately defined (Grigorenko 2001; Francks *et al*. 2002; Taipale *et al*. 2003).

The biologic tendency for learning disabilities appears to manifest as abnormalities in brain anatomy. Pathologic studies have demonstrated a lack of asymmetry of the planum temporale (posterior portion of the superior temporal lobe), microscopic ectopias and dysplasia in both frontal and left language areas and minicolumnar abnormalities. Volumetric MRI studies have been equivocal in confirming the lack of planum temporale asymmetry, although differences from control subjects in other anatomic areas, such as the basal ganglia, frontal language region and parietal lobe, have been reported. This lack of concordance between studies may be explained by measurement techniques and

specific characteristics of the test subjects (Habib 2000; Grogorenko 2001; Casanova *et al*. 2002).

Functional studies of reading dysfunction using electrophysiologic techniques such as EEG activity and event-related potentials have shown that dyslexic individuals fail to differentiate between meaningful compared to meaningless reading stimuli. However, localization of the area of dysfunction using electrophysiology is limited (although magnetoencephalography has been helpful). Functional neuroimaging has revolutionized the examination of reading ability by using PET and fMRI techniques. Studies using these techniques have resulted in identification of brain areas activated by reading. In the left hemisphere there is a posterior reading system with ventral and dorsal components. The dorsal part (the angular and supramarginal gyri of the parietal lobe and posterior portion of the superior temporal gyrus) is thought to mediate phonologic analysis. The ventral portion, located in the lateral extra-striate and inferior occipital-temporal region, is related to memory-based word identification. The left hemispheric anterior system is located around Broca's area in the inferior frontal lobe and is involved in silent reading, naming and phonemic articulatory processing (Habib 2000; Grigorenko 2001; Pugh *et al.* 2000).

The prevailing theory about the functional disruption in dyslexia is based on the need for appropriate processing of phonologic and lexical-semantic features of words. Dysfunction of the dorsal component of the posterior circuits leads to failure to adequately phonologically decode the written word and may be caused by the anatomic abnormalities described in neuropathologic studies. The dysfunction does not allow transference of processed information to the ventral component. Therefore, the individual is unable to develop fast and automated "sight word" reading ability. As a consequence the dyslexic reader tries to compensate by relying more on the anterior circuit and by activating the right hemispheric areas homologous to the posterior circuitry. This results in a reliance on covert pronunciation as a means of phonologic decoding (inferior frontal region based) and nonphonologic visuo-semantic pattern recognition (right posterior hemisphere based), both less efficient in developing mature and functional reading skills. Whether the initial dysfunction has a selective effect on one cognitive process or results in disruption of all processes in the area of the initial abnormality is still debated (Shaywitz & Shaywitz 1999; Habib 2000; Grigorenko 2001; McCandliss & Noble 2003).

Several other theories exist (Habib 2000). The "magnosystem" theory is based on the concept of a visual processing deficit. Children with dyslexia process visual information more slowly than their peers and have problems with letter confusion. The underlying dysfunction involves the visual processing of information by sustained (parvosystem)

PEARLS & PERILS

- Disorders of higher cortical function are more prevalent in children with genetic syndromes and acquired conditions that directly impact on brain development. Individuals with these disorders require close monitoring and heightened vigilance and awareness to ensure early identification of learning difficulties.
- Evidence supports the impression that there is a neuropathologic underpinning for disorders of higher cerebral function in children. This should be clearly communicated to parents, affected individuals and educational personnel to avoid inappropriate conclusions of laziness or poor effort as reasons for poor performance.
- Testing instruments used to identify intellectual potential and patterns of achievement or processing performance are imprecise and potentially influenced by many factors. The way in which a child achieves the score is more significant than the score itself. Therefore, caution in interpretation of raw data is necessary.
- Cultural and stylistic differences must be considered when interpreting the test or school performance of children from minority populations.
- It is important to remember that tests, such as those of memory or perception, are related to skills such as reading and mathematics by theoretical assumptions. These theories can change over time. Therefore, the physician, psychologist and allied educational personnel must be aware of the way in which this relationship is represented, especially to individuals who are not familiar with the theoretical basis of test conclusions.
- Effective intervention should be developmentally appropriate and based on proven theoretical constructs and evaluation results. Use of predetermined rote remedial treatments that are not based on the child's specific areas of strength and weakness and required needs can compromise generalization and transfer of learning.
- It is important to understand the impact of disorders of higher cortical function on the child's school, home and social environments.
- Identification of common comorbid conditions, such as ADHD, dyspraxia and social skills impairment, is needed for the development of appropriate educational interventions and the understanding of the impact of disorders of higher cortical function on the child's daily functioning.
- The pursuit of alternative therapies by families of children with disorders of higher cortical function should be done in conjunction with implementation of proven interventions. This will provide the child with the greatest opportunity for earliest intervention and maximal achievement.

and transient (magnosystem) visual channels. Usually, the sustained channel inhibits the transient channel and allows processing of the written word without interference from preceding words. Failure of this inhibition results in dyslexia. There is anatomic and electrophysiological evidence for this theory, although not all studies are confirmatory.

The temporal-processing theory states that reading problems are caused by deficits in the brain's ability to process the rate and temporal features of stimuli. This could cause problems processing transient auditory stimuli, such as consonants, and result in difficulties with rapid processing skills in reading, such as letter order and sight word perception, and a generalized dysfunction in temporal order skills. Electrophysiologic studies have demonstrated problems in analyzing temporal sound features in individuals with developmental dyslexia. Children with developmental language disorder have been shown to have impairment in processing rapidly changing auditory stimuli, such as consonant-vowel syllables (Tallal 2000). However, this finding has not been consistently corroborated for visually based language (reading). Finally, individuals with dyslexia have problems with motor skills, time awareness, calendar sequencing, and temporal distance. These observations have been used to support this theory and to extend the sphere of dysfunction to spelling and mathematics.

The cerebellar deficit hypothesis claims that there is a general impairment in the ability to automatically perform skills. This leads to an inability to develop fluency in reading and other skills, such as motor coordination, spelling and writing. The core deficit resides within the cerebellum (Nicolson *et al*. 2001).

The biologic basis of other learning disabilities is less well defined. Investigations into normal mathematics skills suggest involvement of anterior and posterior areas in cerebral hemispheres, including simple multiplication in the left parietal cortex, arithmetic in both prefrontal and inferior frontal cortices and number size/relations in both parietal lobes. Only a limited number of studies have examined individuals with dyscalculia. Functional studies localized dysfunction to the parietal regions. Volumetric MRI studies in prematurely born children with dyscalculia demonstrated less gray matter in an area of the left parietal lobe. Problems with motor coordination may be due to cerebellar deficits, although the research in this area is sparse and does not exclude dysfunction in other areas such as the peri-rolandic region and basal ganglia (Shalev *et al*. 2000; Isaacs 2001; Shalev & Gross-Tsur 2001; Bruandet *et al*. 2004).

Evaluation

Frequently, the physician is the first professional approached by the family with concerns regarding developmental functioning. The goals of the assessment should include recognition of learning problems, referral for appropriate academic testing, monitoring of intervention methods and their impact, and identification of comorbid conditions.

A complete and detailed history is essential in the diagnosis of learning disabilities. Information about prenatal and perinatal events as well as developmental milestones can identify risk factors (Table 20.6). Review of available school records and teacher reports can contribute important information.

The medical examination can help identify underlying syndromes (such as neurofibromatosis or Fragile X syndrome) that can be associated with learning disabilities. Screening of hearing and vision is important. However, a child may pass the screening but still have a hearing or visual impairment that the screening was not sensitive enough to detect. For instance, a child may have difficulty hearing only when background noise is present. In a screening this would not be evident, as all background noise is blocked out during the evaluation, however, in the classroom this would place the child at a severe disadvantage as there is often a constant background noise of peers and classroom materials. The neurological exam can identify associated conditions such as dyspraxia (developmental coordination disorder) that can aggravate learning problems. This requires knowledge of milestones for gross and fine motor skills that can be assessed during the examination (Table 20.7). Motor skills mature over time, with overflow and mirror movements common in preschool and early school-age children. However, the persistence of choreiform movements with arm extension and arm posturing with heel and toe walking, or the failure to develop mature trunk and extremity movements with gait (walk, run, skip) by middle school and adolescence may indicate the presence of immature neural integration and inherent clumsiness. Commonly used assessment scales include the Bruininks-Oseretsky Test of Motor Proficiency Scale, the Henderson Test of Motor Performance, the Test of

TABLE 20.6

Medical History — Clues of Underlying Learning Diabilities

- Family history
- Prematurity
- Underlying syndrome
- Past central nervous system insult
- Development
  - Developmental language disorder
  - Difficulty learning alphabet letters/number symbols
  - Problem with letter-sound association
- Present skills
  - Isolated academic difficulty (reading, math)
  - Slow and dysfluent reading
  - Impaired spelling
  - Inability to learn rote math skills
  - Poor school performance with normal development

TABLE 20.7

Motor Milestones

Skill	Age(years)
Stand on one foot	3
Draw a circle	3
Draw a cross	3.5
Throw a ball	4
Button	4
Draw a square	4.5
Cut with scissors	5
Print name	5
Hop (repetitive)	5
Draw a triangle	5.5
Skip	6
Catch a thrown ball	6
Finger identification	8
Rapid finger apposition	9
Absent mirror movements	11
Necker cube	12

Visuomotor Integration and the Physical And Neurological Examination for Soft Signs (PANESS) (Denckla 1985; Blondis 1999).

While the clinician's office is not usually the place for extensive psychoeducational testing, screening for potential learning problems can be done. The child can be evaluated for ability to identify letters and numbers, demonstrate letter-sound relationships, read simple words, sentences, or paragraphs, write basic text, like names or dictated sentences, and show skills in mathematical calculation. These screening methods are not a replacement for the formal psychoeducational assessment that is mandatory for the identification of learning disabilities.

Comorbid conditions can aggravate or mimic learning disabilities. Therefore, the assessment should screen for features of attention-deficit/hyperactivity disorder, anxiety disorders, depression, and social skills deficits. Ongoing monitoring is necessary since learning problems can result in poor self-esteem, school avoidance or social regression, especially during adolescence or with worsening academic performance or inappropriate classroom placement. Psychiatric consultation may be advisable.

Medical testing is usually not necessary in most children with learning disabilities. EEG and neuroimaging should only be ordered if history or findings on examination suggest a structural brain abnormality or seizures. Epileptiform activity is sometimes present on the EEG of individuals with learning disabilities and may be secondary to the structural abnormalities causing the disability rather than to the cognitive effects of epileptiform activity. Therefore, its significance is uncertain. Treatment clearly depends on the facts of the clinical scenario. Similarly, clinical indications, not solely the presence of learning disabilities, should be the basis for ordering chromosomal analysis or metabolic testing. Research tools, such as PET scan, functional MRI, magnetoencephalography or specialized electrophysiologic testing, have no role in the clinical evaluation. Educational assessment can assist in providing insights to an individual's strengths and learning style.

The physician should be part of a multidisciplinary team, including a psychologist/neuropsychologist, speech and language therapist, teachers, occupational therapist, physical therapist and social worker. These specialists are necessary for the formal assessment of intelligence, academic achievement, language, and motor abilities that can identify learning disabilities and their comorbid disorders. The extent of the evaluation should be tailored to the concerns and needs of the individual child. The psychoeducational evaluation is most often completed through the local school system (an entitlement under the Individuals with Disabilities Education Act, IDEA), although concerns about school personnel bias, waiting lists and funding limitations lead many parents to seek an evaluation outside the school system.

Treatment

Intervention is a long-term program requiring the input and cooperation of the child, family, school personnel, outside consultants and therapists, and physicians. The child and family need to become educated about the diagnosis and its impact. Learning the facts about learning disabilities and the entitlements provided by the Individuals with Disabilities Education Act (Office of Special Education Rehabilitative Services) is essential when planning for intervention. IDEA provides for modifications and accommodations in daily instruction and testing (both state and local), specialized instruction, and fundamentally, a free and appropriate education. Knowing the law and the medical implications of a learning disability can assist in making the individual an "informed consumer" and strong advocate for needed intervention and instruction. The family should know how to request a multidisciplinary evaluation and how to develop an individualized educational plan (IEP), including participation on the IEP team. Referral to local and national parent and consumer organizations helps establish a local network and support system. These include International Dyslexia Society (http://www.interdys.org), Learning Disabilities Association of America (http://www.ldanatl.org), and National Center for Learning Disabilities (http://www.ncld.org). In short, "knowledge is power."

Most academic interventions will occur within the school setting. Public schools are required by law to provide support services to any student who qualifies under the guidelines outlined in IDEA. There are a number of laws that guide the education of all students. The newest comprehensive policy is No Child Left Behind (NCLB). A portion of this law specif-

ically addresses the selection of intervention programs and limits schools to utilizing only scientifically based practices. Exactly which practices meet these requirements is still being debated as the regulations are implemented in the schools. Treatments that are based on existing theories of dyslexia are supported by brain imaging research (Kujala *et al.* 2001; Aylward *et al.* 2003; Temple *et al.* 2003). Functional MRI studies show improved activation from normal reading associated areas that mirrors the clinical improvement in reading ability and is not based on a specific type of intervention. However, since the clinical study populations have been small, study results have been marginal or not necessarily transferable to the real world environment, and reproduction of results has not always been successful; further validation is required before these techniques are widely implemented or meet the requirements of NCLB. Most programs that focus on phonemic awareness and phonics, such as Wilson, have been shown to be effective by cognitive neuroscience and educational research. These programs provide direct instruction in using phonemes to determine words, recall the word quickly, and provide meaning. For more information on scientifically based practices, refer to The Council for Excellence in Government (http://www.excelgov.org), or the NCLB website (http://www.nclb.gov).

Law, policy, regulations, and neuroscience are the foundation for the chosen intervention. However, the key to an intervention's success is the child and the professionals supporting that child. Teachers, special education teachers, occupational therapists, physical therapists, speech and language therapists, psychologists, social workers, parents, and therapists for specific interventions or programs work together to create a cohesive environment to support the needs of the child while building on strengths. The teacher and special education support personnel work on the basics of reading, writing and math skills. This includes using exercises for helping the student learn techniques such as phonologic awareness and decoding or mathematical computation. Occupational therapists can help improve motor skills in writing and daily living activities such as dressing and eating. Adaptive physical education can improve gross motor coordination. Speech and language therapists can improve a child's speech and language processing. Social skills training can strengthen the individual's ability to interact with peers and adults. All individuals need to work together for each intervention to be most effective. Regular communication between home, school, and outside therapists should be established early in the process. This does not necessarily mean a face-to-face meeting. Technology such as phone conferences, email, and interactive webpages or chat rooms can be utilized. The result of this communication will be a list of accommodations or modifications that will ensure success and learning.

Accommodations are slight changes to the environment. These may include multiplication tables, calculators, word processors, preferential seating, assignments given in small pieces or steps, and extended time. There are three types of modifications: process, product, and content. Process refers to how a student will learn the content. Pre-written notes, small chunks of lecture at a time or videotaped lecture, and standing versus sitting are all examples of modified process. Product refers to what the student does to give evidence of knowledge. The most common product is a test or paper. For a student with dysgraphia, an oral report may provide a better measure of what the student has learned. Finally, content can be modified. The Revolutionary War may be difficult for a student with dysphasia or a nonverbal learning disability to conceptualize. However, a paper on why they think a school rule is unfair may help the student understand the basic premise and make a connection that is elaborated and abstracted as the student's level of educational sophistication increases. Modifications and accommodations can be provided throughout a student's education. Some universities and colleges also provide support for students with learning disabilities.

Periodic reevaluation of the effectiveness of any chosen treatment on a regular basis and implementation of needed program changes is important. The affective needs of the individual also should be regularly evaluated. The stresses of learning disabilities can impact on the involved individual and family members and result in poor self-esteem, acquisition of bad habits, depression, and, in some cases, family disruption such as divorce. Counseling can help address these issues, provide advice on behavior management strategies and teach coping skills to deal with stressors. Utilization of an individual's strengths is another way to support self-esteem and self-concept.

While medication has no significant effect on learning disabilities, it can lessen dysfunction by reducing the impact of comorbid conditions. Attention deficit/hyperactivity disorder, depression, and anxiety can be effectively treated with multimodal interventions that include the judicious use of medication. Claims of the efficacy of treatments using vitamins and minerals, elimination diets, vision training, special eyeglasses, and electrophysiologic retraining continue to be made. At this time, these have little, if any, research to support their use. The physician should be knowledgeable about these claims and should be able to answer family questions.

Prognosis

Outcome studies in learning disabilities suggest that these are chronic and persistent disorders. The majority of individuals with dyslexia continue to be poor readers and do not catch up to their peers in reading abilities. Moderate-severe dyslexia and a lower socioeconomic status appear to be predictors of a less-than-optimal outcome. Positive influences include positive self-esteem and appropriate decisions on

KEY CLINICAL QUESTIONS

- Are there other family members who have had:
  (a) attention disorders
  (b) reading difficulty
  (c) poor handwriting or
  (d) experienced academic difficulties?
- Are there other family members who have taken medication for any attention disorders?

future goals and work choices. However, vocational placement is at a lower level than expected for intellectual level (Shaywitz *et al.* 1999; Sanchez & Coppel 2000).

Functional MRI studies have shown improved activation closer to normal controls in left hemispheric reading areas and in the right hemisphere for those who respond to intervention. In young adults with a history of dyslexia, functional MRI demonstrated underactivation of posterior reading areas by compensated, but not fluent, readers, and different activation patterns by those with continued impairment (Shaywitz *et al.* 2003).

Follow-up information on individuals with dyscalculia is limited. Short-term improvement has been reported during the early school years. Adolescent outcomes of individuals who were symptomatic at age 10–11 years were poor, with 95% still scoring in the lowest 25% of their grade. Predictors of poor outcome included the severity of the dyscalculia and a positive family history. Those with nonverbal learning disabilities may also have difficulties in adulthood, this was also dependent on the severity of the childhood disorder (Dughartey 2000; Shalev *et al.* 2000).

Psychiatric problems can occur during adolescence and adulthood. There is an increased rate of delinquency, depression, anxiety, and impaired social/interpersonal skills. Occupational placement is adversely influenced by a lower percentage of individuals who attend and graduate college, the severity and type of childhood learning disability, the individual's level of self-esteem, and the presence of comorbid psychiatric disorders. However, even if the learning disability limits job opportunities, most individuals achieve gainful employment and independent living (Beitchman *et al.* 1998).

With early intervention and coordinated services, the prognosis for children with learning disabilities can be positive. Continuing research will increase the likelihood that individuals with learning disabilities will have a successful future.

Acknowledgment

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CONSIDER CONSULTATION WHEN...

- Initial psychoeducational testing does not identify the reason for the child's underachievement.
- There are discrepancies in the findings of different evaluations.
- Present educational intervention has not successfully narrowed the discrepancy between achievement and potential.
- There is a concern about the appropriateness of service delivery for the child.
- The school is not fulfilling its legal obligation to provide a free and appropriate public education that meets the child's needs and fosters the achievement of their maximum potential in a least restrictive placement.
- Features of significant psychiatric disorders, such as anxiety or depression, are identified.
- Medical conditions or their treatment adversely affect the child's educational abilities.
- A disorder of higher cortical function is identified after years of adequate educational performance. Alternative causes for a deterioration in academic ability, such as epilepsy, brain tumor, stroke or degenerative or neuropsychiatric disorders, must be considered.
- Poor academic performance is present in children who are at higher risk for disorders of higher cortical function.

Annotated bibliography

Gaddes W, Edgell D: Learning disabilities and brain function. New York, 1994, Springer-Verlag.
The authors begin their volume by presenting information about the brain and learning and behavior, and relate this information to perceptual disorders, sensorimotor pathways in learning, attention, language, and learning disorders in academic areas. Clinical cases and associated treatment suggestions are also illustrative.

Johnson D, Myklebust H: Learning disabilities: educational principles and practices. New York, 1967, Grune and Stratton.
A classic in the field of learning disabilities, this volume contains a series of informative chapters on the characteristics and treatment of childhood disorders of higher cognitive functioning. Chapters are organized according to areas of dysfunction and there is an explicit attempt to relate underlying deficits in processing to behavioural manifestations in reading, arithmetic, and other areas of underachievement, and associated treatments useful for educators.

Lyon, GR, editor: Frames of reference for the assessment of learning disabilities. Baltimore, 1994, Brookes.
This volume provides a current understanding of assessment in learning disabilities in attention, executive function, oral language, and academic areas; and brings insight to a number of controversial issues related to assessment such as the use of discrepancy formulas and measuring change over time.

Obrzut J, Hynd G, editors: Neuropsychological foundations of learning disabilities. San Diego, 1994, Academic Press.

This volume represents a scholarly treatment of the field of learning disabilities, including neurologic and genetic etiologic evidence, neuropsychological models of learning disabilities, treatments suggestions, and case studies.

Rourke BP, Fisk JL, Strnag JD: The neuropsychological assessment of children: a treatment-oriented approach. New York, 1986, Guilford.

This volume presents a coherent treatment-oriented framework for evaluating and discussing assessment issues and provides detailed case studies that illustrate this framework as well as major assessment and intervention issues in childhood neuropsychology. The strength of the text is in its use of illustrative case studies and attention to treatment issues, which are often neglected in favor of assessment issues.

Wong B, editor: Learning about learning disabilities. San Diego, 1991, Academic Press.

Wong's edited volume presents a varied treatment of learning disabilities including historical and research aspects of the field, and assessment and instructional issues from a number of perspectives and across the lifespan.

SECTION 3

Common Pediatric Neurologic Problems

Barbara Olson, MD

CHAPTER 21

Coma and Other States of Altered Awareness in Children

Stavros M. Hadjiloizou, MD and James J. Riviello Jr, MD

OUTLINE

Terminology
The anatomic and physiologic basis of consciousness
Coma etiology: a pathophysiologic approach
Herniation syndromes
Approach to diagnosis
Initial evaluation and emergency management
Initial lab workup
Differential diagnosis
Outcome and prognosis
Brain death

Coma is the extreme state of altered awareness with total unawareness of self and environment. Coma is a symptom not a disease, its presence indicates a significant central nervous system (CNS) insult, and its management constitutes a medical emergency. The pathophysiology of coma involves either bilateral cortical dysfunction, brainstem dysfunction, or diffuse (metabolic) dysfunction.

The goals of coma therapy are: (1) adhere to the basic principles of neuroresuscitation, the A, B, and Cs; (2) immediately identify signs of intracranial pathology: herniation, increased intracranial pressure, or focality to the neurologic examination; (3) identify and specifically treat the underlying cause; (4) determine prognosis; and (5) plan appropriate long-term therapy. This chapter emphasizes the important aspects of the history, physical examination, and neurologic examination in the evaluation and treatment of coma.

Terminology

"Consciousness" may be defined as the state of awareness of one's self and environment. In children, this definition should also consider the patient's age and developmental level. Coma is the extreme state of total unawareness of self and environment. In this state, there is no spontaneous eye opening or verbalization, and no purposeful response to external stimulation of any type. However, between full consciousness and coma, there exist "gradations of altered consciousness" with imprecise, and at times, ambiguous terminology, differentiated by the degree of stimulation necessary to achieve a purposeful response. This continuum may be further characterized by whether consciousness is decreased or heightened. The terms most commonly used in clinical practice are described below, although to avoid miscommunication, is better for the clinician to describe the actual mental state and the type of responses evoked by various stimuli as observed at the bedside, rather than just use a specific term.

Delirium is the typical example of heightened mental state. It is characterized by disorientation, irritability, fearful responses, and sensory misperception. Hallucinations, usually visual, as well as delusions may be also present. Confusion implies the state of impaired ability to think and reason clearly resulting in difficulty with orientation, simple cognitive processing, and acquisition of new memory. Confusion may be part of either a depressed or activated mental state.

Within the depressed mental status spectrum, different gradations may exist. Drowsiness is a light sleep-like state with easy arousals and brief periods of alertness. Obtundation describes a patient who appears to be asleep when not stimulated although no normal sleep pattern appears on EEG. Stupor is a state in which the child does not respond to verbal commands but can be aroused to some degree by vigorous, painful or noxious stimulation.

The anatomic and physiologic basis of consciousness

Both wakefulness (arousal) and awareness are fundamental to maintain consciousness. Wakefulness, an autonomic brain function, requires the integrity of the reticular activating system (RAS), a diffuse population of neurons located in the upper brainstem and thalamus. The regions of the reticular formation critical to the maintenance of wakefulness extend from the rostral brainstem (midbrain and upper pontine tegmentum) to the lower thalamus (Moruzzi & Magoun 1949). Several human conditions suggest that the hypothalamus is also important for consciousness. Awareness, a higher cognitive function, is

the combination of cognition and affect and is determined by the cerebral hemispheres. The importance of neurochemical regulation among the RAS, thalamus and cortex, should not be diminished. The different neurotransmitter systems involved in this modulation include cholinergic, noradrenergic, dopaminergic, serotonergic, and histaminergic pathways. As a consequence, integral consciousness requires an intact RAS, cerebral hemispheres, and healthy projections between the two systems to modulate their interactions.

Unconsciousness (unawareness of self and environment) can be a physiologic phenomenon when it occurs during sleep; the person is able to return to normal consciousness with the appropriate stimulus. Almost all other states of diminished consciousness are considered abnormal. Coma and other alterations of consciousness will result from three primary causes, which may occur separately or in combination: (1) diffuse or multifocal bilateral cerebral dysfunction, (2) substantial damage to the RAS, or (3) impaired communication between these two regions. Derangements affecting neurotransmitter pathways may occur with diffuse metabolic causes (i.e. drugs or toxins). In regard to cerebral disease, the level of overall depression of consciousness is proportionate to the degree of cortical dysfunction. Unilateral cortical lesions should not impair arousal function unless there is secondary compression or compromise of the other hemisphere or reticular structures, as sometimes occurs with herniation syndromes. Small cortical lesions confined to one or both cerebral hemispheres or small portions of the RAS do not typically affect consciousness.

For neurologic localization, it is important to recognize the anatomic proximity of structures involved in the regulation of consciousness, and specifically the RAS, with structures that provide valuable localizing information, such as brainstem nuclei regulating ocular movements and pupillary function. For example, pupillary enlargement and loss of ocular vertical and adduction movements suggest upper brainstem damage.

Coma etiology: a pathophysiologic approach

A practical and logical approach in the investigation of coma or other states of altered awareness takes into consideration the pathophysiology of consciousness as well as the immediate neuroresuscitation priorities. After stabilization, the clinician must immediately decide whether coma has a surgical cause, i.e. a structural brain lesion with necessary emergency neurosurgical intervention or a medical cause (diffuse encephalopathic process caused by meningitis, seizures or a metabolic reason).

Coma is typically divided into traumatic and nontraumatic causes. The basic mechanisms for coma are divided into two broad categories: structural lesions (usually more focal, may include trauma) or metabolic disorders (diffuse and symmetric). Structural lesions are further divided into supratentorial (hemispheric) and infratentorial (brainstem). Diffuse axonal injury is also considered in the structural group, occurring typically following trauma.

Focal neurologic signs are suggestive of a structural etiology, although may occasionally occur with diffuse or metabolic disorders. Supratentorial structural lesions are bilateral or cause secondary damage to the RAS (i.e. herniation). Unilateral cerebral hemisphere lesions cause focal neurologic signs but usually not coma. Examples of structural lesions include trauma, subdural or epidural hematomas, tumors, stroke and hydrocephalus. Nonaccidental trauma should be specifically considered in the infant. The most common cause of hemorrhagic stroke in children is an arteriovenous malformation (AVM) (Lin *et al.* 1999). Congenital malformations should be excluded as a cause of hydrocephalus in the infant.

Infratentorial lesions may directly damage the RAS and may be relatively small in size. Examples include brainstem infarctions, hemorrhage or tumors. Due to the anatomic proximity of the cerebellum, its lesions may cause secondary brainstem compression (i.e. cerebellar tumors in children or cerebellar hemorrhage in adults).

Metabolic etiologies cause the majority of cases in children and interfere with the availability of brain substrate. Metabolic disorders usually cause diffuse brain dysfunction and the neurologic examination is typically nonfocal. Examples of common pediatric primary neurologic causes include seizures (nonconvulsive status epilepticus or postictal state) and meningoencephalitis. Examples of systemic metabolic derangement that secondarily affect the CNS include accidental and intentional ingestions of drugs and toxins, systemic infections, anoxia, and metabolic disease. Inborn errors of metabolism and intussusception should be specifically considered in the infant. Of note, focality may be seen at times with some metabolic disorders like hyperglycemia, hypoglycemia, hypercalcemia or hypocalcemia, hepatic encephalopathy, uremia, and some toxic ingestions. Subarachnoid hemorrhage, even if not metabolic in origin, may also be included in this category as it affects the brain in a more diffuse manner.

Herniation syndromes

The intracranial contents have a fixed volume (V) because of the bony confines of the skull. The normal intracranial contents include brain tissue, the ventricular system containing cerebrospinal fluid (CSF), the interstitial spaces, and the vascular structures, both arterial and venous. If a brain lesion is present, its volume should also be included in the intracranial (IC) volume. This relation is shown by the Monro–Kellie Doctrine (Stern 1963).

$$V_{IC} = V_{brain} + V_{CSF} + V_{blood} + V_{lesion}, \text{ (if present)}$$

The intracranial pressure (ICP) is determined by the volume of these constituents. Within any fixed space, if the volume of any one component increases, then there must be a compensatory decrease in the volume of the other components, or else the pressure will rise. This relationship is described by the volume-pressure curve. Brain tissue also needs perfusion to supply oxygen and glucose, as well as other nutrients that support brain metabolism. The perfusion of any organ relies on a pressure gradient between the inflow and outflow circuits, with inflow pressure greater than the outflow pressure. If the outflow pressure increases above a certain pressure, then there will be no perfusion. Since the intracranial volume is fixed, pressure increases within the skull have a particular effect on blood flow. The inflow pressure is best related to the mean arterial pressure (MAP) and the outflow pressure is best related to the intracranial pressure, and the cerebral venous pressure. Some compensation may occur for volume increases in one component; initially the CSF may shift into the spinal subarachnoid spaces, or the lesion might compress venous or interstitial structures.

The intracranial cavity is further divided by projections of the dura into smaller compartments; the tentorium separates the anterior and posterior fossae and the falx separates the two cerebral hemispheres. *Herniation* is the shifting of brain tissue – due to a pressure effect – from its normal position into a different compartment. This may affect neuronal function by compression, with resultant ischemia and hypoxemia. In order to compensate for initial increases in the ICP, the MAP will increase, thereby promoting perfusion. Within certain limits of the MAP, there is a constant delivery of blood to brain tissue; this is called cerebral auto-regulation. However, when a certain MAP is reached, then there is an increase in CBF. Ultimately this increased blood pressure may further increase the ICP.

Different herniation syndromes have been described according to the direction of tissue displacement and/or dura in-folding involvement. A practical approach (Fig. 21.1) is to divide herniation into vertical and horizontal. Coma associated with herniation was classically considered secondary to the vertical displacement of brain compartments. In a study (Ropper 1986) of altered awareness with a unilateral hemisphere mass, early alterations in awareness were associated with horizontal, rather than vertical displacement. Horizontal displacement of the pineal body of 0–3 mm from the midline was associated with alertness, 3–4 mm with drowsiness, 6–8 mm with stupor, and 8–13 mm with coma. Vertical herniation (downward/descending or upward/ascending) may be transtentorial (through the tentorial opening) or foraminal (through the foramen magnum). Two transtentorial syndromes have been described: the syndrome of central transtentorial herniation and the syndrome of lateral mass (uncal or hippocampal) transtentorial herniation. Horizontal herniation occurs when the cingulate gyrus shifts under the falx (transfalcial) and across the midline. Transcranial herniation refers to displacement of brain tissue after an open head injury.

Central transtentorial herniation syndrome is the result of increased supratentorial pressure which secondarily causes caudal displacement of the diencephalon through the tentorial notch. Depending on the degree of pressure, there is a rostrocaudal progression of brainstem involvement, which is reflected by the clinical findings. RAS involvement results in alteration of consciousness, and small but reactive pupils, at least initially, result from sympathetic hypothalamic output damage.

Lateral mass (uncal or parahippocampal) transtentorial herniation syndrome is the result of lateral extracerebral or temporal lobe masses pushing the mesial temporal lobe (uncus anteriorly, parahippocampal gyrus posteriorly) between the ipsilateral aspect of the midbrain and the free edge of the tentorium (Brazis 2002). This results in compression of the third cranial nerve with subsequent dilatation of the ipsilateral pupil, and a contralateral hemiparesis. It is vital to recognize this stage promptly and intervene before occlusion of the posterior cerebral artery occurs, which may cause infarction. Altered consciousness is usually the result of lateral compression of the midbrain against the opposite tentorial edge by the displaced parahippocampal gyrus. Kernohan's

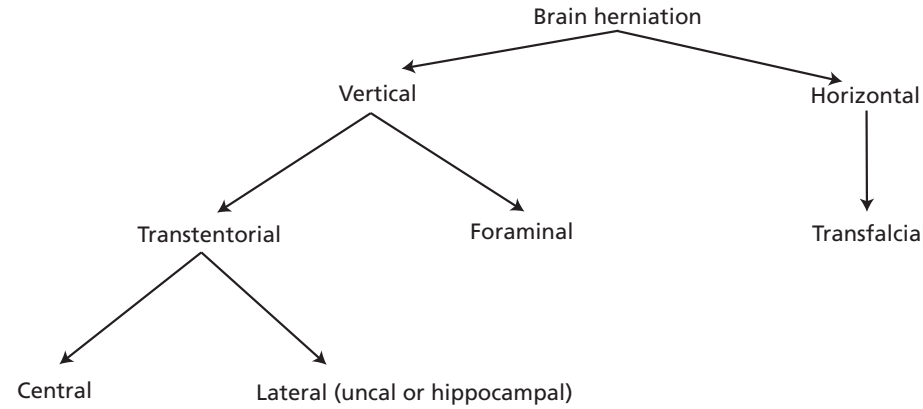

Fig. 21.1 Different types of brain herniation

notch sign ("false localizing sign") may be found occasionally and refers to hemiparesis and a Babinski response ipsilateral to the original lesion as a result of compression of the opposite cerebral peduncle.

Upward transtentorial herniation may occur with a cerebellar mass lesion which may displace the cerebellum through the tentorial notch. This is most likely to happen in patients with ventriculostomy. Decerebrate posturing occurs with initially reactive and miotic pupils, progressing to anisocoria and pupillary dilatation.

Foraminal herniation occurs usually with downward displacement of the cerebellar tonsils into the foramen magnum (called coning) and secondary obstructive hydrocephalus. Compression of the medulla may produce apnea.

Transfalcial herniation: Compression of one hemisphere by the other anteriorly was inconsistently related to alertness, though very large anterior displacements may have caused stupor in some patients (Ropper 1986).

Approach to diagnosis

History

It is important to know the time period over which coma develops, since the tempo of onset provides clues about the underlying disease. Coma usually presents in one of three ways: a predictable progression of an underlying illness (i.e. widespread malignancy), an unpredictable event on a known medical background (i.e. cardiac arrhythmia), or a totally unexpected event (i.e. trauma, intoxication). Knowledge about specific pre-existing conditions may provide clues for particular diagnostic considerations (Table 21.1).

TABLE 21.1 Useful Historical Hints Related to Particular Diagnostic Entities

Condition	Consider
Recent trauma	Hematoma or brain injury
Recent infection	Sepsis or meningitis
Headaches or personality change	Increased ICP
Seizure disorder	Status epilepticus or postictal state
Medications or potential toxins	Ingestion (purposeful or accidental)
Metabolic disorder, i.e. diabetes	Hypo- or hyperglycemic coma
Cardiac disease	Arrhythmias or cardiac arrest
Pulmonary disease	CNS infections, increased ICP

General physical examination

A thorough systematic physical examination is important, especially when no history is available (an unresponsive patient). Table 21.2 lists useful findings in physical that may help make a diagnosis.

Neurologic examination

The neurologic examination is the cornerstone of localization in the comatose patient (Fisher 1969) and helps identify the underlying pathogenesis. It is important to examine the following (Riviello 1988):

1. *Mental status (coma scales)*: Determination of the level of awareness is important. The continuum of different mental status changes has already been described. Given that these terms are vague and to avoid miscommunication, it is better to describe the patient's spontaneous activity as well as responses to different stimuli (verbal, noxious, painful). Objective criteria are needed to describe the patient's initial state and follow-up examination on changes, especially when assessing a response to therapy or to make a prognosis. Objective criteria are important since multiple caregivers are involved in patient management. For example, the criteria for various states of altered awareness (lethargy to coma), may differ from one observer to another (inter-observer unreliability). The Glasgow Coma Scale (GCS) (Teasdale & Jennett 1974) was devised as an objective measure of neurologic function (Table 21.3). It relies on motor and verbal responses, some of which may not be entirely appropriate for infants and younger children. Although the scale had been modified for children (Hahn *et al.* 1988), it was still not entirely appropriate for those less than 2 years of age, did not have high inter-rater reliability, and was difficult to apply when the child was intubated (Table 21.4). The CHOP infant face scale (Table 21.5) was developed primarily for children less than 2 years of age (Durham *et al.* 2000). This has also been referred to as the Infant Face Scale (IFS), since it relies on an assessment of the infant's crying and facial expression. It differs from other scales by reliance on objective behavioral observations and assesses cortical and brainstem function; it parallels the GCS in scoring, but is based on infant behaviors and can be applied to the intubated child. In their prospective study, the inter-rater reliability was almost perfect when applied to infants, and when compared to the GCS, the GCS inter-rater reliability was fair.
2. *Pupils (size, shape, reactivity)*: A preserved pupillary reaction to light implies a metabolic rather than structural etiology. Pupillary pathways are relatively resistant to metabolic insults. The pupils may be small, but they are

TABLE 21.2

Physical Examination Findings Related to Particular Diagnostic Entities

Finding	Consider
Skin	
Ecchymoses	Trauma, child abuse, bleeding disorder
Petechiae	Meningococcal disease, Rocky Mountain spotted fever, bleeding disorder
Cyanosis	Inadequate oxygenation (cardiac or pulmonary disease)
Excessive sweating or pallor	Hypoglycemia or shock
Decreased skin turgor	Dehydration
Head	
Battle sign ("raccoon eyes")	Basilar skull fracture or bleeding disorder
Fundi	
Papilledema	Increased ICP
Retinal hemorrhages	Child abuse, i.e. whiplash shaken infant syndrome
Ears	
Otitis	Meningitis or venous sinus thrombosis
Hemotympanum or otorrhea	Basilar skull fracture
Nose	
Rhinorrhea	Basilar skull fracture
Mouth	
Intraoral laceration	Trauma, seizure, stroke
Oral smell	Metabolic disorder, i.e. fruity with DKA; ethanol, etc.
Neck	
Nuchal rigidity	Meningitis, subarachnoid hemorrhage
Chest	
Respiratory distress	Airway obstruction or pneumonia
Heart	
Murmur or dysrhythmia	Embolism, brain abscess, endocarditis
Abdomen	
Hepatosplenomegaly	Liver disease
Tenderness	Perforation or trauma

TABLE 21.3

The Glasgow Coma Scale

Activity	Best response	Score
Eye opening	Spontaneous	4
	To verbal stimuli	3
	To pain	2
	None	1
Verbal	Oriented	5
	Confused	4
	Inappropriate words	3
	Nonspecific sounds	2
	None	1
Motor	Follows commands	6
	Localizes pain	5
	Withdraws in response to pain	4
	Flexion in response to pain	3
	Extension in response to pain	2
	None	1

TABLE 21.4

Modified Coma Score for Infants

Activity	Best response	Score
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Verbal	Coos, babbles	5
	Irritable cries	4
	Cries to pain	3
	Moans to pain	2
	None	1
Motor	Normal spontaneous movements	6
	Withdraws to touch	5
	Withdraws to pain	4
	Abnormal flexion	3
	Abnormal extension	2
	None	1

generally symmetric and reactive. This signifies an intact midbrain. Unreactive pupils signify midbrain dysfunction (usually structural in etiology). A unilaterally dilated and unresponsive pupil indicates ipsilateral third nerve compression, usually related to uncal herniation of the temporal lobe associated with a contralateral hemiplegia. Midposition dilated pupils imply structural damage to the midbrain and may be seen with central herniation. However, several ingestions (atropine, scopolamine) may lead to unreactive large pupils. Small pupils may be seen

TABLE 21.5 The CHOP Infant Coma Scale (Infant Face Scale)

Eye opening	
Spontaneous	4
Verbal stimulation to touch	3
Painful stimulation	2
None	1
Motor	
Spontaneous normal movements	6
Spontaneous normal movements, reduced in frequency or excursion; hypoactive	5
Nonspecific movement to deep pain only (trapezius pinch)	4
Abnormal rhythmic spontaneous movements: seizure-like activity	3
Extension, either spontaneous, or to painful stimuli	2
Flaccid	1
Verbal/face	
Cries spontaneously or with handling, or to minor pain, alternating with periods of quiet wakefulness	5
Cries spontaneously, or with handling, or to minor pain, alternating with sleep only	4
Cries to deep pain only (trapezius pinch)	3
Grimaces only to pain	2
No facial expression to pain	1

with narcotic, barbiturate ingestions or with pontine lesions.

3 *Oculomotor movements (normal, asymmetric or absent)*: Conjugate gaze requires intact cranial nerves III, IV, and VI and their connections via the medial longitudinal fasciculus (MLF). Asymmetrical oculomotor responses usually imply a structural brainstem lesion rather than a metabolic lesion (however, phenytoin and carbamazepine may cause oculomotor dysfunction). Tonic conjugate deviation implies either a unilateral hemisphere or brainstem lesion, although seizure activity may also cause tonic deviation. Both a destructive lesion and a focal seizure can be accompanied by a hemiparesis. In a destructive lesion, the eyes deviate away from the side of the hemiparesis and a focal seizure, an "irritative lesion," causes eye deviation to the contralateral side (i.e. the eyes look toward the hemiparesis). In the unconscious patient two main reflexes are used to test extraocular function. The oculocephalic ("doll's eyes") reflex is elicited by holding the eyelids open and turning the head briskly to each side. When the response is normal, the eyes shift to left when the head is turned right and vice versa. If a low brainstem lesion is present, the eyes will move along with the head mimicking oculoparesis. This reflex should not be performed in a patient with suspected spinal cord injury. The oculovestibular reflex (cold caloric) is elicited by elevating the head 30° and inserting a small catheter into the external auditory canal, near the tympanic membrane. The eyes are held open while ice water is flushed into the ear. The normal response in an unconscious patient is nystagmus with the slow component toward the ear being irrigated and the fast component away from the irrigated side (the reverse is true in conscious patients). In patients with a unilateral MLF lesion, the eye will deviate only on the unaffected side while those with low brainstem lesions will not move either eye in response to this maneuver.

4 *Motor responses to pain (normal, decorticate, decerebrate, or flaccid)*: With a mild insult, the patient has purposeful withdrawal to noxious stimuli. Hemiplegia suggests either a cortical or brainstem lesion. Hyperreflexia and the Babinski (plantar extensor) sign classically signify an upper motor neuron lesion. Hyporeflexia may be seen in metabolic or toxic (ingestion) disorders or with acute structural lesions. With more severe brain impairment, two typical reflex responses to painful stimuli are described. Decorticate posturing (adduction of the arm at the shoulder with elbow flexion and leg extension) usually suggests contralateral hemispheric or diencephalic damage. Decerebrate posturing (arm extension, adduction and internal rotation along with leg extension) usually implies more severe brain damage and may be suggestive of upper brainstem involvement, including downward herniation, as well as a metabolic insult (hypoglycemia, hepatic encephalopathy, or severe anoxia). Flaccid posturing is an ominous sign and indicates compression of the medulla, a terminal event.

5 *Respiratory patterns*: Different processes may damage the respiratory centers in the brainstem and give rise to particular abnormal respiratory patterns. Cheyne–Stokes respiration (hyperpnea in a crescendo and decrescendo pattern followed by an apneic phase) was described in diffuse rather than focal processes (i.e. metabolic insults). Central neurogenic hyperventilation (a sustained, rapid, and deep respiratory pattern) is suggestive of midbrain or pontine lesions. Apneustic breathing (deep inspiration followed by a pause) is consistent with damage to the pons. Ataxic (irregular) breathing, which may progress to apnea, results from medulla damage, where the respiratory centers responsible for the normal rhythm of breathing are located.

Initial evaluation and emergency management

Comatose patients are in a critical, life-threatening condition. Immediate stabilization is needed, with adherence to the principles of neuroresuscitation: the A, B, and Cs. These general principles (Table 21.6) are applied initially regard-

TABLE 21.6 Priorities During the Initial Evaluation and Stabilization of the Comatose Patient

	Assure	Exclude	Consider
Airway	Patency	Obstruction (posterior displacement of the soft tissues, i.e. tongue, mucous, or foreign bodies)	Oropharyngeal or nasopharyngeal airway or intubation
Breathing	Oxygenation	Apnea (primary or secondary causes) Ingestions	Oxygen Positive pressure ventilation
Circulation	BP and HR	Shock (hemorrhagic, septic, cardiac) and dehydration	IV access
Dextrose	Normoglycemia	Hypoglycemia	Glucose IV (with thiamine in malnourished patients)
Temperature	Normothermia	Severe infection, i.e. meningitis or sepsis	Lumbar puncture Antibiotics IV
ICP	Normal ICP	Herniation (Focal exam?)	CT brain Hyperventilation Hyperosmolar agents Neurosurgical intervention?
Antidotes		Overdose Intoxication	Specific antidotes, i.e. naloxone for opiates or nonspecific elimination procedures (activate charcoal, gastric lavage, catharsis, dialysis, etc.)
Seizures		Status epilepticus or postictal state	EEG

less of the underlying etiology. This will hopefully prevent secondary brain injury. The next step is to identify and specifically treat the underlying cause.

The first priority is to ensure the adequate delivery of oxygen and glucose; acute respiratory and cardiovascular problems should be attended to prior to a formal neurologic assessment. Then, the neurologic assessment must immediately identify (a) signs of increased intracranial pressure, or focality, both suggestive of a structural (mass) lesion or brain herniation, in which emergency neurosurgical intervention may be critical; (b) evidence of meningitis, encephalitis, or other systemic infections; (c) a severe metabolic derangement, including intoxication; and (d) seizures as the cause of altered awareness. Again, it is important to identify disorders that have specific treatment.

Initial lab workup

Table 21.7 summarizes investigations that should be considered during the initial evaluation of a patient with altered consciousness that may help identify particular coma etiologies.

Differential diagnosis

The clinician should be able to differentiate coma from conditions that may share similar features but have other distinctive differences.

Vegetative state (VS): This is a deafferented state of wakefulness with complete unawareness, and it may evolve when recovering from coma. VS is the result of a relatively intact brainstem combined with severe bihemispheric damage. There is partial or complete preservation of vital hypothalamic and brainstem functions although the patient remains unaware of self and environment. It is now generally preferred to avoid the term "permanent vegetative state" and rather describe the exact duration and cause of this condition (Ashwal & Cranford 2002). Three main patterns of pathology are described (Zeman 1997): (1) diffuse axonal injury, (2) extensive laminar necrosis of the cerebral cortex, and (3) occasionally thalamic necrosis. Distinguishing features from coma include spontaneous eye opening and the presence of sleep-wake cycles. This state may persist for years and until death. Most common acute causes are head trauma (diffuse axonal injury) and hypoxic-ischemic encephalopathy. The prognosis 1 month after brain injury was analyzed by the American Multi-Society Task Force on PVS in 1994. Three factors clearly influencing the chances of recovery were: age, etiology, and time already spent in the vegetative state. The outlook is better in children and after traumatic brain injury, and worse with longer durations.

Minimally conscious state: This is a condition of severely altered consciousness in which minimal and inconsistent, but clearly visible, behavioral evidence of consciousness is demonstrated (Giacino *et al.* 1997). Diagnostic criteria which help to distinguish the minimally conscious state from the VS include: (1) ability to follow simple commands, (2) gestural or verbal "yes/no" responses (regardless of accuracy), (3) intelligible verbalization and (4) purposeful behavior

TABLE 21.7

Initial Investigations in the Comatose Patient

Study	Consider	Test
Blood	Encephalopathies • Metabolic (including SIADH) • Toxic, or • Drug-induced	Electrolytes, glucose, calcium, phosphorus, osmolarity, BUN and creatinine, ammonia and liver enzymes Arterial blood gas Toxicologic analysis Blood cultures
Urine	Same	Toxicologic analysis Urine cultures
CSF	Meningitis Encephalitis Subarachnoid hemorrhage Increased ICP	Glucose, protein, white and red blood cells as well as CSF cultures (bacterial and viral) Look for xanthochromia Opening pressure
EKG	Cardiovascular integrity	Cardiac monitoring
Neuroimaging	Hydrocephalus, various intracranial hemorrhages, tumors	CT MRI
Electrophysiology	Nonconvulsive status epilepticus Herpes encephalitis and SSPE	EEG

(Giacino *et al.* 2002). Common causes include perinatal or genetic conditions as well as acquired brain injuries (Strauss *et al.* 2000). As this is a newly defined condition, long-term prognostic data are not yet available for children, although it is assumed that this state may become permanent 12 months after traumatic brain injury and 3 months after nontraumatic injury (Ashwal 2003).

"Locked-in" syndrome (LIS): This de-efferented condition is quite rare in children. It consists of quadriplegia, paralysis of lower cranial nerves (inability to speak and swallow), and bilateral paresis of horizontal gaze. It is usually the result of corticospinal and corticobulbar pathway interruption due to lesions at the base of the pons. The two hemispheres are intact retaining consciousness and cognition but due to interruption of the efferent connections the message cannot be transmitted to the motor system. The patient is awake with eye opening and sleep-wake cycles but movement and communication are markedly impaired. Attention should be paid to the vertical eye movements which remain intact. In a study of 29 adults with the LIS followed for a minimum of 5 years (Katz *et al.* 1992) cerebrovascular disease was the most common cause and survival ranged from 2 to 18 years. Other possible causes include tumors and central pontine myelinolysis. Early recovery of lateral eye movements has been suggested as a favorable prognostic sign (Yang *et al.* 1989).

Akinetic mutism: This term was introduced by Cairns *et al.* in 1941 to indicate a syndrome characterized by lack of responsiveness in the presence of apparently preserved vigilance (Ackermann & Ziegler 1995). The patient shows slow or nearly absent body movements and loss of speech, particularly when nonstimulated, although remains aware of self and environment. The EEG shows slow-wave abnormalities. This state is the result of reduced motor activation following damage to (a) the bilateral frontal lobes (Mega & Cohenour 1997), (b) the diencephalo-mesencephalic reticular formation, (c) the globus pallidus, and d) the hypothalamus. Common causes include anoxia, head trauma, infarctions, acute hydrocephalus (Lin & Wang 1997), and tumors.

Outcome and prognosis

As with neurologic diseases in general, etiology is a very important determinant of prognosis. As noted above, coma may be divided, especially on clinical grounds, into traumatic and nontraumatic causes. Head injury is one of the major causes of coma in children. Hypoxic-ischemic encephalopathy is a major cause of nontraumatic coma (Trubel *et al.*2003). There has been only one population-based study (in the UK) of nontraumatic coma in children (Wong & Forsyth 2001). The incidence of nontraumatic coma in children less than 16 years of age was 31 in 100 000 (six in 100 000 in the general population). Inclusion criteria were a period of altered awareness greater than 6 hours, if ultimately admitted to the hospital. Exclusion criteria were newborns (<1 month of age), a traumatic cause, those in the expected terminal phase of a chronic illness, or sudden infant death syndrome (SIDS). Two hundred and seventy-eight individual children were identified. The incidence was higher in the first year of life and included 160 in 100 000 children per year. Infection was the most common etiology, occurring in 37.9%, followed by intoxication in 10.3%, epilepsy in 9.6%, congenital causes in 8.2%, accident (smoke inhalation, strangulation, burns, and

drowning) in 6.7%, and others in 7.8%. Unknown causes were present in 14.5%.

In this study, age-dependent clinical presentations were identified. The presenting symptoms were assigned to three groups: CNS-specific (altered level of consciousness, convulsion, headache, irritability, photophobia, and behavioral change), organ-specific (rash, UTI, cutaneous hemorrhage, sore throat), and systemic (vomiting, nausea, fever, lethargy, poor feeding, shortness of breath, palor, cyanosis, respiratory arrest, poor weight gain, limb weakness). Systemic presentations occurred more frequently in infants whereas CNS specific presentations were frequent in children older than 5 years. The overall mortality was 127 in 278 (45.6%); there were 59 prehospital deaths.

Another significant aspect related to outcome and prognosis is the neurologic course, and specifically the duration of the comatose state. Several prognostic factors have been identified in a prospective study of adult coma, which excluded trauma and intoxication (Bates & Caronna 1977). In the first 310 adults identified, the occurrence of severe disability or the vegetative state was related to the duration of coma, occurring in 25% of those comatose for greater than 6 hours, and in 79% of those comatose after a week. Regaining an independent existence was greater in those who by day one could obey commands or move limbs appropriately to noxious stimuli, had normal motor tone, had normal responses to oculocephalic or oculocaloric testing, or had orienting eye movements. In a larger follow-up study of 500 patients (Levy *et al.* 1981) only one of 120 patients lacking two of corneal, pupillary, and oculovestibular responses ever regained independent function. In a study of serial neurologic examinations (Levy *et al.* 1985), at the initial examination 52 out of 210 patients had absent pupillary light responses, and none of these recovered independent daily function. Out of 27 patients who had pupillary light reflexes, spontaneous or conjugate eye movements, or motor responses to pain, 11 of those (41%) regained independence.

How to follow the patient

The clinical examination

The comatose patient is followed by sequential neurologic examinations. These are important to determine the response to therapy. If there is no clinical improvement, then perhaps the treatment plan needs re-evaluation. It is best to use objective scales, such as the Glasgow Coma Scale (GCS), the modified scale for children, or the CHOP Coma Scale, which uses the Infant Face Scale. There are also two different scales, the Pediatric Risk of Mortality (PRISM) Score (Balakrishnan *et al.* 1992) and the Acute Physiology and Chronic Health (APACHE) Scale (Knaus *et al.* 1989), both of which have prognostic value when applied at the initial evaluation. The PRISM III score has 17 physiologic variables (Pollack 1996). Those most predictive of mortality are: minimum systolic blood pressure, abnormal pupillary light reflexes, and stupor or coma. The APACHE scale uses 12 routine physiologic measurements, age, and previous health status. These include temperature, mean arterial blood pressure, and GCS.

Neurophysiology

Neurophysiologic testing is used to monitor patients and provide prognostic information. These studies include EEG and evoked potentials, either visual (VEP), auditory (AEP), or somatosensory (SSEP). There are only a few actual studies that specifically analyze their prognostic value.

The utility of EEG in the evaluation of comatose children is similar to adults (Shewmon 2000). In all causes of coma (traumatic and nontraumatic, including hypoxic-ischemic or metabolic disorders), an invariant EEG background, without reactivity, carries a poor prognosis. Invariant backgrounds include electrocerebral inactivity, burst-suppression or suppression-burst, or low-voltage invariant. Burst-suppression refers to an EEG background that although discontinuous, has consistently present EEG activity. Suppression-burst refers to an EEG with marked suppression and occasional or rare bursts of EEG activity. Postanoxic myoclonus also carries a poor prognosis in children.

EEG is used for the diagnosis of brain death, especially outside of the neonatal period. There has been concern about using the EEG in the diagnosis of neonatal brain death. However, when using EEG for prognostic purposes and as a confirmatory test for brain death, it is important to exclude conditions that alter EEG background, yet are potentially reversible (refer to brain death discussion).

The utility of EEG in pediatric coma was evaluated in 201 children, ages ranging from 1 month to 14 years (Fois & Malandrini 1983). No specific patterns were seen. Diffuse slowing occurred with infectious, postictal, metabolic, and post-traumatic etiologies. Mixed fast and slow activity occurred with intoxications, especially benzodiazepines, barbiturates, and alcohol. Intracerebral hemorrhages had focal slowing associated with generalized slow activity, and in trauma, generalized slowing with focal attenuation occurred. A poor prognosis was seen with extreme slowing or electrocerebral inactivity. The reappearance of sleep spindles carried a good prognosis.

EEG is used in the management of status epilepticus (SE), particularly to monitor the response to therapy in difficult to control cases. It may be also used to monitor the treatment of increased intracranial pressure (ICP), especially with head trauma. ICP changes have been associated with an EEG correlate (Munari & Calbucci 1979). When the ICP was stable, the EEG tracing was nonreactive, with low frequency, monomorphic, large amplitude waveforms. When ICP elevations occurred, an EEG pattern with bursts of slow waves alternating with periods of rapid activity developed, and there was a waveform suppression with the reappearance of slow waves.

PEARLS & PERILS

- Describe the actual mental state – avoid ambiguous terms. Describe the responses evoked by various stimuli.
- Keep fundamental anatomy and physiology in mind. Coma results from bilateral cortical and/or brainstem dysfunction, or diffuse (metabolic) dysfunction.
- During the initial evaluation and treatment, adhere to the fundamental principles of resuscitation, regardless of etiology.
- After stabilization, immediately decide whether focal signs suggestive of a structural process or signs of increased intracranial pressure exist and if emergency neurosurgical consultation is needed.
- Remember: papilledema may be absent even with documented increased ICP. If you have evidence of increased ICP, don't be reassured by its absence as it may take several hours to develop.
- Order a head CT scan as soon as the patient is stabilized:
  - in the presence of focal signs
  - prior to an LP when concerned about increased ICP.
- Do not delay antibiotic therapy while awaiting results or head CT scan, if meningitis is strongly suspected.
- Retrieve the tempo (evolution) of coma onset whenever possible – it will provide important clues about the underlying pathology.
- A detailed general physical examination is invaluable especially when the history is not available; always exclude trauma, including nonaccidental.
- Localization clues:
  - the brainstem nuclei are in close proximity to structures involved in regulation of consciousness.
  - ocular movement and pupillary function abnormalities are of critical importance.
- The most important factors to determine the outcome and prognosis are the underlying etiology and the duration of the comatose state.
- SSEPs have high positive predictive value for outcome.

In the prospective study of SE (Towne *et al.* 2000) in ages greater than 1 month, nonconvulsive status epilepticus (NCSE) was detected in 14% following the successful treatment of convulsive SE, and NCSE was found in 8% of patients with unexplained coma. Periodic findings, such as paroxysmal lateralizing epileptiform discharges (PLEDs) are useful, suggesting herpes simplex virus (HSV), although PLEDs have been seen in many different infectious disorders. Periodic EEG patterns are also seen with subacute sclerosing pariencephalitis (SSPE), or triphasic waves may be seen in metabolic encephalopathies.

The EEG has been studied in specific disorders. In near drowning, which is an hypoxic-ischemic encephalopathy, a poor prognosis is associated with a loss of beta rhythms, diffuse delta activity, often with admixed alpha or beta activity (alpha–delta and beta–delta pattern), poor sleep-waking differentiation, abnormal reactivity, biphasic sharp waves, and either an invariant or burst-suppression EEG background (Janati & Erba 1982; Cheliout-Heraut *et al.* 1991). Repetitive focal or multifocal biphasic or triphasic wave forms occurred only in those that died. The development of cerebral edema and decerebration was associated with attenuation or disappearance of fast frequencies and reactivity to painful stimuli, or the development of slow and biphasic sharp waves. In severe head injury, patients with electrocerebral inactivity died. Reactivity of the EEG to external stimulation was associated with a favorable outcome (Hutchinson 1991).

Rhythmic EEG patterns consisting of invariant, nonreactive, diffuse cortical activity of a specific frequency have been described in comatose children. Various etiologies were present and the prognosis was not dependent on the actual waveform frequency. The alpha-frequency (called alpha coma) had a better prognosis than that seen in adults (Horton 1990). Alpha coma has been reported with Japanese encephalitis (Kalita & Misra 1998).

Evoked potentials also have prognostic value and are used as confirmatory studies for brain death. A particular benefit of EPs is that the waveform may be preserved in metabolic or "therapeutic" comas (for example, pentobarbital therapy for increased ICP). In evoked potential interpretation, the significance of an absent cortical response cannot be made when the entire waveform, including the proximal response, is absent. For example, if a brainstem auditory evoked potential (BAEP) is done as a confirmatory test for brain death, this study can not be used for confirmation if the entire waveform is absent. If the peripheral component (wave I, the acoustic nerve) is present, then the absence of the more proximal waves does signify an absence of brainstem function. It should be noted that wave II of the BAEP may be present in brain death, since it may also originate from the distal portion of the VIII nerve. Similarly, the absence of the proximal responses applies to the somatosensory evoked potential (SSEP) (median or tibial nerve responses) and the visual evoked potential (VEP) (retinal response).

VEPs have had less predictive value than either AEPs or SSEPs (Taylor & Farrell 1989). In a study of SSEPs in 73 comatose children upon admission to the PICU (De Meirleir & Taylor 1987), 50 children had a GCS <7 upon admission, and only 3 had normal SSEPs; 37 had either unilateral or bilaterally absent waveforms. Of the 27 patients that died, none had a normal SSEP and in the 14 patients with a normal outcome, 9 had normal waveform. The SSEP was not altered by

KEY CLINICAL QUESTIONS

- What is the tempo of coma development?
- What is the patient's baseline function level?
- Is there history of trauma (including nonaccidental)?
- Is there evidence of meningitis?
- Is there history of seizures or status epilepticus?
- Is there history or evidence of substance abuse or toxicity?
- What is the patient's past medical history (i.e. diabetes)?
- Are there focal findings on neurological examination?
- Are there signs of increased ICP or herniation on neurological examination?

etiology. SSEPs have also demonstrated predictive value in traumatic brain injury in children (Beca 1995; Carter 1999).

For a normal SSEP, the positive predictive value (PPV) was 85.4, and for bilaterally absent responses, the PPV was 90.9% (Carter *et al.* 1999). Normal SSEPs within 4 days of coma onset had a PPV for a favorable outcome in 93% whereas with absent SSEPs, there was a PPV of a poor outcome in 92% (Beca *et al*.).

In a prospective study (Mandel 2002) of both clinical and neurophysiologic data on coma outcome in 57 children with HIE, the PPV of a poor outcome was 100% with a discontinuous EEG and either spikes or epileptiform activity on EEG; the PPV was 100% for the bilateral absence of the N20 wave on the SSEP. Clinically, initial CPR for greater than 10 minutes and a GCS <5 at 24 hours after admission had a PPV of an unfavorable outcome in 91%. In an adult study (Rothstein 2000), bilateral absence of cortical evoked responses predicted death without awakening in 19 out of 26 (73%), and a malignant EEG change was predictive in 11 out of 26 (42%). Those with a normal or delayed central conduction time or benign or uncertain EEG findings had an uncertain prognosis. Bilateral absence of cortical evoked responses or malignant EEG changes reliably predicted an unfavorable outcome in 21 out of 26, but did not identify those that awakened with normal outcome.

Neuroradiology

Neuroimaging includes computerized axial tomography (CAT) scan, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), magnetic resonance angiography (MRA), MRI with diffusion-weighted imaging (DWI), and conventional angiography. The CAT scan is used the most because of its availability, and it demonstrates most of the lesions that demand immediate attention such as hydrocephalus, tumor, or various types of hemorrhage which include: acute subdural or epidural hematoma, intracerebral hematoma, or subarachnoid hemorrhage. It also well visualizes the signs of herniation: encroachment of the suprasellar cistern, brainstem displacement, enlargement of the ipsilateral crural subarachnoid space, and compression of the contralateral cerebral peduncle. With disease progression, there is advancing obliteration of the suprasellar and interpeduncular cisterns, elongation or compression of the brainstem, and either inferior or posterior basilar artery displacement. Other findings seen include aqueductal compression, which causes obstructive hydrocephalus, and a widening of the temporal horn occurs on the side contralateral to a mass. Posterior cerebral artery infarction may occur with herniation. Symmetrical thalamic low densities may also occur.

MRI is more sensitive than CAT scan, but is difficult to obtain on an emergent basis and may place the child at a greater risk because of the longer acquisition time. Other studies that can be done with MRI include MRA and MRS. MRI with DWI better images acute ischemia. MRS can measure brain metabolic activity, such as NAA, choline, and lactic acid. An elevation of lactate may have prognostic value in various etiologies: perinatal asphyxia, near-drowning, and head injury. In a study of MRI in children with hypoxic-ischemic coma using an 8-point scoring system based on watershed areas and basal ganglia, there was a strong correlation between the first MRI score and neurologic outcome (Dubowitz *et al.* 1998). However, patients with definite abnormal findings could have a good outcome.

CONSIDER CONSULTATION WHEN...

- Neurology:
  - Unexplained change in mental status
  - Focal neurological signs on examination
  - Suspected increased ICP or meningitis
  - Suspected nonconvulsive status epilepticus
  - Determination of outcome and prognosis is needed
  - Determination of brain death
- Neurosurgery:
  - History of, or suspected, head or neck trauma
  - Focal neurological signs on examination
  - Suspected increased ICP or signs of herniation (clinically or on neuroimaging)
  - Suspected intracranial space-occupied process (i.e. tumor or hemorrhage)
- Intensive care unit:
  - Close monitoring and support of vital functions are needed
  - Certain disorders are best managed in the ICU, such as refractory status epilepticus

TABLE 21.8

Guidelines of the Task Force for the Determination of Brain Death in Children

I. History

Determination of cause of death is necessary to ensure the absence of treatable or reversible conditions

II. Physical examination

1. Coma and apnea must coexist
2. Absence of brainstem function
   - midposition or fully dilated pupils
   - absence of spontaneous eye movements (induced by oculocaloric/oculovestibular testing)
   - absence of movement of facial and oropharyngeal muscles (include corneal, gag, cough, sucking, and rooting reflexes)
   - absence of respiratory movements using standardized testing for apnea
3. Absence of hypothermia or hypotension
4. Flaccid tone and absence of spontaneous or induced movements (spinal cord reflex withdrawal not included)
5. Examination should be consistent with brain death throughout the observation and testing period

III. Age-dependent observation period

Age	Hours between two examinations	Recommended number of EEGs
7 days–2 months	48	2
2 months–1 year	24	2
More than 1 year	12	Optional

TABLE 21.9

Minimum Technical Standards for EEG Recording in Suspected Brain Death

1. Minimum number of scalp electrodes: eight (8)
2. Interelectrode impedances: 100–10 000 Ohms
3. The integrity of the entire recording system should be tested
4. Interelectrode distances: at least 10 cm
5. Sensitivity: must be increased from 7 μV/mm to at least 2 μV/mm for at least 30 minutes of the recording with inclusion of the appropriate calibrations
6. Filter settings: appropriate for the assessment of electrocerebral silence (ECS)
7. Additional monitoring techniques should be employed when necessary (i.e. to exclude artifactual activity)
8. There should be no EEG reactivity to intense somatosensory, auditory or visual stimuli
9. Recording should be made only by a qualified technologist
10. A repeat EEG should be performed if there is doubt about ECS

Brain death

Brain death occurs in up to 2% of PICU admissions (Martinot *et al.* 1995). Caution is urged in making this diagnosis in the newborn. Various criteria for brain death have been employed according to the report of the American Academy of Pediatrics Special Task Force for the Determination of Brain Death in Children (Table 21.8). These include the clinical examination, focusing on both cortical and brainstem functions, done over repeat times, and various confirmatory tests. The later include EEG, evoked potentials, radionuclide brain scanning, and angiography, either conventional four-vessel angiography, or CAT scan angiography. The presence of apnea is crucial for the diagnosis of brain death, and specific apnea testing can be done (Riviello *et al.* 1988). This testing allows elevation of pCO_2, done under controlled circumstances, to prevent cardiovascular instability, while permitting the pCO_2 to raise high enough to actually stimulate respiratory centers. In the comatose patient, either because of therapeutic hyperventilation or because of decreased metabolism, the arterial pCO_2 may be lower than that needed to stimulate respiration, and if pCO_2 values are not determined, it may not be known if the actual pCO_2 value was high enough to stimulate respirations.

The EEG has been the most used confirmatory test. This should demonstrate electrocerebral inactivity (referred to as electrocerebral silence), but must be done under specific circumstance: no hypothermia, cardiovascular instability, hypotension, hypoxemia, metabolic disturbances, intoxication, or electrolyte disturbances. Temperature and intoxica-

tion are the most important of these. The EEG must also be done with specific minimal technical requirements as defined by the American Electroencephalographic Society in 1985 and 1994 (Table 21.9).

The results that are confirmatory for the other studies include: brain scan showing no intracranial blood flow; CAT scan angiography showing no filling of intracranial arteries; BAEP: no proximal brainstem waves (III, IV, or V) but a preserved wave I or II; VEP no P100, with a preserved retinal response, the electroretinalgram (ERG) (the ERG is not always seen normally and depends on the placement of the recording electrodes); SSEP: no cortical responses with preserved brachial plexus (median nerve stimulation) or lumbar plexus (posterior tibial nerve stimulation) potentials.

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CHAPTER 22

Headaches

Andrew D. Hershey, MD, PhD

OUTLINE

Headache diagnosis
Primary headache disorders
Secondary headache disorders
Epidemiology
Headache disability
Headache evaluation
Treatment of headache disorders

Headache is a frequent problem for many adults and children. Historically, it has been recognized as early as 6000 BC in ancient Sumerian writings. This ancient problem persists, frequently unrecognized in adults and children as a significant health problem. Estimates are as high as 40–70% of the population having some form of headache with 25% of 5-year-olds and up to 75% of 15-year-olds having complained of significant headaches (Bille 1962). This makes headache one of the most frequent health conditions for children. The diagnosis, however, is often overlooked because of the patient's inability to recognize headache as a true disease or the physician's inability to appreciate the impact on the child. The first potential step in identifying this illness is asking the patient about headaches and then making the proper diagnosis.

Headache diagnosis

Owing to the common nature of headache, patients often have a preconceived diagnosis of their problems. This, however, is often wrong. Many recent studies demonstrated that adults are more likely to diagnose their headaches as sinus headaches or tension-type headaches when, in fact, up to 90% of the "sinus headaches" are actually migraines.

The initial step is making the proper diagnosis. The International Headache Society has developed a classification scheme that has recently been revised – International Classification of Headache Disorders, 2nd edition (ICHD-II) (2004). This classification scheme serves to aid in diagnosis and divides headaches into either primary or secondary disorders (Tables 22.1 and 22.2). The primary headache disorders are those where the headache is the sole manifestation of the disease, while secondary headache disorders are those headaches directly due to other causes.

One significant change in the ICHD-II requires that the headache be directly *attributed* to the secondary cause, as opposed to only *associated* with a secondary cause; this change in wording emphasizes the fact that the secondary headaches must have a direct cause and effect both in time and anatomical structure. Secondary causes are usually obvious, rarely contributing to recurrent headaches. The primary headache disorders, however, make up a most significant cause of recurrent headache disorders.

Primary headache disorders

Primary headache disorders are divided into four major groups: migraine headaches, tension-type headaches, cluster headaches and other trigeminal autonomic cephalalgias, and other primary headache disorders. Migraine is the most common disabling primary headache disorder in children, accounting for 90% or more of recurrent episodic headaches (Hershey *et al*. 2001a). Although ICHD-I was often criticized for its lack of sensitivity and specificity for diagnosing children's and adolescent's headaches, the ICHD-II tries to answer some of these problems.

For children, the most common type of migraine is migraine without aura. The ICHD-II criteria require this to be a recurrent headache disorder with attacks lasting 4–72 hours untreated. The patient must have at least five attacks. The headaches must have at least two characteristics including unilateral location, pulsatile quality, moderate or severe pain intensity and aggravation with or causing avoidance of physical activity. The headaches must also have the associated symptoms of nausea and/or vomiting, or photophobia and phonophobia; all secondary causes must be ruled out.

Allowances to the criteria recognize that children may have shorter headaches, and a 1–72 hour time range is allowed with documentation if under 2 hours. It was also noted that pain is more commonly bilateral in location with a frontotemporal location being the most common. If occipital pain is present, further evaluation may be necessary. Photophobia and phonophobia may need to be inferred based upon the child's activities and parental observations.

TABLE 22.1

Common Headache Syndromes

Type	Discriminating features	Consistent features	Variable features	Consider referral when
Primary				
Migraine	Unilateral; paroxysmal	Throbbing, accompanied by nausea, vomiting, photophobia	Supraorbital/parietal temporal location	Focality consistent, stable neurologic deficit
Tension	None	Steady pain	Occipital/bifrontal/ bitemporal location	Location consistent, refactory to simple drugs
Secondary				
Tumor	Signs of increased intracranial pressure, progressive neurologic deficit	Constant but worse in the morning; severity progressive	Waxing and waning	Tumor suspected
Trauma	None	History of trauma	Site of trauma or 'contrecoup'	Symptoms progressive or hematoma suspected
Infection	Meningismus	Other evidence of infection	Steady character; photophobia, hyperacusis	Infection warrants
Vascular	Explosive onset	Throbbing character	Focality, meningismus, fundal hemorrhages, focal neurologic deficit	Vascular lesion suspected
Toxic	None	Systemic toxicity	Steady character, vomiting, neuropathy	Toxin not easily dealt with

TABLE 22.2

Headache Diagnosis

International Classification of Headache Disorders, 2nd edn

Primary headaches	Secondary headaches	Cranial neuralgias, central and primary facial pain and other headaches
Migraine	Headache attributed to:	Cranial neuralgias and central causes of facial pain
Migraine with aura	Head and/or neck trauma	
Migraine without aura	Cranial or cervical vascular disorder	Other headache, cranial neuralgia, central or primary facial pain
Tension-type headache	Nonvascular intracranial disorder	
Infrequent episodic	A substance or its withdrawal	
Episodic	Infection	
Chronic	Disorder of homoeostasis	
Cluster headache and other trigeminal autonomic cephalalgias	Disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures	
Other primary headache	Psychiatric disorder	

Migraine without aura makes up approximately 80–90% of childhood migraine The remaining 10–20% is migraine with aura or migraine with aura variants. The aura must have either a fully reversible visual alteration, sensory alteration, or dysphasic speech. The symptoms must be either honomonous visual symptoms or unilateral sensory symptoms. The single aura must increase over 5 minutes or consist of two successive auras in more than 5 minutes, but not last longer than 60 minutes. The most typical type of aura is photopsias (flashing of lights) and is frequently bilateral. Rare subtypes of migraines include cyclical vomiting syndrome and recurrent abdominal pain (abdominal migraines). Both of these may be a gastrointestinal manifestation of the periodic syndromes associated with childhood migraines. In ad-

dition, benign paroxysmal vertigo of childhood is thought to be a migraine variant.

One migraine subtype that has become increasingly recognized in adult tertiary headache centers as well as pediatric headache centers is chronic daily headache (CDH). In ICHD-II a diagnosis of chronic migraine has been added to incorporate this observation. Chronic migraine is defined as having 15 or more headache days per month for more than 3 months with symptoms consistent with the diagnosis of migraine without aura. In the largest pediatric study on CDH, the majority of headaches did have migrainous features and could be further subdivided into daily intermittent, daily continuous and frequent, but not daily headaches (Hershey *et al.* 2001a).

Tension-type headache makes up 10% of the recurrent headache disorders for children. It can be divided into either infrequent episodic tension-type headaches, frequent episodic tension-type headaches, or chronic tension-type headaches associated with or without pericranial muscle tenderness. Tension-type headaches can be thought of as the opposite of migraines. They are defined as lasting from 30 minutes to 7 days or must have at least two characteristic features: bilateral location, a pressing or tightening but not pulsatile quality, mild to moderate intensity, and not aggravated by routine physical activity. There should be no nausea or vomiting, and only photophobia or phonophobia is allowed. One distinguishing feature is the absence of vomiting in tension-type headaches. When children do vomit with their headaches, diagnosis of migraine is more likely.

Two separate models have been developed to explain the relationship between migraine and tension-type headaches. One is the continuum model where migraine with aura is viewed as the most extreme form and infrequent tension-type headache is the most mild with a continuum between these two headache types (Cady *et al.* 2002). This is in contrast to the spectrum model (Lipton *et al.* 2000). This model suggests that migraines and tension-type headaches are two distinct headache types. A patient with migraine can have a full spectrum of headaches ranging from very mild headaches (which may be interpreted as tension-type headache, but are actually mild migraines) to more severe migraines. The patient with pure tension-type headache only has tension-type headaches and never has migrainous features.

In children, the other primary headache disorders include cluster-type headaches and paroxysmal hemicrania although these are rarely seen. There are also rare other primary headache disorders that are outside the scope of this chapter.

Secondary headache disorders

The concern of a secondary headache disorder is often what brings the headaches to attention. Secondary headaches should be thought of as a headache being caused by another etiology. Eight subtypes of secondary headache disorders are defined by the ICHD-II (Table 22.1):

1. Traumatic headache. This headache type is headache due to head and neck trauma, including both acute post-traumatic, chronic post-traumatic and whiplash headaches. One caveat in traumatic headache disorders is that the head trauma may induce a migraine-like headache. Retrospective history is then essential as it may reveal a history of recurrent headaches prior to the head trauma. Acute post-traumatic headache occurs immediately after head trauma (within 7 days), but resolves within 3 months. Chronic post-traumatic headache also starts within 7 days, but persists greater than 3 months. Head trauma, however, is very common in children. Our experience at Cincinnati Children's Headache Center has demonstrated that of 1000 patients 120 reporting a head trauma, and only 20 of these headaches could be directly attributed to the head trauma itself.
2. Vascular headache. Headache attributed to cranial or cervical vascular disorders is seen less commonly in children. These include headaches related to stroke, intracranial hemorrhage that is nontraumatic, vascular malformations and arthritis. This includes cerebrovascular accident associated with the headache and (the "worst headache of my life") subarachnoid hemorrhage. These headaches require acute assessment of the underlying intracranial hemorrhage. Aneurysms and intracranial bleeding are much less frequent in children than adults, but must be considered due to the severe consequences.
3. Nonvascular, intracranial disorder headaches. These headaches include idiopathic intracranial hypertension, intracranial hypertension due to other causes, low cerebral blood pressure, noninfectious inflammatory diseases, and intracranial neoplasm. A rapid increase in headache symptoms may be due to an increased intracranial pressure, either due to the increase in cerebrospinal fluid or due to a mass effect. Idiopathic intracranial hypertension frequently occurs in obese adolescents, girls more so than boys, and most often is associated with papilledema, although case reports have noted increased intracranial hypertension without papilledema. When papilledema is detected, a cause of the intracranial hypertension must be evaluated. This evaluation includes a detailed medical history including medications (e.g. hyper vitamin A has been noted to be associated with intracranial hypertension), clotting disorder symptoms for venous thrombosis, and changes consistent with a mass effect. Imaging studies should be obtained prior to documenting the increased intracranial pressure with a lumbar puncture. The American Academy of Neurology and Child Neurology Society practice parameters state that neoplasms were most often associated with an abnormal neurologic examination (Lewis *et al.* 2002a).
4. Substance abuse or withdrawal headaches. Some medications and food components have been suggested as triggers to headaches, however this is anecdotally based with

little evidence to support a triggering mechanism for most of these compounds. Medication overuse headaches, formally known as analgesic rebound headaches, however, are being seen with increasing frequency. Studies indicate that anywhere from 60 to 100% of chronic daily headaches are due to overusing analgesics, including over-the-counter analgesics and prescription analgesics (Vasconcellos *et al.* 1998; Katsarava *et al.* 2001; Tepper & Dodick 2002). A detailed history of the analgesic use including nonprescribed analgesics is essential for recognizing this disorder, as proper treatment involves the withdrawal of all analgesics.

5 Infection-related headache. These headaches are usually straightforward and occur in direct association with infectious symptoms. A detailed analysis in the emergency department is essential to evaluate and treat symptoms of meningoencephalitis.

6 Headaches due to disorders of homeostasis. This headache type rarely occurs in children and a further detailed description of this can be reviewed in the ICHD-II criteria.

7 Headaches or facial pain attributed to disorders of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures. This type of headache is one of the most frequently over-diagnosed. This type includes headaches attributed to refractory errors and is diagnosed by resolution of the head and eye pain within 7 days of visual correction. Many times, however, patients will see an ophthalmologist for their episodic headache disorders, with a temporary response, but then the headache recurs due to a missed diagnosis of their migraines. Even more common is the misdiagnosis of "sinus headaches." Several studies have demonstrated that up to 90% of adults who believe they have sinus headaches or have been diagnosed with sinus headaches actually have migraines (Cady & Schreiber 2002). To diagnose sinus headaches by the ICHD-II criteria, the headaches must be clearly associated with proven disease in the sinuses, either by nasal endoscopy, CT, MRI or laboratory evidence. Headache and facial pain should develop simultaneously and resolve simultaneously with effective treatment.

8 Headache due to psychiatric disorders. These were included in ICHD-II to establish criteria for further scientific research into headache etiologies and psychiatric association.

The ICHD-II criteria also include two categories for the diagnosis of cranial neuralgias and facial pain and their relationship to headache.

Epidemiology

Epidemiology studies have demonstrated that the most common recurrent headache brought to medical attention is migraine, especially in children. Up to 10.6% of children ages 5–15 years old complain of recurrent headaches that are migraines (Abu-Arafeh & Russell 1994). In the 15–19 age group the estimates are as high as 28% in girls and 15% in boys (Split & Neuman 1999). Of special note in the older age group was the observation that a significant number of these children will suffer from status migrainosus or a migraine that lasts longer than 72 hours. This frequency of headache makes headache and migraine one of the most common disorders of childhood.

Headache disability

Not only is migraine very common, but it has also been noted to cause significant disability in children and adults. In adults, several studies have demonstrated that migraines can cause as much impact on the quality of life as other chronic conditions including arthritis, diabetes and hypertension (Osterhaus *et al.* 1994). Similarly, in children the quality of life may be impacted by migraines at a level similar to juvenile rheumatoid arthritis and diabetes (Powers *et al.* 2003). Successful treatment can improve this impact on quality of life.

An additional area in which migraine impacts a patient is disease-specific disability. Disability is defined as loss of function due to a disease. MIDAS (Migraine Disability Assessment) was developed for measuring disability in adults (Stewart *et al.* 2001). PedMIDAS was subsequently developed for assessing migraine disability in children (Hershey *et al.* 2001b). Not only were children shown to have significant disability due to migraine and recurrent headache, but also that successful treatment would resolve this disability. Using MIDAS for adults or PedMIDAS for children is a simple tool that can be used in a clinical office to track the headache treatment progress with eventual outcome measurement.

Headache evaluation

Headache evaluation requires a detailed medical and headache history with a thorough general pediatric and neurologic exam. Additionally a comprehensive headache exam may be included. The history and examination should be detailed enough to rule out secondary causes for headaches. If there is suspicion of a secondary cause, further evaluation is indicated. Recent practice parameters have been developed by the American Academy of Neurology in association with the Child Neurology Society and the American Academy of Pediatrics for the evaluation, assessment and treatment of childhood headaches (Lewis *et al.* 2002a). Many of these mirror the National Headache Consortium Guideline that was developed for the management of adult headaches (Silberstein & Rosenberg 2000).

The first step in evaluating a child with headache is obtaining a detailed history including both a general medical history as well as a headache-specific history. The purpose of the general medical history, which includes the review of

systems and past medical history, is to identify any potential causes of the headaches leading to a secondary headache disorder. A recent history of trauma, infection, or other acute health changes needs to be clearly identified.

The headache history entails several components, as well as the contribution of the family history and psychosocial interactions. A timeline of headache development can identify many of the features of the headache. First is the often difficult identification of a possible prodrome, the clear recognition that a headache is going to occur. It is distinct from the aura and has been described as a heightened sensitivity to surroundings with the development of food cravings. This development of food cravings is thought to be the basis of the incorrect identification of dietary triggers. Possible triggering mechanisms, however, should be investigated. The most common triggering mechanisms that have been identified in adolescents are skipping meals or inadequate sleep. In the adolescent girls, the identification of a menstrual association may also be important for long-term management.

The presence or absence of aura is also a key component of the headache assessment. Aura is a fully reversible neurologic dysfunction. The most common form is visual, the second most common is sensory, and the third is dysphagia. Historically, the presence of an aura suggested the need for further evaluation in a child including possible neuroimaging and an EEG. However, further review has questioned the usefulness of either of these techniques if the pattern is consistent to cause headaches, and the neurologic exam is normal between headache attacks (Lewis *et al.* 2002a).

Characterization of the headache includes identifying the location of the onset, quality and quantity of the pain, duration of the headache, effects on activity and identification of associated symptoms. A migraine is more typically unilateral in adults, but bifrontal in a child. A face pain scale or a 10-point pain scale is used for quantification of the pain. Children frequently have difficulty describing the quality of the pain. The examiner must be careful not to lead the child. Having the child physically demonstrate what the pain feels like or drawing pictures is often useful in assisting with this assessment. Duration may be difficult to assess due to the child's sleeping with a headache. In this regard, the time of sleep is included as part of the headache duration. The effects on physical activity may also be ascertained, both in terms of whether physical activity is altered due to the headache, as well as whether physical activity exacerbates the headache symptoms.

Headache associated symptoms include the nausea, vomiting, and light and sound sensitivity typified of migraines. Additional associated symptoms can include sensitivity to smell, lightheadedness, vertiginous symptoms, weakness (both perceived and actual), confusion, and difficulty thinking.

Disability due to the headache should also be included. For adults, this can be assessed with MIDAS (migraine disability assessment), while for the younger patient a pediatric version has been developed (PedMIDAS).

Additional headache assessment that may be useful include pattern recognition of the time of day, time of week, time of month, or association with particular events. In adolescent and pubertal girls a monthly pattern may be ascertained.

The family history assessment is especially important in migraine. Other family members are often unaware of their diagnosis; an additional evaluation of one or both parents, as well as siblings may reveal multiple family members with migraine or other primary headache disorders.

Social history assessment may reveal particular psychosocial stressors. An assessment of school function may indicate a fall off in school function due to either school absences or the presence of frequent headaches while in school.

The next step in assessing a child with headaches is a thorough general and neurologic examination. A selective comprehensive headache exam may identify additional particular headache features. For adult headache sufferers, the most sensitive test is the neurologic examination. A thorough and detailed neurologic examination is essential for children as well. This includes a funduscopic evaluation to look for papilledema and lack of venous pulsations which are suggestive of increased intracranial pressure. An asymmetric or abnormal neurologic exam warrants further evaluation.

The comprehensive headache exam may also be considered when evaluating the headache patient. This has been described elsewhere, but in general is a detailed assessment of head and neck structures that may be involved in headache etiology (Linder & Winner 2001). This examination includes an assessment of neck suppleness including pericranial and temporal muscle tightness, lymphadenopathy, temporomandibular joint disease, identification of point tenderness, examination of the ears and the orbits, and a test of neck sublimation including specific testing of the C1-C2 joint as well as the C2-C3 joint. This can be assessed by positioning the head in a forward positioning and flexing to different angle degrees. One test which has been cosidered useful in the assessment of headache patients for sinus disease is the Muller sign. In this test, the patient is asked to pinch their nose, blow against this closed nose to increase the sinus pressure for a count of five seconds and then cough. This creates a positive pressure in the sinuses, followed by a rapid decompression. When sinus disease is present, this causes pain over the involved sinus, whereas if sinus disease is not present no pain is elicited. Caution must be used in doing this procedure when there is an ongoing headache, as it may be misinterpreted as sinus disease if the headache itself worsens. In the setting of increased intracranial pressure,

TABLE 22.3

Headache Treatment

Multidisciplinary treatment

Acute treatment	Prophylactic treatment	Biobehavioral treatment
NSAIDS	Antidepressants	Healthy habits
Aspirin	Amitriptyline	Adequate hydration
Ibuprofen	Imipramine	Regular sleep
Naproxen sodium	Antiepileptic	Regular nutrition
Triptans	Divalproate	Regular exercise
Almotriptan	Gabapentin	Biofeedback-assisted relaxation therapy
Eletriptan	Topiramate	
Frovatriptan	Antiserotonergic	
Naratriptan	Cyproheptadine	
Rizatriptan	Methylsergide	
Sumatriptan	Beta-blockers	
Zolmitriptan	Atenolol	
Dihydroergotamine	Propranolol	
Dopamine antagonist	Timolol	
Prochlorperazine		
Metoclopromide		
Combined treatments (such as aspirin + caffeine)		

intracranial pressure is also increased by this same maneuver. A variation of this maneuver involves light pressure on the jugular veins during this same procedure. If this causes increased headache over the cranium, the possibility of increased intracranial pressure must be considered.

When a secondary cause of headaches has been clearly identified, specific laboratory and/or neuroimaging testing is indicated. For the diagnosis of secondary headache disorders, the headache must be directly attributed to this secondary cause. Oftentimes this attribution cannot be made until the secondary cause has been treated and the headache symptoms have been resolved. For a primary headache disorder, no specific testing has been identified as useful. Recently published practice parameters for childhood headaches show that for primary headache disorders the most sensitive assessment is the neurologic exam. Neuroimaging abnormalities were found in 16% of children with primary headache disorders; the most medically and surgically significant ones all were associated with abnormalities of the neurologic exam. An EEG assessment was done in the past, but only proved useful for the auras where a suspicion of a seizure with secondary headache was clearly identified. Blood and chemical testing has not clearly been identified as useful unless indicated to rule out a secondary cause.

Treatment of headache disorders

Treatment of secondary headache involves the treatment of the underlying cause. In many instances, however, the headache is a primary headache and a secondary cause has been erroneously implicated. When the headache persists after effective treatment of the presumed secondary cause, then a primary headache must be reconsidered.

For primary headache disorders in children, the most frequently needed treatment is for migraine. Treatment can be divided into three components – acute treatment, prophylactic treatment, and biobehavioral treatment (Table 22.3).

Acute treatment

The first component is acute therapy. Acute therapy is the treatment to utilize at the onset of each episodic headache. Key in this treatment is a reliance on the child to recognize the onset of the headache and to notify parents, teachers or caregivers. It is important to use effective doses of a migraine proven medication while avoiding medication overuse. It is also essential to educate the patient and parents about this treatment strategy, as well as to define an effective goal. Furthermore, the National Headache Consortium's recommended goal is for rapid treatment with quick return to functioning without significant sedation or loss of functioning due to the treatment. Although no specific medications have been approved for the use of childhood headache and migraine, several studies have shown the effectiveness of these medications. These can be roughly divided into two groups for outpatient therapy – nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans (5-HT-1_{BD} serotonin agonist).

PEARLS & PERILS

- Headaches are very common in children.
- Migraines are the most prevalent cause of recurrent, disabling headaches.
- Use of standardized criteria (ICDHD-II) is essential for proper diagnosis.
- Headaches are:
  - Primary if no other cause is identified;
  - Secondary if directly related to another cause.
- An abnormal neurologic examination is highly associated with significant abnormalities on neuroimaging.
- Treatment involves several equally important approaches:
  1. Acute therapy (at headache onset)
    - Avoid medication overuse
    - Rescue therapy is considered

  2. Preventative therapy
    - Pain frequency and disability is lowered

  3. Biobehavioral therapy
    - Develop lifelong healthy habits.

NSAIDs, in particular ibuprofen, have been shown in several studies to be effective in childhood headache (Hämäläinen *et al.* 1997; Lewis *et al.* 2002b) and have been proven effective for adult migraine. Early administration with the child catching the headache at the onset, adequate dosing (7.5–10 mg/kg/dose), and limiting the use to not more than 2–3 times per week to avoid medication overuse headaches are important treatment considerations. For children where this is ineffective, other NSAIDs including naproxen sodium and aspirin may be considered, although the use of aspirin in children under age 15 may have the potential risk of the development of Reye's syndrome.

For patients where NSAIDs are ineffective or for more severe headaches, triptans may be employed. Two strategies have been described for using triptans for migraine. In the stratified care model, patients use NSAIDs for mild to moderate headaches, and reserve triptan use for their severe headaches. For most children, this determination is very difficult. In the rescue therapy model, the patient uses an NSAID as their primary headache treatment. When they recognize an unresponsive headache or a conversion to a severe headache a triptan is used for rescue therapy.

A detailed description of these individual triptans and their uses is beyond the scope of this chapter. Triptans are 5-HT-1_{BD} receptor agonists with both a vascular component, and a central effect that has been implicated in the development of central sensitization and allodynia (Burstein & Cutrer 2000). The development of allodynia stresses the importance of early recognition and treatment. Although several of these agents have been tested in children and adolescents, none are currently approved for their use. Several studies have shown their effectiveness, although due to design problems and a high placebo effect, statistical significance has not been reached for the primary end-point of these studies.

When outpatient therapy is not effective, emergency department or inpatient therapy may be necessary. Dopamine antagonists including prochlorperazine and metoclopramide have been historically shown to be effective, although essentially only in IV formulations. Prochlorperazine's usefulness in childhood headaches has been shown to yield a good response in an open labeled study (Kabbouche *et al.* 2001). An adequate dose for prochlorperazine appears to be 0.15 mg/kg IV dose, while for metoclopramide a higher dose of 0.25 mg/kg may be required. The goal of emergency room treatment should be complete cessation of the headache attack. This may be assisted with IV hydration due to the vascular dilatory effect of a migraine attack. If headache freedom is not completely reached, additional IV therapy in an inpatient setting may be required. Additional emergency department treatment that may be considered (although of limited tested value in children and adolescents), includes IV valproic acid, which has been shown to be effective in adult migraine sufferers.

In the inpatient setting, one of the most useful medications is dihydroergotamine. It may be associated with significant nausea and vomiting that can be minimized with premedication with antiemetics (Linder 1994). Additional therapies that have been utilized for inpatient therapy include steroid treatment, IV magnesium infusions and recurrent divalproate infusions.

Prophylactic treatment

For patients with frequent headaches and disability, preventative treatment is indicated. No preventative therapies have been specifically recommended for childhood headache disorders. For adults, there have been several FDA approved options including divalproate, methysergide, propranolol and timolol.

Prophylactic agents can be divided into antiepileptic medications, antidepressant medications (specifically the tricyclic antidepressants), beta-blockers, and antiserotonergic agents (cyproheptadine or methylsergide). Specific uses of these agents can be reviewed elsewhere. The general guidelines are to educate the patients about the goals of therapy, (typically to reduce headache frequency to one to two times per month or less and disability to be returned to normal state). To achieve these goals, adequate doses must be utilized, increasing the dose to a level slowly to minimize side effects, as well as to increase the overall effectiveness. Once an adequate dose has been achieved, the medication must be sustained for a long enough period to observe a treatment effect, typically at least 2–3 months. If the goal of treatment has not been obtained at this point a second prophylactic agent may need to be considered. Once sustained response has been achieved for 4–6 months, withdrawal of

KEY CLINICAL QUESTIONS

- Is the headache primary or secondary?
- Is the neurologic exam normal?
- Does the patient understand and agree with the three-level treatment approach?

CONSIDER CONSULTATION WHEN…

- Abnormalities in the history or neurologic exam are evident.
- Acute therapy is not effective (including both primary and rescue strategies).
- An adequate dose and time of prophylactic therapy has been unsuccessful.

the medicine should be attempted. If this is unsuccessful, the preventative treatment can be restarted. Once a 4–6 month sustained period of headache response has been obtained, a weaning should again be attempted.

Choosing the preventative therapy may be guided by identification of comorbid conditions. For comorbid depression, a tricyclic antidepressant may be useful; if a patient has seizures, an antiepileptic may treat both conditions. Two of the antiepileptics used for headache prevention have weight effects, with the divalproate having a chance of increased weight (and can assist with people who are especially thin), while topiramate may have a weight loss effect (and can assist with obesity). Side effects of medications must be carefully considered. In particular, the beta-blockers are associated with increased depressive symptoms and asthma attacks thus limiting their usefulness.

Biobehavioral treatment

The third component of treatment is biobehavioral treatment. Biobehavioral treatment is essentially managing the day-to-day habits of the child while assisting with reducing triggering events. This can be a combination of lifestyle adjustments, as well as biofeedback-assisted relaxation therapy and psychological intervention. Multidisciplinary headache centers often combine these services to assist in the global management of the patient. Particular lifestyle adjustments that are useful include adequate fluid hydration with limited caffeine intake, adequate exercise on a regular basis, eating a regular healthy diet, and a regular adequate sleep schedule. Adequate hydration corresponds to the vascular dilation and plasma extravasation hypothesis of migraine pathogenesis. Exercise may assist with improving vascular tone both in the cerebral vasculature, and diffusely throughout the body, minimizing the vascular stretch as a triggering phenomenon for migraines. Skipping meals has been shown to be a common trigger for adolescent migraines. Several nutrients have been shown to assist with migraine prevention, and a balanced diet rich in green vegetables should help provide this balanced nutritional support. Sleep deprivation and altered sleep schedules have frequently been demonstrated to be a migraine trigger. This has been noted as a jet lag phenomenon in people with migraine, as well as a frequent trigger in childhood headaches when the sleep schedule is altered from the weekend to the week days.

Biofeedback-assisted relaxation therapy may also be beneficial (Daly *et al.* 1983). Single-session treatment has been shown to be effective and maintained over time in children (Powers & Hershey 2002). The overall use of biofeedback-assisted relaxation therapy is discussed in greater detail elsewhere (Powers & Hershey 2002).

In summary, the management of childhood headache first involves the recognition of the primary versus secondary nature of the headache. For recurrent episodic headaches, primary headaches are most likely to be migraine. A thorough history, physical, neurologic and comprehensive headache examination helps identify any possible secondary headache disorders that require further investigation. Once the diagnosis of primary headache disorders and migraine has been established, then a treatment program needs to be initiated that involves a plan for treating acute headache attacks, preventing future headache attacks, and maintaining a balanced lifestyle. Additional investigative work is oftentimes not needed, but should be directed by the history and physical, and in particular the neurologic examination. Referral to headache specialty care may be necessary when initial treatments fail, or when significant disability or comorbid conditions exist.

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CHAPTER 23

Febrile Seizures

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OUTLINE

Clinical presentation
Epidemiology
Neurologic outcome
Management
Conclusion

Since the time of Hippocrates, infants and young children have been known to be vulnerable to convulsions at the onset of acute febrile illness. Febrile seizures are the most common convulsive disorder of early childhood, occurring in approximately 2–5% of young children in the United States.

A febrile seizure was defined at a National Institutes of Health consensus conference (Consensus Statement 1981) as

> … an event in infancy or childhood, usually occurring between three months and five years of age, associated with fever but without evidence of intracranial infection or defined cause. Seizures with fever in children who have suffered a previous nonfebrile seizure are excluded. Febrile seizures are to be distinguished from epilepsy, which is characterized by recurrent nonfebrile seizures.

Young children may experience seizures during a febrile illness caused by such disorders as meningitis, dehydration, or toxic encephalopathy. These are not considered to be febrile seizures and do not have the same prognosis because the underlying illness may cause central nervous system damage in such cases.

Febrile seizures are often categorized into two subgroups: simple febrile seizures, which are brief and generalized, and complex febrile seizures, which are prolonged, focal, or multiple (more than one seizure in 24 hours) or followed by neurologic deficit. A family history of febrile or afebrile seizures or pre-existing neurologic abnormality may accompany seizures in either of these categories (Table 23.1).

Clinical presentation

Febrile seizures tend to occur early in the course of the febrile illness. Although rapid rise of the fever has been thought to be important, it is actually the height of the temperature that is associated with the occurrence of a febrile seizure (Berg 1993). In some cases the seizure is the first sign of the illness. The age of the child is usually between 3 months and 5 years (Table 23.2). The most common seizure type is tonic–clonic. A typical febrile seizure is manifested by an initial cry, followed by loss of consciousness and muscular rigidity (tonic phase). During the tonic phase, usually lasting less than 30 seconds, there may be apnea and incontinence. This is followed by a clonic phase consisting of repetitive, rhythmic jerking movements of the extremities or face. When movements have ceased a period of postictal sleep or lethargy, which is usually brief, may follow.

Seizure types other than tonic–clonic may also occur. The seizure may consist simply of staring and stiffening or

TABLE 23.1

Febrile Seizures: Definitions

	Simple	Complex
Duration	<15 minutes	May be ≥15 minutes
Type	Generalized	May be generalized or focal
Number during one illness	One	May be multiple
Followed by transient neurologic deficit	Never	Possible
Family history of febrile seizures	Possible	Possible
Family history of nonfebrile seizures	Possible	Possible
Pre-existing neurologic abnormality	Possible	Possible

FEATURES

Table 23.2 Febrile Seizures

Discriminating feature

1. Seizures in the presence of fever

Consistent features

1. Absence of previous afebrile seizure
2. Absence of central nervous system infection

Variable features

1. Usually age 3 months to 5 years
2. Focal or generalized
3. May be multiple within one illness
4. Usually brief, may be prolonged (≥15 minutes)
5. Family history of febrile or afebrile seizures

TABLE 23.3

Diagnoses to be Considered in the Febrile, Convulsing Child

Bacterial or viral infection
Meningitis (bacterial, viral, granulomatous)
Encephalitis
Hypernatremic dehydration
Subdural or epidural empyema
Carotid arteritis complicating pharyngitis
Septic embolization
Reye's syndrome
Lead intoxication
Hemolytic uremic syndrome
Cortical thrombophlebitis

limpness, or the eyes may roll back. There may be jerking movements without prior stiffening. The movements may be focal, starting in one limb or one side of the body, and without generalization. The duration of the seizure is usually less than 15 minutes; in one large study less than 8% of febrile seizures were longer than 15 minutes (Nelson & Ellenberg 1976), and in another study 13% were >10 minutes and 5% were >30 minutes (Berg & Shinnar 1996).

Most of the febrile illnesses associated with febrile seizures are due to infections, such otitis media, tonsillitis, or upper respiratory infections. One study isolated bacterial pathogens in 4% of the cases and implicated common viral infections in 86% (Lewis *et al.* 1979). Human herpesvirus 6 infection can be implicated in many cases (Hall 1994).

In several infectious illnesses of early childhood, seizures may occur with fever, as during the prodrome of roseola infantum or shigella. With roseola infantum, the fever rises abruptly and the child may seize but looks well, and the diagnosis is not made until the appearance of a rash a few days later. Shigella gastroenteritis commonly presents with a seizure and a very high temperature, followed by passage of a green liquid stool sometimes as the lumbar puncture is being done to rule out meningitis. The pathogenesis of seizures in shigella may be related in part to a neurotoxin and not only to the occurrence of fever.

There are serious and potentially fatal conditions, not febrile seizures by definition, that can present as seizures with fever but that require prompt and specific treatment (Table 23.3). The possibility of bacterial meningitis should always be considered, particularly if the child is too young to exhibit typical symptoms such as meningismus. Viral meningitis or encephalitis may also present with seizures and fever, as may hypernatremic dehydration owing to gastrointestinal infection, acute toxic encephalopathy, or cerebrovascular accidents of infancy.

Children with pre-existing epilepsy or brain damage may have their seizure thresholds lowered by fever. If a child has previously had one or more afebrile seizures, a seizure occurring with fever should be treated as an epileptic seizure and not as a febrile convulsion.

Epidemiology

In the United States, South America, and Western Europe, between 2% and 5% of all children experience convulsions with febrile illness before age 5 years (Hauser 1981). Febrile seizures are reported to be about twice as common in certain Asian countries as in Europe and America. A study by Tsuboi (1984) found prevalence rates among 3-year-old children from two locations in Japan to be 8.3% and 9.9%. The reported rate of febrile seizures in Asian countries may be higher because of closer observation, with children sleeping in parents' rooms, and high housing density. However, there may be true racial or geographic differences.

The first febrile seizure was complex in approximately 20–35% of all cases reported in three large studies (Nelson & Ellenberg 1976; Verity *et al.* 1985a,b; Berg & Shinnar 1996), of cases; it either lasted longer than 15 minutes, was multiple (two seizures or more within 24 hours), or was focal. Two-thirds of the children had only a single febrile seizure and about 10% had three or more seizures (Nelson & Ellenberg 1976; Verity *et al.* 1985; Annegers *et al.* 1990; Offringa *et al.* 1992; Berg *et al.* 1997), and the seizure lasted ≥30 minutes in 5% (Berg & Shinnar 1996–2).

In about half of the children with febrile convulsions, the onset is in the second year of life. About 90% begin by 3 years. The average age of onset is 18–22 months. Febrile seizures are more common in males.

The incidence of febrile convulsions is slightly but not statistically significantly higher in black people than in white people. In the National Birth Cohort Study, the prevalence of a history of febrile convulsions was not related to social class. There was also no increased incidence in children with a history of allergic conditions.

Genetics

Febrile convulsions are more frequently found among family members of children with febrile convulsions than in the general population. In Japan (Tsuboi 1984) as many as 17% of parents and 22% of siblings are affected, while reports from Western countries have cited lower frequencies. In the NCPP, a family history of febrile seizures was identified in 7.3% of parents or prior-born siblings on prenatal questionnaires (Nelson & Ellenberg 1978), and in the study by Verity and associates (1985a,b) a history of febrile convulsions was present in 16% of family members (including all relatives) of children with febrile convulsions. In Rochester, Minnesota, all relatives of febrile convulsions probands had a two-to-threefold increase in risk for convulsions with fever (Hauser *et al.* 1985), and a more recent case-control study found that a history of febrile seizures in a first-degree relative was a significant risk factor for a first febrile seizure (Berg *et al.* 1995).

There may be an increase in family history of afebrile seizures for children with febrile seizures, but the evidence is not clear. Some studies have ascertained that afebrile seizure disorders are more frequent in siblings of children with febrile seizures (Metrakos & Metrakos 1970; van den Berg 1974). A history of seizures without fever in a parent or sibling was present in 6% of children with febrile seizures and in 2% of controls (Berg *et al.* 1995), and it was present in 9.7% of all relatives in the British study (Verity *et al.* 1985a,b). Hauser and colleagues (1985) found that the relative risk for epilepsy was raised in siblings of children with febrile seizures (2.5) but was not increased in other relatives.

Younger siblings of the child with febrile convulsions have a 10–20% risk of having febrile convulsions. If both parents and a previous child have had febrile convulsions, the risk for another sibling may be increased to as high as one in three (Baraitser 1983).

Although it is well accepted that familial factors, probably genetic, cause a predisposition to febrile seizures, the pattern of heredity is not known. A polygenetic mode of inheritance is likely in children who experience a single febrile convulsion. Either maternal or paternal genes are associated with increased risk for febrile convulsions. In a child with more than three febrile convulsions, a single major locus model with a nearly dominant seizure susceptibility has been determined (Verstergaard 2002). Genetic influences may be mediated through involvement of sodium channels, GABA receptors, and additional proteins (Hirose 2003).

Recurrence

About one-third of children who experience a single febrile seizure will experience a second. Of those who have a second, half will have two or more subsequent recurrences. About 9% of children with febrile seizures will have three or more. Approximately three-fourths of recurrences take place within 1 year, and 90% within 2 years.

The earlier the age at which the first febrile convulsion occurs, the greater the chance that there will be additional convulsions (Table 23.4). A family history of febrile or afebrile convulsions, or both, also has been associated with an increased recurrence rate (Berg *et al.* 1995; El-Radhi 1998). Another study reported that the number of febrile episodes and a positive family history for febrile seizures were significant as risk factors for recurrence (Rantala & Uhari 1994).

In neither the NCPP nor the British Birth Cohort Study were complex convulsions (that is, focal, lasting longer than 15 minutes, followed by neurologic deficit, or multiple within 1 day) more often followed by recurrences. If the initial seizure was complex, the risk of a recurrence being complex was not increased. If the initial febrile seizure was brief, prolonged recurrence was very unlikely (only 1.4% in the NCPP). If the initial seizure was prolonged a recurrence was no more likely to happen, but if it did, it was more likely to be prolonged than if the first seizure was brief (Berg *et al.* 1995; Offringa 1997).

A higher number of febrile seizure recurrences does not appear to influence the prognosis adversely with regard to later epilepsy or intellectual function. In two large studies, risk factors were more important than number of recurrences in predicting later epilepsy.

Epilepsy

Most population-based studies estimate that between 2% and 10% of children with febrile seizures go on to develop epilepsy (Ellenberg & Nelson 1980; Annegers 1987; Verity *et al.* 1991; Berg 1996). Other reports from selected populations of children with febrile seizures tend to cite a much higher rate of development of epilepsy than those from large population-based studies. For example, the report from the British National Child Development Study emphasizes that the differences seem to depend to a large extent on sample selection: of 202 febrile seizure patients seen by general practitioners, 0.5% later had afebrile seizures. In contrast, 12% of children admitted to hospitals or referred to specialists had subsequent afebrile seizures (Ross *et al.* 1980).

TABLE 23.4 Likelihood of Recurrence by Age at First Febrile Seizure

Age at first febrile seizure	Proportion with at least one recurrence
≤1 year	1/2
≤2 years	1/3
≤3 years	1/4
≤4 years	1/5

Nelson and Ellenberg (1976) found the following factors to be associated with increased risk for epilepsy: suspect or abnormal neurologic development before the first febrile seizures, a history of afebrile seizures in a parent or sibling, and a complex first febrile seizure, that is, one that is focal, lasts over 15 minutes, or is multiple within 1 day. About 60% of the children in the NCPP had none of the above-mentioned risk factors, and of these about 2% developed one or more afebrile seizures by age 7 years, a rate no different from that for children with no febrile seizures. About 34% of the children with febrile seizures had one risk factor; of these, 3% later experienced at least one afebrile seizure. An increase in the rate of later epilepsy appeared in those children with two or more risk factors: Thirteen per cent of these children later had one or more afebrile seizures (Fig. 23.1).

A neurologic abnormality occurring in the child before any seizure tends to be an important factor increasing the risk of epilepsy (Addy 1986). In the NCPP prolonged convulsions were followed by epilepsy in 1.4% of children with no prior neurologic abnormality and in 9% of children who were neurologicially abnormal (Nelson & Ellenberg 1978). Similarly the risk of epilepsy after a first complex convulsion was 10% in a neurologically abnormal child but was not significantly increased in normal children (1.7% vs. 1.1%) (Nelson & Ellenberg 1978). Of the features of complex febrile convulsions, the most important in prediction of later epilepsy is partial or focal seizure type.

A variety of afebrile seizures may occur following febrile seizures (Nelson & Ellenberg 1978; Berg *et al.* 1995). Sofijanov and associates (1983) found that all types of epilepsy were seen in patients with febrile convulsions. Camfield and colleagues (1994) reported that febrile seizures preceded 15% of childhood-onset epilepsy, more often among those with generalized tonic–clonic seizures. Febrile seizures may be the first sign of an epileptic syndrome such as juvenile myoclonic epilepsy (Dravet 1992).

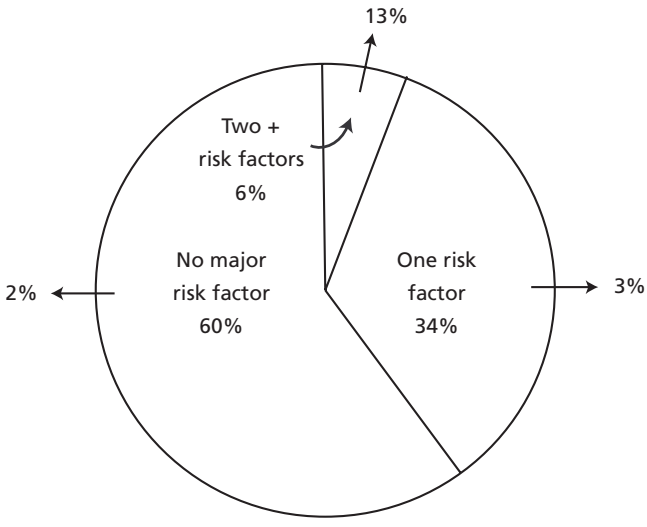

Fig. 23.1 Afebrile seizures by age 7 years in children with febrile seizures, based on results from the NCPP on the outcomes of 1706 children. The risk factors evaluated were history of afebrile seizures in the immediate family, suspect or abnormal status in the child before first febrile seizure, and complex first febrile seizure. (Reproduced from Nelson KB and Ellenberg JH, editors: *Febrile Seizures.* New York, 1981, Raven Press, p. 270, with permission.)

Partial complex seizures

Some authors have suggested that febrile seizures, particularly if they are not prolonged, may predispose the individual to later complex partial seizures (temporal lobe or psychomotor epilepsy) (Falconer 1971; Rassmussen 1979). However, the early reports were from retrospective, uncontrolled series that did not exclude patients who may have had acute central nervous system (CNS) infections.

The bulk of the recent evidence supporting this hypothesis comes from experimental studies in rats. Evidence from clinical studies is more controversial. In several large studies, when epilepsy develops following febrile seizures, the proportion of complex partial seizures is no higher than that in the general population of epileptics. Others report an increased frequency of complex partial seizures in children with prolonged or focal febrile seizures. However, only a very small percentage of children with febrile seizures develop complex partial seizures, and a causal relationship has not been proven (Camfield *et al.* 1994). Schmidt and colleagues (1985) studied 155 patients with complex partial seizures and concluded that there may be an association between febrile convulsions with complicating features and complex partial seizures. Epidemiologic studies from the Rochester, Minnesota, population (Hauser 1981) have also shown that children with febrile seizures with focal features, repeated episodes, and long duration were at somewhat increased risk for later partial seizures. But population-based studies and prospective studies do not confirm an association of mesial temporal lobe epilepsy and prolonged or atypical febrile seizures in childhood (Annegers 1987; Verity 1985; Nelson 1978; Berg 1996; Verity 1993).

According to Leviton and Cowan (1981) three theories may account for the association. The febrile seizures could cause the increase in risk for complex partial seizures; the febrile seizure could be the first manifestation of a seizure disorder; or separate but associated risk factors could exist for both orders.

Neurologic outcome

Children who have febrile seizures generally have no difference from controls in cognitive abilities and school performance. The British National Birth Cohort Study confirmed the lack of any significant impact of febrile seizures on later intellectual ability. Children in this study with a history of

febrile convulsions did not differ from their peers in behavior, height, head circumference, or performance on simple intellectual tests. Children with simple as compared with complex febrile convulsions also did not differ in outcome. Children with febrile seizures did have an increased rate of hearing and speech problems (which may have been secondary to a higher rate of ear infections) and reported sleep disturbances more frequently (Verity *et al.* 1985a,b). However, this observation was of uncertain significance.

Two other large prospective studies agree that children with febrile seizures are normally intelligent. In the NCPP, in a sibling study there was no effect on intelligence quotient (IQ) or academic performance at age 7 years in children who were neurologically normal before the first febrile seizures and who did not develop afebrile seizures (Ellenberg & Nelson 1978). In the National Child Development Study in Great Britain (Ross *et al.* 1980), children with febrile convulsions did as well as the remainder of the population in school performance at 7 and 11 years. With regard to motor handicap following febrile seizures, two large prospective series have not found any apparent association with febrile seizures (Nelson & Ellenberg 1978; Verity *et al.* 1985a,b).

A recent study from Taiwan in which 6-year-old children with a history of febrile convulsions were compared to controls showed no disadvantage and even a trend towards better performance on achievement tests (Chang 2000).

In summary, there is no evidence that febrile seizures cause a decrease in intellectual capacity.

Management

Acute management

In most cases, a child with a febrile seizure is not brought to medical attention until after the seizure had ended. But an actively convulsing febrile child may present to an emergency room or doctor's office. In that case, the airway must be kept clear, proper oxygenation maintained, intravenous access established, and medication administered to stop the convulsion. Diazepam (0.2–0.3 mg/kg given at a maximum rate of 1 mg/min intravenously) is usually the first drug used and may be repeated up to a total dose of no more than 5 mg. Phenobarbital (10 mg/kg intravenously) may be used or rectal diazepam in a dose of 0.5 mg/kg if an intravenous line cannot be readily established. It is important to be alert for, and be prepared to deal with, respiratory depression, particularly if other anticonvulsant drugs have been previously administered.

When the child is seen following a febrile convulsion and is no longer convulsing, the most important task is to identify whether there is an underlying illness that may require treatment. A medical history should include a review of the patient's developmental progress, and a family history of febrile and afebrile seizures. If this was not the first episode, details of previous seizures should be noted. Particular attention in the physical examination should be paid to the level of consciousness, the presence of meningismus or a tense or bulging fontanel, measurement of head circumference, and muscle strength, tone, and symmetry. These items should be part of the initial examination and repeated, if possible, a few hours later.

Lumbar puncture

The most urgent diagnostic decision is whether or not a lumbar puncture (LP) should be performed to rule out meningitis. In the younger child, classic meningeal signs may not be present and the index of suspicion should be very high; this is especially true for infants younger than 1 year of age. Various guidelines have been suggested based on age or the number of previous febrile convulsions (Ouelette 1977; Wolf 1978). Clearly, cerebrospinal fluid must be obtained if there is clinical suspicion of meningitis (such as prolonged lethargy), regardless of the child's age, number of prior febrile seizures, or family history, or the presence of another source of infection. Many authors recommend routine LP if the child is either younger than 2 years or younger than 18 months old because specific signs such as a stiff neck or bulging fontanel may be absent. The American Academy of Pediatrics (1996) has recommended that in the case of a single febrile seizure, an LP should be performed in all children younger than 1 year of age, and considered between 12 and 18 months, but is not necessary in the absence of clinical indications over 18 months. For children with complex febrile convulsions, recommendations have not been published and clinical practice varies, as well as in children who are already taking oral antibiotics (Rosenberg 1992).

Joffe and associates (1983) reviewed the records of 241 children of ages 6 months to 6 years who were seen for a first episode of seizure and fever in order to identify factors that could serve as guidelines in selection of patients warranting an LP. They found five items in the history and physical examination that identified all of the 13 children with meningitis and would have spared 62% of those without meningitis from LP. The findings were the following: a physician visit within 48 hours before the seizure, the occurrence of convulsions on arrival at the emergency room, a focal seizure, and suspicious findings on physical or neurologic examination (for example, rash or petechiae, cyanosis, hypotension, respiratory distress, stiff neck, increased tone, lack of responsiveness, or tense fontanel). However, use of these criteria is only recommended if a careful history and physical examination have been performed and if close follow-up for children not receiving LP is available.

A British physician (Clarke 1985) cautions that there may be some circumstances under which an LP may be hazardous if carried out during or immediately after a seizure. Bacterial meningitis may be associated with increased in-

tracranial pressure. Focal neurologic signs or coma may be present in a child with a febrile seizure and meningitis, and may indicate increased intracranial pressure. In this situation LP may be hazardous. Clarke suggests that in such cases it may be safer to give mannitol before the LP, or even to treat bacterial meningitis with antibiotics while deferring the LP. Clearly should increased intracranial pressure be suspected clinically, the decision to perform LP must be made by an experienced physician, who will weigh the risk in delaying a diagnosis of meningitis against the risk of lumbar puncture.

Laboratory studies

The search for a cause for the fever should begin with a careful examination. Laboratory evaluation in cases of febrile seizure should be guided by specific clinical indications (Table 23.5).

The recent trend is toward reducing the number of diagnostic tests performed in children presenting with febrile seizures, because physicians are under pressure to reduce unnecessary expenditures and because the yield from these tests, routinely used, is negligible. Electrolytes, blood glucose, blood urea nitrogen, calcium, and phosphorus should be evaluated when there is a specific indication, such as the presence of vomiting, diarrhea, or a history consistent with possible hypoglycemia. A computed tomographic (CT) or magnetic resonance imaging scan is indicated only if there is a history of significant head trauma or progressive neurologic changes, neurologic abnormalities present after the seizure is over, or specific clinical features suggesting possible focal pathology.

TABLE 23.5

Evaluation After Febrile Convulsions

1. Workup of fever:
   - History
   - Physical examination
   - Blood culture
   - Throat culture
   - Chest x-ray study
   - Urinalysis
   - Urine culture
   - Complete blood count
   - Lumbar puncture
2. As clinically indicated, measurement of:
   - Electrolytes
   - Blood urea nitrogen
   - Calcium
   - Phosphorus
   - Glucose
   - Toxins
3. If there are focal abnormalities, a history of trauma, or a specific neurologic deficit present following the seizure:
   - CT scan or magnetic resonance imaging
   - EEG

Although there may be a higher incidence of EEG abnormalities in children with febrile seizures, the EEG has not been shown to be helpful in predicting recurrences or the risk for later epilepsy (Stores 1991). An EEG performed within 1 week of a febrile seizure usually is normal (Maytal 2000) although up to one-third may have occipital slowing. The incidence of paroxysmal abnormalities increases with age (Sofijanov 1992). Alvarez and associates (1983) have noted the presence of hypnagogic paroxysmal spike-wave activity in almost a quarter of children with febrile convulsions, an incidence significantly higher than that in a control population. However, the children who had this abnormality could not be distinguished clinically from those who did not.

Hospitalization

Hospitalization is usually unnecessary after a febrile seizure. The decision to hospitalize a child with a febrile seizure depends largely on the specific clinical situation and the family. Whenever possible, children presenting with a febrile seizure should be kept in an emergency room holding area for up to several hours and then reevaluated. The majority of children will have improved after a short time. If they are alert and the etiology of the fever is clear, they can be sent home, provided that follow-up care can be ensured. It is advisable to schedule a follow-up appointment within a few days for reevaluation and education of the parents. If the child's clinical condition is still unstable, or if there is any question concerning the etiology of the seizure or the possibility of meningitis, the child should be admitted. If follow-up contact with the family is uncertain, or if the parents seem unreliable or unable to cope, hospitalization may be advisable.

The current trend is away from hospitalization when possible, for reasons that include pressure to avoid unnecessary costs, increased awareness of the favorable outlook for these patients, and the wish to avoid exposure of other hospitalization children to the viral illnesses commonly present in youngsters with febrile seizures.

One study was designed to determine if it was possible to predict which children with febrile seizures would have a second seizure during the same febrile illness (Green & MacFaul 1985). Of 199 children with febrile seizures, 32 (16%) experienced more than one seizure in the same illness, 13 occurring before hospital admission and 19 after admission. All of these seizures occurred within 24 hours of admission. No factors were found that were predictive of which seizures would be multiple, that is, recurring during the same illness.

Parental counseling

The parents of a child with a first febrile convulsion are likely to be extremely upset and in a state of panic. When a seizure

is first witnessed, parents often think the child is dead or dying (Hansen 1984). They may pick up and shake the child, bang him or her on the back, try to insert fingers or an object between the teeth, or desperately attempt mouth-to-mouth resuscitation. These actions may actually endanger a convulsing child.

After the convulsion has ceased, medical evaluation has been performed, and the parents have had an opportunity to calm down and are assured that their child is alive and in no great danger, they need instructions on management of possible recurrences, which may occur either during the same illness or later on. Information and counseling are needed after the acute event and also later, when parents have had a chance to formulate questions. Information and instructions in a written format are helpful. The following points need to be stressed:

1 Although the seizure may have been frightening to witness, the child will not have suffered brain damage as a result of the fit, and the likelihood of future epilepsy is very small.
2 There is a risk of another convulsion when the child has another febrile illness, as well as a small risk of another convulsion within 24 hours.
3 If a febrile seizure recurs, parents must be told to stay calm, to place the child on his or her side or stomach with the face downward on a protected surface, and not to force anything between the teeth. It is very important that parents observe the child, note any focal features (especially at onset), and time the duration of the seizure. If the seizure lasts longer than 10 minutes, then the child should be brought to the nearest medical facility by car or ambulance.
4 If treatment is prescribed, clear and exact instructions regarding its use should be given and repeated on a later visit (Shinnar 2000).

It is reasonable to avoid high fevers when possible in a child who has experienced a febrile seizure, so parents should be instructed in temperature taking and fever management. However, it has not been shown that using antipyretics will lower the risk of a febrile convulsion (Camfield 1980).

The parents may ask questions and should be counseled on the prognosis for their child. It should be stressed that, in general, children with febrile seizures do very well. Physicians can feel comfortable in reassuring parents that children do not die because of febrile convulsions; in large cohort studies no deaths were reported. Earlier studies reporting deaths among hospitalized children with febrile seizures included cases of severe pre-existing handicap and meningitis. Factors affecting recurrence rate and risk of epilepsy should be discussed. The parents' views should be considered in any decision regarding medication, and if medication is prescribed, a full discussion of the goals, risks, benefits, and side effects is needed. A successful strategy used in selected cases has been home treatment with rectal diazepam once a seizure begins, a regimen designed to prevent the convulsion from being prolonged. In cases such as where the child lives far from medical care or has a history of prolonged seizures, rectal diazepam may be used at home as an acute treatment to stop the seizure (Camfield 1989; Morton 1997). It should only be used by trained, reliable caregivers.

Questions regarding the advisability of continuation of routine childhood immunizations may arise, because most routine immunizations are scheduled at the age of susceptibility to febrile seizures. In the NCPP, seizures following childhood immunizations had the characteristics and benign outcome of febrile seizures (Hirtz *et al.* 1983). Other studies have noted an increase in febrile but not afebrile seizures following diphtheria-pertussis-tetanus immunization (Griffin *et al.* 1990; Walker *et al.* 1988). In each child the advantages of the protection offered by the vaccine must be weighed against the possible complications of immunization, and the advisability of immunization with pertussis should be reevaluated at each subsequent medical visit. The risks and benefits of immunization should be discussed fully with parents and a record made of the discussion, whatever the conclusion.

Long-term management

Although antipyretics reduce fever, they cannot be relied on to prevent febrile seizures. Often, a febrile seizure may be the first sign that the child is feverish. Nevertheless, it is important to make certain that parents are aware of proper dosage and administration of antipyretics and that they try to reduce their child's fever to promote the comfort of the child and to prevent dehydration. Treatment of the primary illness causing the fever should be instituted as soon as possible when there is a treatment, for example in cases of otitiis media.

There is no convincing evidence to date that treating children with febrile seizures with anticonvulsant therapy can prevent the development of epilepsy (Hirata 1985). Studies showing a reduction in risk of recurrence have not demonstrated an effect on the risk of developing later epilepsy (Knudsen 1996; Wolf 1989; Rosman 1993; Shinnar 1996).

The intermittent use of phenobarbital at the time of febrile illness has been tried in the past with the intent of preventing febrile seizure recurrences. This therapy is not effective. An acute dose does not achieve a therapeutic blood level unless the dose is so large as to be dangerous, because the half-life of phenobarbital is 24–100 hours and it takes at least five half-lives to achieve a steady-state blood level.

A number of series have reported that continuous daily treatment with phenobarbital or valproate decreases the risk of recurrent febrile seizures (Lee & Melchior 1981; Mamelle *et al.* 1984; Wolf *et al.* 1977). Most of these studies have dealt with children with a first uncomplicated febrile seizure. Not all reports have confirmed the efficacy of the treatment.

Febrile seizures

PEARLS & PERILS

- Most children with febrile seizures do extremely well. The closer the clinical picture to the typical case, the more ensured is a good prognosis.
- The earlier the age at which the first febrile convulsion occurs, the more likely are recurrences.
- There is no increase in risk of intellectual deficit owing to the occurrence of febrile seizures.
- The number of febrile seizure recurrences does not directly relate to the risk of later epilepsy.
- Intermittent administration of phenobarbital at the time of fever only is not effective in preventing recurrences.
- Diagnostic laboratory tests should never be routine but should be justified by the specific clinical setting.
- The risk for later epilepsy after febrile seizures is relatively increased but still low when:
  - **a.** There is neurologic or developmental abnormality before any seizures.
  - **b.** There is a history of seizures without fever in a parent or sibling.
  - **c.** The first febrile seizure is focal, is multiple, or lasts longer than 15 minutes.

Newton (1988) has questioned whether many of the studies with positive results were methodologically appropriate. Pooled analysis of British trials of treatment with phenobarbital and trials of treatment with phenobarbital or valproate, including both published and previously unpublished trials (Newton 1988) did not show significant reduction in recurrence seizures with either agent. Two randomized trials (Farwell *et al.* 1990; McKinlay & Newton 1989), which examined selected populations of children with febrile seizures at increased risk of subsequent seizures and analysed according to intention to treat, do not demonstrate efficacy for phenobarbital (in the former) or valproate for the chronic treatment of febrile seizures.

There has been concern that barbiturates may pose a risk to cognitive and behavioral function in children. In a randomized clinical trial designed to address this question, mean IQ was 7 points lower in children with early, complex, or repeated febrile seizures who were randomly assigned to treatment for 2 years with phenobarbital, as compared with children given a placebo (Farwell *et al.* 1990). There was no difference in the occurrence of subsequent seizures between the group assigned to phenobarbital and the group assigned to the placebo. Thus evidence based on samples of children selected for characteristics that make them candidates for consideration of long-term medical therapy after febrile seizures suggests that phenobarbital may adversely affect congnitive function and may offer no countervailing benefit in reducing the risk of later seizures.

Sodium valproate has been found to be effective in the prevention of febrile seizure recurrences (Lee & Melchior 1981; Mamelle *et al.* 1984). The incidence of side effects was very low in these studies. However, rare but life-threatening complications of pancreatitis and acute liver failure have been reported with sodium valproate. Less serious complications include weight gain, gastrointestinal dysfunction, and hair loss. Its use in children for prevention of febrile seizures is generally unwarranted.

Intermittent oral and rectal diazepam has been used successfully for febrile seizure prophylaxis. When rectal administration of diazepam at the onset of illness was compared with daily phenobarbital, febrile seizure recurrences were less frequent with diazepam, even though in a few cases parents did not recognize illness was present until the seizure occurred (Thorn 1981). Diazepam administered rectally was given every 12 hours for fever (38.5°C) and was effective in preventing recurrences. However, some mild transient sedation was seen in one-third of the children (Knudsen 1985).

Oral diazepam has been used at the onset of fever (Dianese 1979; Minagowa *et al.* 1985). Rosman and others (1993) showed a 44% reduction in risk of febrile seizure recurrence with oral diazepam (1 mg/kg/day given every 8 hours) administered when the child is febrile. There were fairly frequent moderate side effects of lethargy or ataxia, which decreased when dosage was reduced. The primary concern of this treatment is the possibility of sedation of a sick child that may mask underlying serious illness. However, for the rare situation in which prophylactic treatment is appropriate, either prophylactic oral diazepam at the time of febrile illness or rectal diazepam gel to be administered in the event of a seizure are at present the best treatment options available.

Conclusion

Although febrile seizures may be frightening to witness, the child who has one or several will usually do well. Only a small number of children will later develop epilepsy, and unless they are exceedingly lengthy, the seizures do not appear to cause brain damage or result in later intellectual or motor handicaps.

Parental reassurance and counseling form the cornerstone of management of the child with febrile seizures. Treatment has not been shown to prevent development of epilepsy. Few children need be placed on treatment to prevent recurrences. These would predominantly be children whose clinical picture is atypical, such as the child who has experienced focal paralysis following a febrile seizure, or who has had very many recurrences, some of them lengthy, at a young age. Potential risks of anticonvulsant therapy must be weighed against its benefits. Further investigations of new therapies are needed before we can be assured that they are both safe

CONSIDER CONSULTATION WHEN...

- A child has more than two or three febrile convulsions.
- A child has a pre-existing neurodevelopmental abnormality.
- A febrile convulsion is prolonged, e.g. more than 30 minutes.
- A child has a pre-existing neurodevelopmental abnormality.

and efficacious. Fortunately, the great majority of children with febrile seizures will have a good outcome whatever management strategy the physician and family choose.

Annotated bibliography

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This article reports the results of a randomized, double-blind, placebo-controlled study to investigate the side effects of phenobarbital for prevention of febrile seizures. An adverse effect on intellectual function was seen.

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This study gives the results of follow-up of about 16 000 neonatal survivors born in 1 week in Britain in 1970. Children with febrile convulsions were compared with their peers at 5 years. This study is in good agreement with the results of the previous large American studies but unfortunately also repeats some of their weaknesses, such as lack of reporting for treatment.

Shinnar S, Glauser TA: Febrile seizures. J Child Neurol 17:544–552, 2002.

This is a current review of the epidemiology, evaluation, and management of febrile seizures.

CHAPTER 24

The Child with Attention Deficit Hyperactivity Disorder

Russell A. Barkley, PhD and Michelle M. Macias, MD

OUTLINE

Signs and symptoms
Workup and diagnosis
Etiology
Treatment
Prognosis

Attention deficit hyperactivity disorder (ADHD) is perhaps the most common neurobehavioral disorder. It is characterized by developmentally inappropriate degrees of inattention, impulsiveness, and/or hyperactivity that most often arise in early to middle childhood, result in impairment across multiple domains of daily life activities, and remain relatively persistent over time. The prevalence was once estimated to be 3–5% of school-age children (American Psychiatric Association 2001), but current studies that include the more recently recognized inattentive only subtype place the figure closer to 7–8% of school-age children (Barbaresi *et al.* 2001) and 5% of adults (Murphy & Barkley 1996). Prevalence clearly varies as a function of age, male gender, chronic health problems, family dysfunction, low socioeconomic status, presence of a developmental impairment, and urban living (Lavigne *et al.* 1996). The disorder is found in all countries surveyed with rates similar to if not higher than those found in North America (see Barkley 2005). Differences across ethnic groups within the North America are sometimes found but seem to be more a function of social class than ethnicity (Szatmari 1992). Though diagnosed as a categorical disorder, ADHD may actually represent an extreme end along a normal continuum for the traits of attention, inhibition and the regulation of motor activity (Levy 1997).

The syndrome of attention difficulties, impulsive behavior, distractibility and overactivity has been known for many years (see Barkley 2005 for a historical summary). Numerous attempts have been made at definition and nomenclature, including Strauss syndrome, minimal brain dysfunction or damage, hyperkinetic child syndrome (or hyperkinesis), and attention deficit disorder with and without hyperactivity. Currently, the disorder is labeled attention deficit hyperactivity disorder with the subtype of the disorder further specified (predominantly inattentive, predominantly hyperactive-impulsive, or combined type) (American Psychiatric Association 2001).

The most recent edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, sets forth the diagnostic criteria to be used in diagnosis. These symptoms are classified under three categories: inattention, impulsivity, and hyperactivity. Developmentally inappropriate levels of *inattention* are signaled by six or more of the following symptoms that have persisted for at least 6 months:

1. Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities;
2. Often has difficulty sustaining attention in tasks or play activities;
3. Often does not seem to listen when spoken to directly;
4. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions);
5. Often has difficulty organizing tasks and activities;
6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework);
7. Often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools);
8. Is often easily distracted by extraneous stimuli;
9. Is often forgetful in daily activities.

To diagnose *hyperactive-impulsive* behavior, developmentally inappropriate levels of six or more of the following symptoms must likewise be present for 6 months:

1. Often fidgets with hands or feet or squirms in seat;
2. Often leaves seat in classroom or in other situations in which remaining seated is expected;
3. Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, this may be limited to subjective feelings of restlessness);

4 Often has difficulty playing or engaging in leisure activities quietly;
5 Is often "on the go" or often acts as if "driven by a motor";
6 Often talks excessively;
7 Often blurts out answers before the questions have been completed;
8 Often has difficulty awaiting turn;
9 Often interrupts or intrudes on others (e.g. butts into conversations or games).

Other diagnostic criteria include the presence of some inattention or hyperactive-impulsive symptoms prior to age 7 years and in two or more settings (home and school, for instance) with these symptoms resulting in impairment in major life activities (family, school, peers, community) and not being easily attributable to other mental disorders. The inclusion of the age of onset of 7 years has been challenged (Barkley & Biederman 1997) as without scientific foundation and can probably be ignored in favor of the more general criterion that the disorder develop during childhood (e.g. onset before puberty). Other disorders may coexist (are comorbid) with ADHD. The most frequent of these are listed in Table 24.1.

Despite the prevalence of the hyperactive syndrome and its description in the medical literature since the turn of the century (Still 1902), its existence as a clinical entity has been questioned continually, particularly in the popular media. Some social critics believe that the term has been used as a wastebasket diagnosis for children who present with a variety of socially unacceptable behaviors, or that the diagnosis is too often used to excuse aggressive, disruptive, or poorly disciplined children. However, numerous professionals who have worked with or studied children with ADHD have mounted a plethora of evidence to show that ADHD symptomatology constitutes a cluster distinct from those of other disorders, is associated with specific neuroimaging and genetic findings, comprises a distinct and persistent developmental course with numerous risks for various harms, and responds to various treatment approaches (Barkley 2002; Barkley 2005).

Physicians may not always be able to detect an abnormality in the child's behavior during an office examination despite reports by parents and/or teachers that their patience and sanity is being sorely challenged on a daily basis (Sleator & Ullman 1981). Yet a physician surveying the devastation of the waiting room after such a visit may be the first to suggest that the child's activity level falls outside normal bounds. For this reason, the evaluation must include multiple sources of information from informants gathered across several major domains of daily life activities (home, school, community).

There is near universal agreement that more boys than girls qualify for the diagnosis with an average of 3:1 in community samples, though this may rise to as much as 5:1 to 9:1 in tertiary care or specialty clinics (Szatmari 1992; American Psychiatric Association 2001). The reason for this sex difference is not clear though it may be partly due to multifactorial neurological and genetic factors for which males are more at risk than females. Higher sex ratios in specialty clinics may also be partly due to factors related to referral bias, such as greater aggression and conduct problems among males.

FEATURES

Table 24.1 Attention-deficit/hyperactivity Disorder

Discriminating features

1. Difficulties with sustained attention, persistence, and resistance to distraction and/or
2. Difficulties with impulse control, regulating activity level, and self-regulation

Consistent features

For Combined and hyperactive-impulsive types:

1. Difficulties with concentration, forgetfulness, disorganization, procrastination
2. Excessively talkative, blurts out comments thoughtlessly
3. Can't wait for things in line or for taking turns; impatient
4. Busy, on the go, fidgety, restless

Or (for predominantly inattentive type):

1. Passive, sluggish, lethargic, or hypoactive
2. Daydreamy, spacy, easily confused, stares, "in a fog"

Variable features

1. Specific learning disability (20–70%)
2. Specific language disorder (15–60%)
3. Oppositional defiant disorder (45–65%)
4. Conduct disorder (25–45%)
5. Dysthymia or major depression (20–30%)
6. Anxiety disorder (10–25%)
7. Childhood bipolar disorder (3–10%)
8. Poor peer relations (50–70%)
9. Developmental coordination disorder (50%+)
10. Poor educational performance (70–90%+), grade retention (25–50%), or suspension/expulsion (15–30%)

(Adapted from Barkley 1998)

Signs and symptoms

The primary symptoms that distinguish children with ADHD from others are their significant difficulties with inhibition (including hyperactivity) and/or their inability to attend to tasks for an age-appropriate period of time while resisting distractions (American Psychiatric Association 2001; Barkley 2005). For some children this may occur in nearly all situations, including those with high-interest activities. But for most children these difficulties with attention and inhibition are manifested primarily in settings

requiring self-restraint, persistence, and a high level of concentration to relatively uninteresting activities with low saliency to the child (Zentall 1985). This can be viewed as an exaggeration of the normal response to having to study or work on a project that demands sustained attention and resistance to interference. These difficulties obviously have a major impact on classroom functioning, where they may result in limited learning, disruption of class activities, poor work completion, impaired peer interactions, and increased conflict with teachers.

Distractibility is a major component of the difficulties with attention seen in children with ADHD. This inability to inhibit responding to task-irrelevant events or information leads the child to frequently and inappropriately attend to sights, sounds, and movements within range of vision or hearing. In the classroom, a teacher who finds that the child is unable to remember what has been said or leaves most work assignments unfinished may label the child as lazy or unmotivated. At home, the parent who finds the son or daughter diverted from a requested task is understandably upset and may interpret the behavior as frank disobedience. In community settings such as stores, restaurants, or church, observers may interpret the child's hyperactive, restless, inattentive, and otherwise challenging behavior as a result of poor parenting and lack of proper discipline.

Another common symptom in most children with ADHD (except the inattentive type) is impulsivity, or poor behavioral inhibition (Barkley 1999; Nigg 2001). This is often associated with excessive talking, touching of nearby objects, exploration of nearby areas, difficulties waiting, and poor delayed gratification. Teachers describe a youngster who blurts out comments without much reflection, prepares papers or takes tests too quickly, carelessly, and inaccurately, and talks out inappropriately in class. Problems with taking turns, sharing, cooperation, and following rules are also commonplace.

Excessive motor activity is sometimes the symptom that prompts the parents to seek professional assistance, especially in younger children (Porrino *et al.* 1983; Luk 1985). A mother may report a history of a baby overactive since birth or even while in the womb, but more commonly the excessive activity is first noticed when the child is a toddler or preschooler (2–4 years of age). At this age, the child's waking hours may be a whirlwind of activity, with much energy expended in climbing on or jumping off things, and excessive movement as if driven by a motor. At this age, children with ADHD may put themselves in dangerous situations through lack of forethought or insight resulting in caretakers being constantly vigilant for the safety of the child, siblings, or possessions.

As many as 30–50% of children diagnosed with ADHD show minimal problems with hyperactivity. This group is now subtyped as having the predominantly inattentive form of ADHD. A large minority manifests a sluggish cognitive tempo, show passive and sometimes withdrawn behavior, may stare and daydream more than others, and are often withdrawn or reticent in social interactions (Milich *et al*. 2001). It is not yet clear whether this represents a qualitatively different subtype of ADHD or an entirely separate disorder of attention. Regardless, such children are unlikely to show impulsive or hyperactive behavior, have far less comorbidity for oppositional defiant or conduct disorders, may not respond well to stimulant medications, yet may be more responsive to social skills training (Milich *et al.* 2001).

In the preschool years, there is often more opportunity to compare a child's inhibition, activity level, or attention span with those of other children. Nursery school teachers point out that the children with ADHD cannot stay with a task, sit for a story, sustain attention to some assigned activity, or complete a task as well as other children of the same age (Campbell 1980). These children cannot sit still for snacks, circle time, or other sedentary activities and thereby demands a considerable amount of staff attention, supervision, and engagement. Mother may be called to the preschool setting to pick up her unruly or overactive child earlier than normal dismissal or be summoned to the home of another child to extract their wayward child from a birthday party or play sessions because of his or her disruptive behavior.

It is in elementary or grammar school, however, that the child's inattention, impulsiveness, or hyperactivity tends to be most troublesome. This is often manifested in the first few years of schooling. Prior dismissals of the child's excess energy, activity, or zeal as "just normal boy behavior" or as an immaturity to be outgrown are now a real impediment to the ability to adjust to and learn in the classroom. This often earns the child negative teacher attention, peer rejection, and a greater than normal amount of punishment. The hours spent in the classroom are the time when a child's behavior is most expected to conform to that of others of the same age, and walking around in the classroom, disturbing other children, playing the class clown or otherwise getting into trouble are poorly tolerated. At home, this is the youngster who has trouble sitting through meal times with the rest of the family and who, while watching a TV program, may be in and out of the room constantly, moving about or doing somersaults or headstands in front of the screen, antagonizing a sibling, or throwing toys about the room.

As the child enters the second decade, he often is more able to control the gross motor movements such as running about or climbing on objects, but still may be noted to be fidgety, to be restless while seated, to change positions frequently, to play with objects constantly and to be talkative (Weiss & Hechtman 1993). Excessive talking is often evident in settings requiring restraint or quiet behavior, such as in church, in movie theaters, while others are talking, or in the classroom.

The majority of normal children seem to acquire, by a combination of instinct and learning, appropriate social

skills such as reciprocity, sharing, turn taking, recognition of ownership, and empathy. In contrast, the child with ADHD is likely to be self-centered, demanding, selfish, disruptive and to have little regard for the effect of their behavior on others. They may often view themselves as more competent in tasks or activities than they actually are in reality, may be more boastful of their talents, and are less attentive to the emotional behavior of others and other social cues. Signs of peer displeasure or even rejection may appear within minutes of being introduced to a new play group (Cunningham & Siegel 1987). By grammar school, the social isolation may be further compounded by peer teasing or other provocation, and by fourth grade, most ADHD children have no close friendships. These mutual experiences among ADHD or other socially rejected children may lead them to seek out each others' companionship and thus sow the seeds for a deviant peer group that may even come to celebrate antisocial behavior.

Besides the difficulties in school that may result from the symptoms of ADHD, children with the disorder are also more likely to have learning disabilities, language delays and developmental coordination disorders. The learning and language disorders are separate primary conditions that will require distinct interventions in their own right apart from those introduced for the management of ADHD. Though many ADHD children may seem like ideal candidates for retention in grade so as to address their apparent behavioral and academic immaturity, the urge to carry out such a recommendation should be resisted in view of recent evidence that school retention results in no benefits and multiple harms (Pagani *et al.* 2001).

Sometimes early gross and fine motor milestones are reached early by some ADHD children, as when caregivers remark that the child went straight from crawling to running. But more often motor milestones are met behind schedule consistent with developmental coordination disorder (Hartsough & Lambert 1985; Kadesjo & Gillberg 1998). Such children may be clumsy in the gym or during sports, show less physical fitness, stamina and endurance, and have poor graphomotor skills.

Many parents complain of discipline problems with their ADHD children, with as many as 45–65% or more meeting criteria for oppositional defiant disorder. In these children, temper outbursts are common. Stubborn, defiant, and otherwise resistant behavior is the norm, and aggressive and destructive behavior may appear. Research suggests that as many as half of these oppositional children will progress to early onset conduct disorder such as lying, stealing, fighting and otherwise violating the rights of others (Barkley *et al*. 1990; Weiss & Hechtman 1993).

A smaller but still significant proportion of ADHD children (20–30%) may eventually develop signs of major depression (see Pliszka *et al.* 2000; Brown 2001). These are the children most characterized by low self-esteem, statements of self-hatred, apparent demoralization, social withdrawal, and sometimes suicidal ideation. Though less apparent in childhood, these problems may become more obvious by adolescence, particularly among ADHD teens having conduct disorder. Repeated family stress, economic disadvantage, and exposure to physical or emotional trauma is more common among such children, potentially triggering events for their otherwise genetic vulnerability toward depression. Anxiety disorders may also be seen in a minority of ADHD children (10–30%), though often this is simply a reflection of their poor emotional self-control. Persons with the predominantly inattentive type of ADHD arguably may be more prone to such internalizing disorders (Carlson 1986; Milich *et al.* 2001).

Controversy abounds on the overlap of ADHD with childhood bipolar disorder (see Spencer *et al.* 2001). This may represent a one-way comorbidity in that having ADHD may not elevate risk for bipolar disorder while childhood bipolar illness (CBI) may be commonly associated with ADHD (up to 97%). The differential between ADHD and CBI can often be quite difficult and is compounded by the lack of consensus for CBI diagnostic criteria. CBI often lacks the periodic episodes of manic behavior more typical of adult bipolar disorder, instead being characterized by longer duration episodes with continuous or rapid ultradian mood swings, dysphoric mood or frank depression, elated mood marked by severe irritability punctuated by explosive rage, aggression, destructive behavior and grandiose thinking. Irrational behavior is typical during the emotional storms that can arise with minimal provocation in such children. CBI is also often characterized by decreased need for sleep. Differential diagnosis of CBI from ADHD is often predicated not only on symptom presentation and severity, but also a family history of bipolar disorder in the former but rarely the latter disorder. Convergent symptoms include hyperactivity, impulsivity, distractibility, disorganization and conduct problems. Moreover, CBI is associated with severe ratings of both internalizing and externalizing scores using common child behavior rating scales whereas ADHD manifests as predominantly elevated externalizing scores. CBI shows severe and capricious mood swings having little to do with rational environmental precipitants whereas ADHD children often show poor emotional self-control to routine emotionally provocative events. Clearly more research is needed on CBI and its defining features as well as its overlap with ADHD.

Etiology of ADHD

Significant advances in the understanding of the neurobiology of ADHD have taken place over the last decade using CNS neuroimaging, molecular genetics, family genetic studies and neuropharmacology. The etiology of ADHD most likely involves multiple potential biological causes possibly interacting with psychosocial ones (Connor 2002). Despite

this, the existing research clearly identifies ADHD as a neurobiological disorder. Initial understanding of the neurobiological abnormalities in ADHD came from our knowledge of the CNS action of medications effective in treating ADHD. Neuropharmacological studies support a central dopamine/norepinephrine dysregulation etiology for ADHD. The proposed model involves dysregulation in the primarily noradrenergic inhibitory influence of prefrontal cortical activity on primarily dopaminergic subcortical CNS structures.

ADHD is now viewed as largely a genetic disorder having striking levels of heritability rivaling some physical traits, such as height, and exceeding most psychological traits, such as intelligence or personality (Levy & Hay 2001). Family, adoption, and twin studies have investigated the genetic component to ADHD. The studies show that the ability to inherit ADHD ranges from 0.6 to almost 1 (average 0.8) indicating it is one of the most heritable disorders. Significant advances in the molecular genetics of ADHD have also been made. Researchers have focused on genes in the dopamine pathway as the pathophysiology of ADHD has implicated dopaminergic dysfunction. The dopamine transporter (DAT1) gene and the D4 receptor (DRD4) gene on chromosome 11 have been implicated in ADHD but inconsistent results have been found (Levy & Hay 2001). Large-scale molecular genetic studies are needed to more completely investigate the genetic heterogeneity of ADHD.

In a minority of cases, risk factors including pregnancy complications, fetal exposure to alcohol and tobacco, prematurity of birth with low birth weight and/or associated minor hemorrhagic CNS lesions, pre-, peri-, or postnatal hypoxia, CNS infection, head trauma, CNS cancers or leukemia or their treatments (radiation or chemotherapy), or significantly elevated lead levels during the first 3 years of life may be contributory to the disorder. Males may be somewhat more likely to have ADHD secondary to acquired disturbances of CNS development than females but it is increasingly clear that the majority of both sexes can derive their ADHD entirely from genetic contributions. However, etiology may be difficult to establish and may not be especially pertinent to treatment planning. Acquired cases may arguably be somewhat less responsive to stimulant medications (see Greenhill & Osmon 2002). While evidence of obvious etiology for the disorder may exist and can be informative, it may not be present. The clinician should allay parental feelings of guilt over having socially induced the disorder through poor child rearing as there is no convincing evidence that ADHD can arise through purely social origins. Some conditions may exacerbate the disorder, especially symptoms of inattention, such as treatment with some anticonvulsants (e.g. phenobarbital, phenytoin), limited sleep, excessive ingestion of food dyes or preservatives in the preschool years, bouts of otitis media and even recurring mild closed head trauma from some routine sports (soccer, football).

Workup and diagnosis

Both the American Academy of Child and Adolescent Psychiatry (AACAP 1997) and the American Academy of Pediatrics (AAP 2000, 2001) have established guidelines for the assessment and treatment of ADHD. There is a consensus that laboratory testing is unhelpful in the diagnosis of ADHD. No neurological, genetic, neuropsychological or behavioral tests have proven themselves to have sufficient positive and negative predictive power to accurately classify ADHD cases with sufficient success to recommend them for clinical diagnosis (Barkley 2005). This is not to say that groups of ADHD children cannot be differentiated from groups of control children in studies comparing them on these various parameters (Tannock 1999), but clinicians do not compare group means using modern statistics. They classify individual cases and for such purposes current tests have proven grossly inadequate (Gordon & Barkley 1998).

Like all other mental disorders and many medical ones, clinical diagnosis is based largely on careful history taking, use of structured interviews containing DSM-IV criteria for ADHD and related disorders, and the expert knowledge of the clinician in the differential diagnosis among childhood mental disorders. Paramount in the evaluative process is the time to listen to parental concerns, probe for details concerning nature, onset, and course, elaborate the specific impairments resulting from these concerns, and place them in the larger framework of the clinical taxonomy of mental disorders. The evaluation is the first step of intervention. The clinical interview is then supplemented with the use of parent and teacher behavior rating scales to assess developmental deviance of symptoms, screening of intelligence and academic achievement skills by standardized testing, brief observation of the child during unstructured and structured activities, contact with school personnel concerning classroom functioning and compilation of prior school and mental health records available on the child.

As ADHD is included within the Individuals with Disabilities in Education Act as well as Section 504 of the Rehabilitation Act of 1973, many children with ADHD are eligible for free educational evaluations through their school districts and in many cases access to a variety of special educational services and 504 accommodations. A child can be eligible for 504 accommodations (classroom and curriculum modifications and adaptations) if it can be demonstrated that a child's ADHD adversely affects his or her learning. Under the IDEA, ADHD may be considered under the specific category of "Other Health Impaired" and special education and related services can be provided. If such evaluations and services have not yet been instituted, clinicians should encourage families to initiate this process with their school district as the evaluations alone can take 3–9 months to complete and school services are often predicated on those results, not the physician's exam, diagnosis, or recommen-

dations (see DuPaul & Stoner 2003 for a thorough treatment of ADHD in the schools).

Medical assessment involves taking a thorough medical history, including probing for potential etiologic factors previously mentioned. This includes pregnancy, birth, and detailed postnatal history. When taking the medical history, it is useful to know not only of major trauma but also minor trauma and whether this is a child who has sustained more than his or her share of cuts, bumps, scrapes, or broken bones. The ADHD child's impulsiveness, lack of judgment, inattention, hyperactivity, and poor motor coordination often earn preferred customer status at the local emergency room (Barkley 2002b). Accidental ingestions of poisons are also more common in children with ADHD, warranting explicit forewarning of parents of this likelihood and the need for more aggressive childproofing of the home from these substances and from dangerous objects such as power tools and firearms. Children with ADHD may be more prone to physical abuse by virtue of the stress they may impose on already compromised caretakers. The risk for such abuse may be even more elevated in those children with comorbid oppositional defiant disorder (ODD) or comorbid CBI. Given that anywhere from 10 to 40% of children exposed to physically traumatic events may manifest symptoms of or meet criteria for post-traumatic stress disorder (PTSD) within 4–12 weeks after exposure, the greater risk of ADHD/ODD and ADHD/CBI children for exposure to such trauma would suggest an elevated rate of PTSD among these subgroups as well.

Developmental history frequently identifies an onset of disorder between 3 and 8 years, though it may be somewhat later for those children manifesting the predominantly inattentive type (Applegate *et al.* 1997; Barkley & Biederman 1997). Earlier onset may be arguably associated with more severe disorder and higher risk for school failure or psychiatric comorbidity. Infancy may be uneventful though a significant minority of ADHD children is described as having been difficult or colicky babies. Once locomotor behavior emerges, however, the hyperactive subtype of ADHD children are likely to be identified by caregivers as excessively active and on the go. Developmental milestones may be met at normal ages in many ADHD children but a significant subset (50%+) may show developmental coordination disorder or language disorders. If not evident beforehand, impairment due to ADHD symptoms is frequently present within the first few years of beginning formal education. The presence of other children in the home obviously has some bearing on the parents' ability to identify when the ADHD child became noticeably different from normal behavioral standards.

In a large number of cases (15–40%), family history reveals at least one other immediate family member as having ADHD or symptoms sufficient to warrant that diagnosis (Biederman *et al.* 1986). Up to 35% of siblings may have ADHD, whereas 15–20% of mothers and 15–30% of fathers may be eligible for that diagnosis as adults. If the parent has a diagnosis of ADHD, the risk to offspring may be as high as 52–54% (Barkley 2005). Gentle probing may be needed to unearth educational or behavioral problems in the history of the parents as children or teens, who may be embarrassed to bring it up spontaneously. Questioning parents about their own educational attainment, adjustment problems in school, poor grades on report cards, grade retention and any extra assistance received at school often produce a surprising number of positive endorsements. Frequently, one may learn that a grandparent has pronounced this grandchild to be just like one of the parents when they were children. Obviously, medical and psychiatric conditions occurring on either side of the family should be recorded, and any neurologic problems such as seizures, tic disorders or Tourette's syndrome. The occurrence of mental retardation or other developmental disorders is also relevant. Physicians are sometimes reluctant to inquire about the occurrence of mental health problems such as depression, alcoholism, other substance dependencies or sociopathy in family members. However, if the questioning is conducted sensitively in the context of completing a family medical history, it seldom causes offense and can provide significant information in view of the elevated risk of such disorders among biological family members. Parents may be relieved and want to discuss the topic as they may have been worried that their child will end up with a similar condition. The child's educational history should be elicited from preschool through the years of formal education noting particularly any grades that have been repeated, testing performed by the schools in the past and whether extra services have been provided. Have there been moves involving different school systems? It is also useful to know whether the family is pleased with the services the school is providing, and if they have a good relationship and maintain good communication with the school personnel working with their child.

Detailed accounting of behavioral problems should include when and in what situations the offenses occur. It is also useful to record how parents and other supervisors react to the behaviors and what subsequent interactions take place as a result of those reactions. In sum, what are the social contingencies that might be cueing, exacerbating, or sustaining inappropriate behavior, if any? (See Barkley 2005 for more information.) What disciplinary methods are used in the home now and in the past, and what formalized help have parents sought and obtained for managing the problems?

The examination of the child should include a complete physical examination, formal neurologic examination and an extended neurodevelopmental assessment. In the course of the physical examination, height, weight, and head circumference should be measured and plotted on standardized graphs. Hearing and vision should be screened, and

Attention Deficit Hyperactivity Disorder 1

PEARLS & PERILS

- You are only as good as your Rolodex or Personal Data Assistant. It is critical that clinicians maintain an extensive file of potential referral agencies and professionals to whom families of children with ADHD can be directed for the myriad of additional, nonmedical services they are likely to require (parent training, special educational services, tutoring, counseling, parent support groups, residential treatment, substance abuse treatments, vocational assessments, as well as treatments for parents, etc.).
- Base the diagnosis on several sources of information rather than relying exclusively on office behavior or parental report alone. Teacher information, reports from other caregivers, past records including report cards, prior evaluations, etc., are indispensable in providing a multi-source evaluation. Each source has its limitations that can be partially corrected by other sources.
- There is no set age at which one can initiate or terminate medication treatment. While children 5 years of age and older arguably respond better than preschool children, some preschoolers require and can benefit from medication. If needed and effective, medications can be continued into adulthood.
- Avoid the diagnosis of ADHD in children younger than age 3 years as there may not be sufficient history of persistent symptoms on which to confidently render a diagnosis. Moreover, mental disorders at this age often have yet to differentiate themselves and thus what may become ADHD, ODD/CD, CBI, or even autistic spectrum disorders often cannot be discerned from each other at this age. Below this age, consider using the term "at risk for" or "probable" ADHD and follow the case for further development of symptoms before giving a confident diagnosis.
- Watch for and query parents about parental psychopathology including ADHD, depression, anxiety disorders, substance use disorders, or marital discord, among others. When present, these can result in a worse prognosis for the child, greater risk for comorbid disorders such as ODD or CD, poorer compliance with treatment recommendations, and consequently less effective intervention for the child. As many as 25% of parents may require treatment for their own conditions.
- Be attuned to the possibilities of child physical abuse and PTSD, particularly when comorbid ODD and CBI are present, or when genetically unrelated adults reside in the home. The child with ADHD, especially when these other parental disorders are comorbid, can be exceptionally stressful for caregivers particularly when the caregiver is compromised by psychopathology. The threshold for eliciting physical abuse from others in these instances may be lower than usual.

Attention Deficit Hyperactivity Disorder 1 (*continued*)

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- While titrating medications, always obtain information directly from the school staff rather than rely exclusively on parental filtering of such information. This can be repeated quarterly as part of routine monitoring of the child's medication.
- Not all children who are inattentive have ADHD. Children with anxiety, depression, sleep disorders, otitis media, autistic spectrum disorders, PTSD, and the LDs among others can all have periodic difficulties with attention as part of the presenting complaints. Hence knowledge of and careful attention to differential diagnosis is paramount in the evaluation of children with ADHD.
- Medications may diminish irritating and disruptive behaviors in a child sufficiently that he or she is no longer an overt problem. Take care that other less obvious disorders or impairments are not overlooked (educational under-achievement, LDs, PTSD, etc.).

blood pressure should be measured. Although it is unlikely that medical conditions significantly impacting on the child's functioning would not have been noted previously, any findings on the examination suggestive of hyper- or hypothyroidism, lead exposure, anemia, or other chronic illness obviously need to be pursued further. Certain medical conditions warrant closer consideration of medication management in ADHD. For instance, stimulants are primarily central-acting sympathomimetic amines, but may have peripheral effects. Therefore, the presence of hypertension is not a contraindication to stimulant medication usage, but needs to be closely monitored and treated appropriately.

On the neurological examination one looks for subtle signs of previous central nervous system insult or progressive neurological conditions. Abnormalities of muscle tone or a difference in strength, tone, or deep tendon reflex responses between the two sides previously may have gone unnoticed. Nystagmus, ataxia, tremor, decreased visual field, or fundal abnormalities also should be noted and investigated.

The extended neurological examination provides a systematic approach for describing the progression of higher neurological function in the areas of motor coordination, visuoperceptual skills, language skills, and global cognitive function through the school-age years. Test items have been developed in an attempt to find a clinical window allowing identification of more specific areas of functional deficit. Formal testing is possibly most useful as a means for observing the child over a period of time and while engaged in a variety of tasks. Often the behavioral symptoms prompting the appointment are evident only if the child is seen for a

more extended period. If the appointment is the standard 10-minute physical examination, many parents are been frustrated to find that their child demonstrates none of the "referral" behaviors (Sleator & Ullman 1981). If the physician then declares the child to be normal and in no need of treatment, the parent is forced to seek help and support elsewhere.

Several neurodevelopmental test batteries have been developed for use by physicians in office settings (e.g. Pediatric Examination of Educational Readiness, Levine 1985). Many clinicians choose a few test items in the various areas so that they become familiar with their administration and age norms and are able to judge where a particular child falls on the continuum. The developmental areas assessed should include gross and fine motor coordination with recording of any motor impersistence, synkinesia, or motor overflow movements. The efficiency of eye tracking and rapid alternating movements should be observed, as well as the ability to identify right and left body parts both on the child and on a person standing opposite. For a more thorough evaluation of neuropsychological status (intellect, memory, visual-spatial abilities, inhibition, attention, executive functioning, etc.), the physician should refer the child to a clinical neuropsychologist unless the school is already planning to undertake such an examination as part of the child's application for services under the IDEA.

When the examiner sits with the child at a table for paper and pencil tasks, fidgety and distractible behavior may become more apparent (Barkley *et al.* 2001). Useful activities for this part of the examination are spontaneous or directed handwriting and form copying. Handwriting allows observation of pencil grasp, as well as facility of execution and the finished product. Form copying allows the examiner to assess the child's visuoperceptual skills. Solving a few math problems at the child's current grade level demonstrates how he or she may tackle schoolwork. In all tasks, the examiner has an opportunity to see how the child organizes the work on the page, whether he monitors and self-corrects, whether his approach to the task is impulsive, and how well he or she is able to maintain attention on the work. Once again, the absence of behavioral difficulties or symptoms of ADHD is not evidence against the diagnosis of the disorder as many ADHD children function well in such one-to-one encounters. However, evidence suggests that behavioral problems that do occur in this context are reasonably predictive of similar such problems in the school setting (Campbell 1990; Barkley *et al.* 2001).

Whether the physician wishes to include one of the standardized reading tests or screening for receptive and expressive language abilities depends on other testing already performed or planned by other professionals as well as the interest of the individual clinician and his or her training in conducting such tests. Again, clinical or educational psychologists may be requested to assist with such evaluations where a more thorough assessment of psycho-educational functioning seems in order. Other sources of information essential for the diagnostic process are behavioral rating scales or checklists on which normative data are available. These include "broad band" questionnaires, such as the Behavioral Assessment System for Children (Kamphaus & Reynolds 1995) or Child Behavior Checklist (Achenbach 2001) for screening the major dimensions of childhood psychopathology (e.g. anxiety, depression, attention, hyperactivity, aggression, etc.). "Narrow band" questionnaires specifically evaluate the symptoms of ADHD as set forth in DSM-IV. Rating scales can reliably, validly and efficiently measure DSM-IV-based ADHD symptoms. Some examples of instruments demonstrating appropriate psychometric properties with a strong normative base include the ADHD Rating Scale IV (DuPaul *et al.* 1998) and the Conners Rating Scales-Revised (Conners 1997). Reports of prior assessments are important to obtain and written permission should be obtained from parents to communicate with school personnel concerning the child's school behavior and performance. Telephone contact with school staff can then be initiated.

A number of specific tests have been devised to provide objective measures of a subject's vigilance and impulse control, such as the Gordon Diagnostic System, Conners Continuous Performance Test or the Test of Variables of Attention, among others (see Gordon & Barkley 1998). Research suggests, however, that these tests are not especially accurate at classifying children as ADHD as the 20–50% false negative rate is too high and thus the clinician would incorrectly "rule out" the disorder. While the presence of abnormal scores on such tests indicate the presence of a disorder in as many as 90% of children who perform poorly, such scores cannot indicate the specific disorder present. Moreover, the ecological validity of these tests is low thus precluding the ability to predict from the test scores how the child will function in more natural settings, such as home and school (Barkley 1990). These tests are therefore not recommended for routine diagnostic evaluations of children with ADHD, although they may be used in clinics specializing in ADHD as part of research or drug trials. More useful information is likely to be obtained from the parent and teacher rating scales discussed above. These ratings can be supplemented with more specific ratings of executive functioning from these sources using the BRIEF scale (Behavior Rating Inventory of Executive Functioning) (Isquith *et al.* 1998) or the BADDES (Brown Attention-Deficit Disorder Scales for Children and Adolescents)(Brown 2001).

Laboratory tests such as blood or urine panels, EEG and neuroimaging scans are seldom of help in making the diagnosis of ADHD. As a rule, they should be undertaken only if there is a clinical indication by the history or physical examination. An EEG can be performed when there is suspicion of a seizure disorder including absence spells. To

order one on every child presenting with concerns about ADHD, however, is economically wasteful, resulting in a low positive yield, and may lead to a number of readings in the "slightly abnormal" category, putting the clinician in the dilemma of having to interpret the significance of this to the family. Other tests that may be helpful in specific cases include a complete blood count, lead level, blood glucose and thyroid studies.

Treatment

As previously stated, the AACAP (AACAP 1997) and the AAP (AAP 2001) have established guidelines for the treatment of ADHD. Treatment for ADHD in children typically involves three components: parent and child education and support, classroom accommodations, and medication. As described earlier, the child with ADHD presents with problems in several areas of adaptive functioning (home, school, community, peers, etc.) and often with additional comorbidity for other disorders (ODD, compulsive disorder [CD], learning disabilities [LD], etc.). In formulating a treatment plan, all of these problems and settings must be considered. The initial explanation and discussion of the disorder is in itself very helpful and therapeutic. A child who has been putting forth his best effort to obey directions, finish his work, and remember facts but is constantly chastised for being lazy and disobedient can be very relieved to know that someone believes that he is trying and understands his difficulties. He needs to hear too that he is not "dumb," "retarded," or "stupid" as classmates may have concluded. For the parent, who may have been told on the one hand that there is nothing wrong with the child, or that he will grow out of it, or on the other hand, that the fault lies with their poor child-rearing practices and lack of adequate disciplinary measures, a description of the syndrome can help dispel years of guilt and frustration. At the same time, one needs to convey the message that freedom from blame does not relieve the child or his parent from the responsibility of managing the problem as best as they can.

For most children with ADHD, individual psychotherapy is *not* indicated, unless there is evidence of a reactive form of depression, PTSD, or some other emotional upheaval occurring as a consequence or correlate of family or other forms of stress, trauma, or disruption. This is not to say that the child and family cannot benefit from some counseling about the disorder and its management. It is to say that traditional forms of play therapy, psychotherapy, or some other psychodynamically or psychoanalytically founded therapy has no scientific evidence of efficacy for ADHD at this time.

Group treatment with other children may seem sensible at first blush given the significant social problems experienced by most children with ADHD. Recent studies, however, indicate that group social skills training is of little benefit to children with the combined type of ADHD. The greatest hope for improving the efficacy of such treatment is to incorporate parents and teachers into the training program to try to generalize the skills being conveyed in the treatment group to more natural settings. Even then, evidence for effectiveness is scant. In contrast, recent studies indicate that the inattentive subtype, especially those manifesting the sluggish cognitive tempo noted earlier, may benefit from this treatment approach. Such children are more passive and possibly anxious in social settings and may respond better to social skills initiatives. Caution is warranted in placing the ADHD child into any social skills group as evidence is mounting that putting nonaggressive ADHD children in with more aggressive peers may increase aggression or other forms of antisocial conduct.

Substantial evidence exists to show that training parents in child behavior management skills can be of significant benefit in the reduction of parent–child conflict and improvement in child success within the home (see Anastopoulos *et al.* 1993; Barkley 1997). Such an intervention does not ameliorate the symptoms of ADHD, given their substantial neurogenetic origins. Instead, it reduces oppositional, defiant, and noncompliant behavior through improvement in parental reinforcement and disciplinary tactics and instruction giving, among other skills. Such training can occur in groups. It is important that both parents be involved if both have contact with the child. At the very least, the nonattending parent must be supportive of the one attending training if the transfer of skills from the group to the home setting is to be enhanced. If there are others regularly caring for the child, they may be involved in the training also so that the child can experience consistency across the routine caregivers in his life. Family therapy or training is maximally effective with preschool or elementary school aged children and may decline sharply in effectiveness after 12–14 years of age. Thereafter, interventions will need to be added that address influences outside the family, such as peers, school, and others. Other forms of family therapy can be used where there are interactional issues needing attention, as in marital discord, parenting stress, or parent-ADHD teen conflict.

The school setting frequently requires adjustment to meet the special needs of the child with ADHD (DuPaul & Stoner 2003). As previously stated, these modifications can be obtained under "504 accommodations" for ADHD, or if more intensive intervention is needed, under the "Other Health Impaired" classification. These may include alterations to the curriculum and work load to better mesh with the limited attention, persistence, and disorganization of the child with ADHD; special educational services (push in or mainstreaming assistance to regular teachers, pull out services to focus on more individualized child training, self-contained classes, etc.); increases in sources of positive reinforcement for work productivity; occasional use of immediate and sys-

tematic negative consequences for disruptive or inappropriate behavior; implementation of a daily school behavior report card (the ratings on which are linked to a home token economy), peer-tutoring or other innovative approaches to using peer influence to achieve classroom goals, and more frequent communication with parents. In short, greater accountability of the child to teachers and others including more immediate, frequent, and salient feedback for performance, and increased structuring of the classroom environment and teaching materials have all been shown to benefit the child with ADHD in school. The presence of learning disabilities in 20–50% or more of children with ADHD necessitates additional services to address the specific academic domain of disability (reading, math, spelling, language, handwriting, etc.).

Similar considerations apply to doing homework. A distraction-free setting yet with adult monitoring of homework activities can be helpful as can the incorporation of some of the same methods discussed above for school. More specifically Goldstein and Zentall (1999) recommend the following:

1 Insure assignments are copied correctly and get home with proper books and materials;
2 Select appropriate work place at home;
3 Start assignments by reading all directions and following them carefully;
4 Manage difficult or long-term projects;
5 Maintain attention to boring tasks;
6 Check work for accuracy and completeness;
7 Get homework to school when due.

However, as a general rule parents should not be expected to provide supplementary teaching and there should be a limit set on the amount of unfinished work that is to be completed at home. A reduction in the volume of homework is desirable in keeping with the child's more limited attention and persistence and in view of evidence that homework is of little additional benefit to children until high school. For the most part, school issues should be confined to school hours, and time spent at home should be for social, recreational, and family activities.

The mainstay of treatment for many children with ADHD is medication, frequently the stimulants (DuPaul 1998). Space precludes a detailed consideration of the various medications that may benefit children with ADHD, and the physician should consult more detailed texts on psychopharmacology such as that by Werry and Aman (1999) or the specific chapters in Barkley (1998) dealing with medications for ADHD. Four classes of medication appear to be useful for management of ADHD, these being: stimulants (methylphenidate, amphetamines, pemoline), noradrenergic reuptake inhibitors (such as atomoxetine), tricyclic antidepressants, and antihypertensive medications (clonidine, guanfacine). For most children, this is never the sole solution to the management of their ADHD and related problems, yet evidence is now abundant that it is likely the most effective (MTA Cooperative Group 1999). Also, the patient's response to stimulant medication should not be used as a diagnostic tool given that normal children may also show modest benefits from such medication.

Stimulants have been used to treat ADHD children since 1937. They are the most well-studied medications for the management of ADHD showing efficacy in 75% or more of ADHD children, and possibly more if all stimulant classes are tested in sequence during the drug trial. The response rate for children below 5 years of age may be less robust and side effects may be somewhat greater, but the evidence for drug response among preschoolers is limited for the moment. A large-scale multi-site trial of stimulants in preschoolers sponsored by the National Institute of Mental Health is nearing completion and should give greater guidance to clinicians on this issue. The general benefits and side effects of stimulants are shown in Table 24.2. Beneficial effects are substantial, with 50–60% of children with ADHD being normalized in their behavior during active medication therapy, and another 20% or more improved but not normalized. The side effects of stimulants are quite benign, short-lived, dose related, and often managed through dose or timing adjustments, or by switching to a different delivery system or stimulant. Initial concerns about growth were vastly over-rated, with more recent studies suggesting a relatively limited impact on weight of 1–4 pounds during the first year of treatment with little or no impact thereafter. Effects on height are arguable and may be in the range of 1–2 mm during the initial year of treatment, again with little evidence for any ongoing growth prevention thereafter. However, the fact that a few children may have more significant growth problems on stimulants warrants periodic monitoring and plotting of growth parameters on published standardized growth charts.

The two most commonly used stimulants for management of ADHD are methylphenidate (Ritalin, Ritalin SR, Ritalin LA, Focalin, Concerta, Metadate CD) and the amphetamines (Dexedrine, Adderall, Adderall XR).They are well-studied medications and highly effective for the management of most cases of ADHD. Pemoline (Cylert), a dopamine agonist, is rarely used, as a black box warning to physicians in the mid-1990s was added as a consequence of 14 cases of hepatic toxicity. Hence there is a need for biweekly liver enzyme monitoring. It should be considered as a last resort in the management of ADHD if only for the inconvenience of frequent monitoring of liver functioning. The various methylphenidate and amphetamine delivery systems do not involve this problem and are very safe for use in children with ADHD.

Recent years have witnessed the development of once-daily delivery systems for methylphenidate (Concerta, Metadate CD, Ritalin LA) and the amphetamines (Adderall XR) such that children may not require any administration

TABLE 24.2

Effects, Side Effects, and Common Public Misconceptions of Stimulants

Behavioral effects

Increased concentration and persistence
Decreased impulsivity and hyperactivity
Increased work productivity (~accuracy)
Better emotional control
Decreased aggression and defiance/ODD/CD
Improved compliance and rule-following
Better working memory and internalized language
Improved handwriting and motor coordination
Improved self-esteem
Decreased punishment from others
Improved peer acceptance and interactions
Better awareness of game in sports

Side effects

Insomnia and loss of appetite (50%+)
Headaches and stomach aches (20–40%)
Irritability, prone to crying (<10%)
Nervous habits and mannerisms (<10%)
Tics (<3%) and Tourette's (rare)
Mild weight loss (mean = 0.5–1.8 kg; transient)
Minimal long-term effects on height (1–2 mm in first year)
Increased heart rate (3–10 b.p.m.), blood pressure (1.5–14 mmHg)
(Monitor higher risk African-American males)
<3% stimulant psychosis
5% discontinuation due to adverse events
No discernible long-term adverse consequences to date
Pemoline – requires frequent monitoring of liver enzymes

Common public misconceptions

Stimulants are addictive when used as prescribed
  No, must be inhaled or injected
Stimulants are over-prescribed
  2–3% on medication vs. 7+% prevalence
Stimulants create aggressive, assaultive behavior
  No, decrease aggression and antisocial actions
Stimulants increase the risk of seizures
  No, only at very, very high doses
Stimulants cause Tourette's syndrome
  No, although can increase tics in 30%; decrease tics in 35%
Stimulants create a greater risk of later substance abuse
  No; 14 studies find no such result; a few also found decreased risk if treatment continued through teens (see Barkley *et al.* 2003; Wilens *et al.* 2003).
Stimulants don't improve academic achievement
  Not if one means academic knowledge; no pill contains knowledge
  Improve work productivity often dramatically; less but some effect on accuracy
  Improve classroom conduct and rule-following
  Improve peer interactions
  Can result in improved grades (due to more completed assignments)
  Result in reduced punishment from teachers and peers

of medication while in school. This is a remarkable accomplishment for clinical practice in view of the understandable resistance of children to be singled out at school for dosing with its associated stigma. (The short time course of earlier preparations necessitated for multiple daily dosing.) These compounds provide 8–12 hours of therapeutic benefit in most cases. Recent research suggests Metadate CD and Ritalin LA may be somewhat more effective in the morning than an equivalent dose of Concerta, while the latter may be somewhat more beneficial for afternoon management of ADHD. All provide benefits across the entire school day, however.

These medications appear to increase brain inhibitory mechanisms while providing the child with greater concentration, persistence, and resistance to distractions. Methylphenidate is now known to act primarily by blocking the dopamine and norepinephrine reuptake transporters while the amphetamines have a greater impact on the production and release of dopamine into the extracellular space (and some arguable secondary effects on the transport and inhibition of dopamine metabolism via monoamine oxidase). Both medications result in increased intrasynaptic availability of dopamine and norepinephrine allowing for greater action on postsynaptic binding sites. The evidence on the safety and efficacy of the stimulants is abundant (see Greenhill & Osmon 2002). When prescribed appropriately and monitored carefully, these medications are safe and effective with no evidence currently available suggesting any long-term consequences from years of medication use.

The effects of the immediate release preparations of the stimulants are evident with 15–30 minutes of ingestion, seem to peak in 2–4 hours, and typically dissipate in 3–5 hours. The once-daily extended release preparations result in a considerable extension of this time course such that behavioral effects may last for 8–12 hours, depending on the delivery system.

When prescribing stimulants for a child with ADHD, there are a number of factors to be considered. Whether the patient should take the medication only on school days or 7 days a week and vacation time depends on whether the benefit is mainly in improved classroom performance or needs to include better behavior in nonschool settings. Few children experience problems with growth in weight on stimulants, and thus drug holidays should not be considered for most cases of ADHD based on this rationale alone. Where weight gain and height have been demonstrated to be problematic during stimulant therapy, drug holidays may be indicated. Otherwise, the settings in which impairment exists should determine the schedule and amount of dosing for the vast majority of cases. At least once per year, medication should be discontinued for a period of up to 1 week when the schedule is stable and teachers have had occasion to become familiar with this child on medication (usually by end of October of the new school year) so as to provide informed feedback on efficacy and need for medi-

cation. Medication can be permanently discontinued when the child does just as well without as with it; this is often the result of several years of maturational improvement and/or additional classroom and home accommodations. While for some cases this point is reached in mid-adolescence, there is considerable individual variation. Some are able to stop in elementary school while others require continued treatment into adulthood. Monitoring of growth, heart rate, blood pressure, as well as clinical effectiveness and side effects should be done several times per year of treatment (every 3 months).

In January of 2003, the FDA gave approval to atomoxetine (Strattera) for use in the treatment of both children and adults with ADHD. This is the first nonstimulant approved for management of ADHD, and the first new medication approved since the 1970s. It provides yet another option for management of ADHD. As of this writing, the medication is the most successful new CNS drug ever launched with more than 940 000 new cases being treated and nearly two million prescriptions written in the first 8 months. Atomoxetine is an exclusive noradrenergic reuptake inhibitor and is the first drug indicated for ADHD that is not a Schedule II controlled substance, making it more convenient than the stimulants for sampling, prescribing, and titrating. Available evidence suggests equal efficacy with immediate release methylphenidate yet with fewer side effects (less insomnia, better morning behavior). As with the stimulants, treatment can be dispensed either once or twice daily. Over 75% of children show a positive response and this response has been maintained for up to 2 years in longitudinal research. Studies indicate that atomoxetine reduces ADHD, ODD, aggression, depression, increases school productivity, improves social behavior and self-esteem, benefits parent–child relations, and may improve enuresis where present. Interestingly, "morning after dose" behavior is also improved, perhaps owing to greater sleep the previous evening. Side effects include: sedation (10–20+%), decreased appetite (14–22%); nausea (12%); dizziness (6%); increased blood pressure (2 mmHg diastolic, 3 mmHg systolic); increased heart rate of 8 b.p.m.; temporary weight loss (0.5–2.3 kg) early in therapy with none further in year two of treatment. The CYP2D6 genotype results in poor metabolizers with 2–3× blood levels seen in extensive metabolizers. No differences have been found in side effects, tolerability, or rates of discontinuation due to adverse events in company studies of such metabolizers.

The likelihood of sedation can be reduced by initially starting at half the therapeutic dose (0.5 mg/kg) and then gradually titrated upward over 2–3 weeks to the therapeutic range (1.0–1.8 mg/kg). Or, if nausea is already present, the dose can be split in two and given once per AM/PM or simply reduced if possible. Any risk of nausea or decreased appetite likewise can be reduced by this gradual initial titration and by giving the dose with food. If children are already taking stimulants with some success but a switch to atomoxetine is indicated (typically for reducing side effects such as insomnia), then the child should be maintained on his normal stimulant dose during the gradual titration phase of atomoxetine. The stimulant can be discontinued once the therapeutic range for atomoxetine is achieved. The clinician may wish to consider using atomoxetine for the child with ADHD under those circumstances set forth in Table 24.3.

If the clinician wishes to evaluate drug response to the stimulants or atomoxetine in more detail, he or she can conduct a double-blind placebo-controlled trial alternating doses of medication with placebo on a weekly basis and collecting parent and teacher ratings of ADHD symptoms and side effects each week (see Dupaul *et al.* 1998). The assistance of a pharmacist in preparing the placebo will be required; our own trials utilize lactose powder placed in gelatin capsules with a comparable capsule used to house the comparison medication and dose.

Other medications that may be helpful in the management of ADHD in children in whom the stimulants or atomoxetine are ineffective include bupropion (primarily a noradrenergic reuptake inhibitor) and the tricyclic antidepressants (TCAs) which also probably work by blocking norepinephrine reuptake (see Werry & Aman 1999; Barkley 2005). The TCAs are declining in use due to the availability of the safer noradrenergic agents such as atomoxetine and bupropion. The TCAs require cardiac monitoring both before and during treatment, may be prone to habituation in some cases, and often manifest greater side effects than do atomoxetine or bupropion. The serotonergically mediated antidepressants (SSRIs), such as fluoxetine, as well as the modern anxiolytics are not effective for the management of ADHD symptoms but may be needed for treating cases involving comorbid depression or anxiety. The major and

TABLE 24.3 When to Consider Treating with Atomoxetine

New cases where parents or the clinician are concerned about logistics of stimulant prescribing, addiction potential, or are scared by anti-Ritalin media
Cases that have previously proven unresponsive or have shown a mediocre response to stimulants
Patients having significant insomnia or other sleep problems from stimulants
ADHD children in whom significant morning behavior problems exist while on stimulants
Adolescents with ADHD where concern exists about abuse or street diversion
Cases of ADHD having comorbid tic disorders
The child with ADHD who may have comorbid anxiety/depression
Where enuresis is problematic in the child with ADHD

Attention Deficit Hyperactivity Disorder 2

PEARLS & PERILS

- ADHD symptoms should result in obvious, not subtle impairments in important daily activities.
- Comorbid behavior and mood disorders as well as learning disabilities and language disorders are common.
- ADHD symptoms are not because of mental retardation.
- A visual inspection of the child's handwriting before and after successful medication use frequently reveals a noticeable improvement in legibility.
- Complete medication coverage must be seriously considered for ADHD teenagers who drive after school hours.

minor tranquilizers are not generally indicated for the management of ADHD but may be necessary in cases of serious aggression or otherwise explosive mood and conduct or for management of coexisting Tourette's syndrome.

Clonidine and guanfacine are alpha$_2$-noradrenergic agonists that have some effectiveness for the management of hyperactive-impulsive ADHD symptomatology. They work in part by decreasing arousal via noradrenergic inhibition at the level of the locus coeruleus. Such medications should be considered as a last resort because of greater concerns regarding their safety with children, their markedly longer phase for titration, their need for monitoring of cardiac functioning, as well as the frequent sedation that may occur during the titration and even maintenance stages of management relative to stimulants and atomoxetine. These antihypertensive agents may be indicated where the child demonstrates a failed response to stimulants and atomoxetine, or has significant problems with serious aggressive or destructive/explosive behavior, severe hyperactivity, or tic disorders that have been shown to be exacerbated in a stimulant trial. Dosing for clonidine is typically between 0.25 and 0.3 mg/day given 3–4 times per day in divided doses. Parents must be forewarned not to alter the dose or its scheduling or to skip doses due to the potential for invoking rebound hypertension. A summary table concerning medications for ADHD is shown in Table 24.4.

When a problem affects as many children as does ADHD, parents search far and wide for treatments and cures. It is not surprising, therefore, that a number of controversial treatment methods have been proposed. Because their proponents are generally more available and willing to promote their (often far-fetched) theories in the popular media than are busy clinicians who follow a scientist-practitioner model or than legitimate clinical researchers, these "alternative" therapies often achieve considerable publicity. These unproven or disproven remedies for ADHD include: elimination diets (often removing preservatives, food colorings, and salicylates or sugars) to which only about 5–10% of ADHD cases respond, dietary supplements (typically involving antioxidants, trace elements, minerals, or oils), various allergen therapies, chiropractic manipulations or manual pressure placed on points about the skull, sensory integration therapy, ocular-motor exercises or visual perspective training, EMG or EEG biofeedback, cognitive therapy or self-control training, or social skills training (especially when administered only in clinical settings). Note however, that the cognitive behavioral therapy or social skills training may have some benefit for the inattentive subtype of ADHD, particularly those manifesting symptoms of a sluggish cognitive tempo and social passivity. Parents wishing to try these treatments should be apprised of the lack of scientific evidence in favor of their use and the fact that perceived changes may well result from placebo effects, increased child monitoring, expectancy effects, or (if sufficient time is spent in treatment) maturation.

Prognosis

The outlook for children with ADHD is quite mixed. Though not a life-threatening or completely debilitating disorder, ADHD can result in a rather wide swath of impairments in major life activities (Weiss & Hechtman 1993; Barkley 2005). The disorders likely to be comorbid with ADHD have been discussed above, and many can contribute further to impairments in adaptive functioning beyond that produced by ADHD itself. Current research suggests that upwards of 66% of children diagnosed with ADHD (combined type); continue to demonstrate substantial symptoms of disorder (98th percentile) into young adulthood (Barkley *et al.* 2002) with as many as 80% demonstrating impairment. No longitudinal studies exist of the inattentive type. The remainder

KEY CLINICAL QUESTIONS

- Are the symptoms of inattention, over-activity, and poor impulse control clinically significant and developmentally inappropriate for age? (Distinguishes normal variation in age-typical behavior from clinical levels of severity.)
- Are at least two or more domains of major life activity impaired by these symptoms? (Insures true disorder is present from simply elevated levels of normal temperament.)
- Are there other disorders coexistent with ADHD, such as oppositional or conduct disorder, major depression, anxiety, or learning disorders? (Affects future risks of impairment, types of treatment, and/or response to treatment.)
- Does the parent have ADHD? (May help distinguish familial-genetic forms of disorder from acquired ones; presence adversely impacts delivery of treatment services to child if parental disorder remains untreated.)

TABLE 24.4

Medications for ADHD

Class	Generic (brand) name	Daily dosage	Duration	Mechanism of action	Side effects
Stimulants	***Methylphenidate***	Initial: 0.3–5 mg/kg	3–5 hr	Primary: blocks reuptake of DA, NE	Appetite suppression
	Immediate release/ short-acting (Ritalin, Methylin, Methylin)	BID to TID; can titrate up to ~1 mg/ kg/dose		Secondary: release of DA from storage vesicle	Delay of sleep onset Abdominal pain Headache
	Intermediate-acting (Ritalin SR, Metadate ER, Methylin ER)	QD to BID	3–8 hr		Rebound irritability Tics (motor, vocal) Jitteriness
	Extended release (Concerta, Metadate CD, Ritalin LA)	QD	8–12 hr		
	Dexmethylphenidate (Focalin)	BID to TID: initial ½IR MPH	4–6 hr	Same	Same
	Amphetamine				
	Immediate release/short-acting (Dexedrine, DextroStat)	BID to TID; initial dose ½IR MPH	4–6 hr	Primary: release of DA from storage vesicle Secondary: blocks reuptake of DA, NE	Same
	Intermediate-acting (Adderall, Dexedrine spansule)	QD to BID	4–8 hr		
	Extended release (Adderall-XR)	QD	10–12 hr		
Antidepressants	***Tricyclics (TCAs)***				
	Imipramine (Tofranil) Desipramine (Norpramin)	BID to TID; dose 1–4 mg/kg/day in divided doses		Blocks reuptake of NE	Anticholinergic SE Cardiac SE
	Atypicals				
	Bupropion (Wellbutrin) (Wellbutrin SR)	BID to TID QD to BID 1.5–6 mg/kg/day		NE reuptake inhibitor	Seizure threshold, tic exacerbation
β_2 agonists	**Clonidine** (Catapres, Catapres TTS)	TID to QID; initial dose 0.05 mg QD, titrate slowly to max of 0.4 mg TDD		Arousal at locus coeruleus by NE inhibition	Sedation Low BP
	Guanfacine (Tenex)	BID to TID; initial dose 0.5 mg QD; titrate to max 4 mg TDD			
SNRI	Atomoxetine (Strattera)	QD to BID; initial dose 0.5 mg/kg, increase to max 1.2–1.8 mg/kg		Blocks reuptake of NE in synapse	GI sx Sedation Appetite suppression

is not necessarily normalized by this age but fall short of current diagnostic criteria for full disorder. When followed to adolescence and adulthood, children with ADHD are at greater risk for a variety of adverse outcomes (see Table 24.5) including educational failure, delinquency, substance use disorders, and personality disorders. Most of these risks are associated more with the development of early onset conduct disorder (before age 12) than with ADHD alone, though educational under-performance, nicotine use, drug-related antisocial activities, and driving problems are attributable to severity of ADHD rather than its comorbid disorders. The eventual outcome of ADHD children has been difficult to predict. Modest evidence suggests that earlier onset, greater severity of disorder, comorbidity (especially for conduct disorder), low intelligence, parental psychopathology, family discord, and social disadvantage may worsen the prognosis though even children experiencing one or more of these risk factors may function satisfactorily as adults.

A positive response to medication and implementation of behavioral and educational accommodations can bring about a dramatic change in a child's ability to attend, inhibit, persist, be organized and timely, and produce more school-

TABLE 24.5

Developmental Risks and Adverse Outcomes

Educational risks (ADHD vs. control groups)

More grade retention (25–45% vs. 13%)
More placed in special educational (25–50%)
More are suspended (40–60% vs. 19%)
Greater expulsion rate (10–18% vs. 6%)
Higher drop out rate (30–40% vs.9%)
Lower Class Ranking (69% vs. 50%)
Lower GPA (1.7 vs. 2.6)
Fewer enter college (22% vs. 77%)
Lower college graduation rate (5% vs. 35%)

Driving risks

Poorer steering, more false braking, and slower reaction times to significant events
Rated by self, others, and driving instructors as using fewer safe driving habits
More likely to drive before legally licensed
More accidents (and more at faults) (2–3 vs. 0–2)
- % with 2+ crashes: 40 vs. 6
- % with 3+ crashes: 26 vs.9

More citations (speeding – mean 4–5 vs. 1–2)
Worse accidents ($4200–5000 vs.$1600–2200)
- (% having a crash with injuries: 60 vs.17)

More suspensions/revocations (mean 2.2 vs. 0.7); (% suspended: 22–24 vs. 4–5)

Sexual risks

Begin sexual activity earlier (15 vs. 16 yrs)
More sexual partners (18.6 vs. 6.5)
Less time with each partner
Less likely to employ contraception
Greater risk of teen pregnancy (38 vs. 4%)
Ratio for number of births (42:1)
- 54% do not have custody of offspring

Higher risk for STDs (16% vs. 4%)

Employment risks

Enter workforce at unskilled/semi-skilled level
More likely to be fired (55% vs. 23%; mean 1.1 vs. 0.3 jobs)
Change jobs more often (2.7 vs. 1.3 times over 2–8 years since leaving high school)
More ADHD/ODD symptoms on the job (as rated by current supervisors)
Lower work performance ratings (as reported by current supervisors)
Lower social class (SES) (limited by education)
By 30s, 35% self-employed

From Barkley (1998)

CONSIDER CONSULTATION WHEN...

- A serious psychiatric disorder exists, for instance major depression, generalized anxiety disorder, childhood bipolar illness, psychosis, autistic spectrum disorders.
- The physical exam reveals localized neurological findings not previously detected, the history suggests a degenerative course, or the inattention is consistent with absence or petit mal seizures.
- A movement disorder such as tics or Tourette's syndrome develops or worsens while taking stimulant medications and does not resolve after discontinuation of the drug.
- The child's behavior escalates such that she or he is a danger to self or others or is unable to function in the normal school or home environment.
- The most commonly used psychopharmacological agents (stimulants, atomoxetine) have not proven effective and the symptoms warrant further trials on other medications.

work as well as his or her ability to interact more positively and reasonably with others. To date there is no evidence that treatment with medication, behavioral therapy, and/or special education that is limited to a few years of childhood results in any sustained improvement in academic functioning or other major life activities into adulthood. A limited amount of evidence suggests that continuation of medication treatment into adolescence might result in a reduced risk for substance use disorders and even antisocial behavior. Evidence from longer-term trials (1–3 years) of medication and behavioral-educational accommodations suggests them to be beneficial so long as treatment is sustained.

Despite this rather negative prognosis for the group of children as a whole, one should be as optimistic as possible when evaluating, advising, and following the individual child and family. With appropriate medical treatment, counseling and parent training, school adjustments, and special educational services as needed, as many as half or more of childhood cases can be expected to grow into a satisfactory level of adult functioning. While the same basic temperamental characteristics usually persist, they can take on a more positive aspect in adulthood where more numerous occupational and social niches exist within which the symptoms of disorder may no longer be impairing. Thus, the child with ADHD has the potential to be more successful and accepted as an adult than during childhood with its formal educational system. The task of professionals working with such a child is to help her or him reach that point along as smooth a course as possible with periodic interventions as required.

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National Resource Center on AD/HD: http://www.help4adhd.org

National Information Center for Children and Youth with Disabilities: http://www.nichcy.org

CHAPTER 25

Sleep Disorders

O'Neill F. D'Cruz, MD and Bradley V. Vaughn, MD

OUTLINE

The normal sleep-wake cycle
The evolution of sleep from infancy to adolescence
Sleep disorders
Sleep characteristics
Sleep amount
Sleep quality
Biologic–environmental interactions
Diagnostic evaluation
Management
Conclusion

Sleep is an inherent biologic phenomenon, comprising two of the three common states of the sleep-wake cycle. Sleep is an excellent marker of biologic integrity and environmental adaptation. However, it is also a sensitive process that is prone to disruption by a variety of neurologic and systemic processes, as well as developmental, behavioral and environmental factors. This chapter provides a brief review of the normal sleep cycle, maturation of the sleep-wake cycle from infancy to the second decade, and a summary of the current understanding of the causes and treatment of common sleep disorders.

The normal sleep-wake cycle

In humans, wakefulness and sleep are noted during any 24-hour period. Sleep, which is often classified as a unitary state, actually consists of periods of nonrapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is further classified into four stages. Stage I and II NREM sleep occur at onset of sleep and during transitions between sleep cycles, while stages III and IV are noted during the early portions of the sleep period. REM sleep is usually noted during the latter portion of the sleep period. Sleep stages follow characteristic patterns of evolution during the sleep period that form the basis of age-appropriate sleep architecture. The amount of normal sleep, as well as its quality, also changes with age.

Sleep states and stages are identified by distinct EEG characteristics. Stage I NREM sleep is associated with desynchronized, low-voltage background patterns with prominent frontocentral beta activity and vertex sharp waves. Stage II NREM is comprised of a well-defined pattern of sleep spindles and K-complexes. Stages III and IV, often grouped together as slow-wave-sleep (SWS) are characterized by predominant and increasing amounts of high-voltage delta activity. NREM sleep is associated with regular respirations and heart rate and moderate muscle tone, and lack of eye and body movements. REM sleep (which is further classified as phasic and tonic REM) is distinguished from NREM sleep by the occurrence of rapid eye movements (hence the name), intermittent brief nonperiodic body movements, variable respiratory and heart rate, low muscle tone and a low voltage, mixed frequency EEG pattern.

Periodicity of sleep and sleep stages is noted consistently during the normal sleep-wake cycle. The occurrence of the major sleep period during the 24-hour day defines the sleep phase of the individual. Sleep onset occurs usually with stage I NREM sleep, and rapidly advances to SWS early in the sleep period. SWS decreases progressively through the night, while REM sleep, occurring at a periodicity of 80–90 minutes during the sleep period, increases in amount with each successive sleep cycle. A normal sleep period consists of several sleep cycles, depending on the amount of sleep.

Sleep duration and amount vary considerably with age. The major sleep period is usually at night, although some cultures retain the mid-afternoon nap (siesta) through adulthood. Nocturnal sleep is usually obtained as a single sleep period, lasting from 7–9 hours in most adults. Fragmentation of sleep, either occurring naturally with increasing age, or due to sleep disruption, adversely affects the restorative quality of sleep at all ages.

The evolution of sleep from infancy to adolescence

Sleep in infancy

During the neonatal period, the sleep-wake cycle consists of short periods of sleep, alternating with wakefulness throughout a 24-hour period. State differentiation is a marker

of biologic maturation, and normal newborns demonstrate sustained states of active sleep (equivalent to REM sleep later), quiet sleep (NREM sleep) and indeterminate sleep (mixed features). Indeterminate sleep is gradually replaced by differentiated sleep states during infancy.

Sleep in infants possesses several distinct characteristics. Sleep is consolidated into longer nocturnal sleep periods between 6 weeks and 3 months of age. The amount of total sleep during a 24-hour period ranges from 10–19 hours at 3 months. Total sleep duration averages around 14 hours between 6 months and 1 year of age. Daytime sleep, included in total sleep time, decreases from 3½ hours at 6 months of age to 2½ hours by 1 year of age. REM sleep in infants occurs at sleep onset and has a shorter period of 50–60 minutes.

Sleep in childhood

Sleep phase is well established in the majority of children by 6 months of age. Daytime naps decrease in duration and number in the preschool years. The number of children taking daytime naps also decreases from over 90% at 1 year of age to around 35% by 4 years of age. Rapid changes in physical, neurodevelopmental and social milestones occur during early childhood (1–5 years), making this group of children vulnerable to sleep disruption for various reasons.

School-aged children have excellent biologic sleep parameters, with sustained efficient nocturnal sleep lasting 10–11 hours. Daytime naps are unusual at this age. Hence, sleep complaints during this period are often secondary to environmental or physical causes.

Sleep in adolescence

Adolescence is a period of rapid physical, emotional and social maturation. Sleep during adolescence reflects the effect of several of these factors. Teenagers experience a physiologic delay in sleep phase (see DSPS, below). While sleep need continues to decrease with age in general, sleep need during adolescence is unchanged from preteen years, and may even increase during periods of rapid growth. This age group is also vulnerable to impaired sleep quality due to poor sleep habits. In the pediatric population, this age group is most likely to have a multi-factorial origin of sleep complaints.

Sleep disorders

Clinical symptoms of pediatric sleep disorders

Symptoms of sleep disorders in children are strikingly different from adults, and hence, are likely to be overlooked or misinterpreted. In young children, sleep disturbances may present as poor growth, persistent fussiness or inconsolability, and increased oppositional behavior. School-aged children may exhibit suboptimal academic performance, inattentive or hyperactive behavior, or appear to be daydreaming in sedentary settings. Adolescents may fall asleep in class, and may present with affective symptoms that need to be differentiated from primary psychiatric disorders. Unrefreshing nocturnal sleep is often a clue to the source of these symptoms in all age groups.

During the sleep period, a variety of clinical symptoms suggest sleep disorders. Sleep apnea, with or without associated effort, may be witnessed by caregivers. Frequent movements in one or more extremities, occurring in a stereotypic or periodic fashion, should raise suspicion of seizures, sleep-related movement disorders or parasomnias. Any nocturnal event associated with injury warrants further investigation.

Classification of sleep disorders

The International Classification of Sleep Disorders (ISCD) categorizes sleep disorders into four groups: dyssomnias, parasomnias, medical/psychiatric sleep disorders and proposed sleep disorders. Dyssomnias are sleep disorders associated with difficulty initiating or maintaining sleep, or excessive sleepiness. Parasomnias are a group of clinical disorders associated with undesirable physical phenomena that occur exclusively or predominantly during sleep. Medical and psychiatric disorders that are associated with sleep disturbance as an associated feature are included as a separate section. Proposed sleep disorders includes conditions that do not presently merit inclusion in one of the other categories.

Several sleep disorders in each category are prevalent in the pediatric population.

Sleep characteristics

Sleep phase

Sleep phase is primarily determined by intrinsic, chronobiologic factors that influence the timing of sleep during the 24-hour period. Recent research has outlined genetic influences that determine propensity for sleep onset. However, environmental factors play an important role in several sleep phase disorders, and the following disorders have intrinsic and extrinsic subtypes in the ISCD classification.

Advanced sleep phase syndrome

Advanced sleep phase syndrome (ASPS) is associated with sleep onset in the early evening hours, followed by early morning awakening. Since sleep onset in children is usually early compared to adults, there are rarely any clinical concerns relating to sleep onset as long as the child is able to complete the day's tasks. Inability to stay awake during homework may be misinterpreted as sleep deprivation or

school avoidance. When allowed to choose their own sleep-wake schedule (e.g. on vacation or weekends) children with ASPS often prefer to wake up earlier, reflecting their chronophysiologic predisposition. If the child awakens earlier than other family members, caregivers may request medications or evaluation for insomnia. If the child is able to function well during the day, there is rarely any need for further evaluation.

Delayed sleep phase syndrome

Delayed sleep phase syndrome (DSPS) is typically seen in the adolescent population, and is partly related to a physiologic phase delay that becomes evident in the early teen years. Inability to fall asleep until early morning hours is a consistent feature in this disorder. Attempts to induce sleep with the use of sedatives are generally unsuccessful. Parents may report an increase in social activities during the late evening hours, or working late at after-school activities, as contributing to the phase delay. Since DSPS is also associated with a delay in awakening, the sleep period often extends into the morning hours, and may overlap with the start of the school day. Compensating for sleep deprivation during the school week by sleeping late on weekends compounds the problem, since this practice introduces a further phase delay at the start of the school week. When allowed to sleep on a self-dictated schedule, most adolescents with DSPS will choose a sleep period that mimics the sleep-wake schedule for "second-shift" workers.

Irregular sleep-wake pattern

The essential characteristic of this disorder is an inability to synchronize the sleep-wake cycle into a consistent diurnal pattern. Sleep is disorganized, without a single, sustained primary sleep period. Multiple sleep periods (at least three) occur throughout the day. While this pattern is rarely seen in the general population, it is normal in the first few weeks of life. Similar patterns of sleep-wake behavior may occur temporarily during the course of an acute, severe illness, and need to be differentiated from the chronic course reported with this disorder. Persistence of this pattern is likely to have a severe impact on the sleep of caregivers. The pattern is most likely to be seen in children with severe and diffuse cerebral dysfunction, and is reported in severely impaired and institutionalized children.

Sleep amount

Insufficient sleep syndrome

In this disorder, the persistent failure to obtain adequate sleep for normal functioning during wakefulness leads to complaints of excessive daytime sleepiness. In children with insufficient sleep, an improvement in symptoms is noted following an increase in the duration of the sleep period. Often, symptoms are related to hectic schedules, and resolve when these are modified to allow adequate rest. This disorder should be distinguished from other conditions where excessive sleepiness is due to sleep disruption or fragmentation, rather than insufficient sleep. In the former, symptoms do not improve with increased sleep duration.

In children with sleep needs that are among the lower percentiles for age, caregivers may be concerned about insufficient sleep. Children with below-normal sleep needs may appear to have insomnia, since their sleep period is much less than time spent in bed. The child with reduced sleep need sleeps consistently and efficiently in a short sleep period, wakes up refreshed, does not take naps and functions well during the waking period. These features distinguish the short sleeper from other sleep disorders.

Long sleeper syndrome

Children with sleep needs that are at the upper percentiles for age are often evaluated for excessive daytime sleepiness. This disorder is classified under a proposed sleep disorder, and is a diagnosis of exclusion. Some children with this disorder continue napping to meet sleep debt. Others have persistent sleepiness or sleep inertia that interferes with daytime activities. Long sleepers function well after adequate sleep, and do not report any problems with the quality of sleep. If there is concern regarding increasing requirements of sleep, or nonrestorative nocturnal sleep, further investigations are warranted.

Hypersomnia

Narcolepsy

Narcolepsy is a primary disorder of sleep, with four cardinal clinical manifestations: excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, and sleep paralysis. The disorder has a familial predisposition and a high association with HLA-DQB1*O6O2. The symptoms of narcolepsy are related to the loss of hypocretin (orexin)-producing neurons in the lateral hypothalamus. Clinical manifestations are due to poor regulation of sleep-wake patterns and dissociation of REM sleep features, with REM intrusion into wakefulness.

EDS is the earliest and most prevalent symptom. Although EDS may be present from early childhood, the diagnosis of narcolepsy is often delayed for several years, unless one or more of the other cardinal manifestations are present in the first decade.

Cataplexy has a high diagnostic value, but symptoms may be infrequent or subtle, especially at the onset of the disorder. During a cataplectic spell, transient weakness occurs due to an abrupt decrease in muscle tone affecting antigravity muscles. Cataplexy may occur spontaneously, but is characteristically provoked by emotional arousal. Consciousness is not affected, although sleep may ensue after the event. There is

complete recall for events, and examination during the spell reveals diminished or absent deep tendon reflexes.

Hypnagogic hallucinations and sleep paralysis occur normally in some children, and are less likely to be primary clinical presentations of narcolepsy without associated EDS or cataplexy. Hypnagogic hallucinations may be described as actual events by young children. The child may avoid going to bed, seek parental company or report the presence of "monsters." Most hallucinations are visual or auditory in nature. Some of these concerns need to be distinguished from normal bedtime conflicts. Sleep paralysis may occur at sleep onset or offset, as REM-related atonia persists during wakefulness. The child appears awake, but lies immobile and unable to move spontaneously in bed. Tactile or other sensory input terminates the event. The child may be distressed if these events occur frequently.

The diagnosis of narcolepsy is confirmed by overnight polysomnography (PSG) and multiple sleep latency tests. Overnight polysomnography is performed to document sleep efficiency and exclude comorbid sleep disturbances. The multiple sleep latency test is performed as a series of naps performed at 2-hour intervals following the overnight study. The occurrence of sleep-onset REM periods during daytime naps, along with an average sleep latency less than 5 minutes, is characteristic of narcolepsy.

In children, symptoms and PSG findings evolve over months to years, and several PSGs may be needed before a diagnosis is established. HLA haplo-typing for DQB1*O6O2 is suggestive of a genetic predisposition, but not diagnostic for narcolepsy. Patients with narcolepsy-cataplexy have a marked reduction in CSF hypocretin (orexin) levels, and this test may be helpful in confirming the diagnosis in cases that do not meet PSG criteria.

Periodic hypersomnia

Periodic hypersomnia is associated with intermittent periods of irresistible sleepiness lasting several days, with symptom-free intervals of weeks to months. Klein-Levin syndrome is a disorder reported predominantly in males, with initial onset during adolescence. During the symptomatic phase, excessive sleepiness is observed, with irritability or aggressive behavior if the child is disturbed. Compulsive eating, sexual disinhibition and affective symptoms are also noted in some patients. Onset may be spontaneous or in the setting of an intercurrent illness or head trauma. Episodes occur at varying intervals and may decrease in severity or frequency over time. Catamenial hypersomnia, associated with periodic hypersomnia in adolescent girls, occurs in the luteal phase of the menstrual cycle, with resolution at the time of menses. The symptoms are most likely related to hormonal imbalance, since onset is most often noted around menarche. Symptoms resolve over time, with pregnancy or use of oral contraceptives.

Pediatric insomnia

Significant and persistent difficulty in initiating and maintaining sleep during childhood adversely affects the quality of life for the child and family. Biologic and environmental factors causing pediatric insomnia are covered in a subsequent section of this chapter. Treatment of pediatric insomnia includes cognitive/behavioral approaches along with judicious use of medications in selected cases.

Sleep quality

Sleep quality is an important, but often underestimated, component of good sleep. Sleep disorders that produce frequent arousals and sleep state transitions lead to sleep fragmentation and disruption of sleep architecture. Sleep fragmentation, along with reduced efficiency of sleep, results in nonrestorative sleep. Attempts to increase sleep amount do not compensate for poor sleep quality. Two common sleep disorders that have an adverse impact on sleep quality are obstructive sleep apnea syndrome (OSAS) and periodic limb movement disorder (PLMD).

Sleep apnea

Sleep apnea is characterized by sleep-related respiratory disturbance that ranges from increased resistance to airflow during sleep (upper airway resistance syndrome) to reduction (hypopnea) or cessation (sleep apnea) of airflow. The absence of effort during a respiratory event is characteristic of central apnea, and distinguishes it from obstructive apnea and hypopnea.

Sleep apnea in childhood is associated with conditions that affect respiratory control during sleep (e.g. central hypoventilation syndrome), craniofacial structural abnormalities (macroglossia, micrognathia), abnormal airway tone (cerebral palsy), or structure (adenotonsillar hypertrophy). Systemic disorders (e.g. sickle cell disease) may be associated with higher risk of complications due to OSAS. Children with neurologic disorders often have a multifactorial etiology to sleep-disordered breathing.

Clinical guidelines have been recently formulated for diagnosis and management of OSAS in children. A history of snoring, presence of adenotonsillar hypertrophy and sleep disturbance provides clinical clues to the presence of OSAS. Overnight polysomnography is the diagnostic study of choice, and adenotonsillectomy is often adequate treatment for uncomplicated OSAS. High-risk patients (with concomitant medical or neurologic disorders) need evaluation by sleep disorder specialists for residual or refractory sleep problems.

Periodic limb movement disorder

Periodic, stereotyped movements of one or more extremities, occurring after sleep onset, that result in insomnia or EDS are classified as periodic limb movement disorder (PLMD). The disorder has a genetic predisposition, and is influenced by age, medical problems (iron deficiency status) and medications (tricyclics, SSRIs, withdrawal from sedatives and anticonvulsants). A history of restless legs syndrome is often reported in adult first-degree relatives. PLMD may also coexist with other primary sleep disorders, including narcolepsy and OSAS. Children with PLMD are noted to have daytime symptoms that are similar to those of attention deficit-hyperactivity disorder. Sometimes the soreness or discomfort in the extremities that is related to PLMD is attributed to growing pains.

A diagnosis of PLMD is confirmed by overnight polysomnography. The accuracy of the study may be increased by utilizing additional EMG recordings, since the movements show considerable variation in location and frequency between sides and extremities. Severity of PLMD correlates with low serum and CSF ferritin levels. Alteration of dopaminergic transmission is postulated, as iron is a cofactor in dopamine synthesis. Iron supplementation, both in oral or parenteral forms, reduces the severity of the disorder. Dopamine agonists are also used in the treatment of PLMD.

Parasomnias

Parasomnias are classified according to their occurrence in the sleep-wake cycle. Primary parasomnias reflect an age-dependent expression of a familial predisposition. Sleep-wake transition parasomnias include sleep starts (Table 25.1), sleep-talking, nocturnal leg cramps and rhythmic movement disorder (Table 25.2). Arousal from NREM sleep is associated with sleepwalking (Table 25.3), confusional arousals and sleep terrors (Table 25.4). REM behavior disorder (RBD), nightmares (Table 25.5) and sleep paralysis occur as REM-sleep related events. Enuresis and bruxism (teeth-grinding) are examples of nonstate specific parasomnias.

Parasomnias may be precipitated in susceptible individuals (secondary parasomnias) by arousals or state transitions due to OSAS and PLMD, with reduction or resolution of symptoms after treatment of the underlying primary sleep disorder. Nocturnal seizures, headaches, dystonic disorders and acid-reflux disease should also be considered in the differential diagnosis of secondary parasomnias.

Parasomnias are often more distressing to the parent than the child. In such situations, education and reassurance may suffice, since most parasomnias resolve with increasing age. In some instances, however, further evaluation is indicated (see Consider Consultation When …) In patients with coexisting medical or neurologic disorders, a low threshold for evaluation is appropriate, since the underlying disorders

FEATURES

Table 25.1 Sleep Starts

Discriminating features

1. Sudden brief contractions of extremities
2. Subjective feeling of falling, or sensory experience
3. Associated with arousal

Consistent features

1. Occurs at sleep onset
2. Benign course and outcome

Variable features

1. Number and frequency of movements
2. Age of occurrence (any age)

FEATURES

Table 25.2 Rhythmic Movement Disorder

Discriminating features

1. Stereotyped, rhythmic movements of large muscles
2. Involve head and neck, rarely limb muscles
3. Body movements (rocking, rolling)

Consistent features

1. Occur prior to sleep onset
2. Common in infants and children
3. Decrease with age

Variable features

1. Associated vocalizations
2. Age of resolution (persists in autistic children)

FEATURES

Table 25.3 Sleepwalking (Somnambulism)

Discriminating features

1. Initiated during NREM sleep
2. Complex behaviors with walking or wandering during event
3. Subsides spontaneously with return to sleep without intervening arousal

Consistent features

1. Amnesia for episode
2. Inability to arouse child during event
3. Occur during slow-wave sleep

Variable features

1. Two subtypes – agitated or quiet walkers
2. Associated sleep talking during event
3. Injury during event
4. Response to attempted arousal or re-direction during event (agitation or compliance)

FEATURES

Table 25.4 Sleep Terrors

Discriminating features

1. Occurs during slow-wave sleep (usually first third of sleep period)
2. Agitation and screaming during event
3. Autonomic arousal during event

Consistent features

1. Inconsolable crying
2. Tachycardia, tachypnea, diaphoresis, terrified look
3. Difficult to arouse
4. Amnesia for event

Variable features

1. Duration of event
2. Degree of agitation and autonomic arousal
3. Recall of fragmentary, vivid hallucinations

FEATURES

Table 25.5 Nightmares

Discriminating features

1. Occur during REM sleep (usually latter part of sleep period)
2. Vivid dream imagery after arousal
3. Arousal at end of event

Consistent features

1. Associated with REM sleep
2. Element of fright or anxiety with dream
4. Arousal (spontaneous or provoked) at end of event
5. Recall of event

Variable features

1. Duration and content of dream
2. Amount of emotional agitation with event

and/or the medical treatment may affect or be influenced by sleep.

Biologic–environmental interactions

Biologic factors

Genetics

Sleep is regulated by the two principal processes; process S and process C. These processes are influenced by genetic mechanisms. Mammalian clock genes (Cry/Per, Bmal/clk) are dynamic dyads that maintain sleep homeostasis (Process S). Circadian rhythm (process C) is regulated by the suprachiasmatic nucleus, with input from the melanopsin receptors in the retinal ganglion cells. Process C determines the sleep phase in a 24-hour period, and recent studies have outlined a genetic component to sleep phase disorders.

Genetic predispositions may be expressed as primary sleep disorders, or disorders manifest during sleep. Narcolepsy and periodic limb movement disorders have a marked familial preponderance. Nocturnal seizure disorders, including benign epilepsy with centro-temporal spikes (benign rolandic epilepsy) and autosomal dominant nocturnal frontal lobe epilepsy, are state-dependent expressions of a genetic tendency. Fatal familial insomnia is associated with sleep disorders at the onset of a neurodegenerative disorder.

Gender

Several sleep disorders exhibit a gender difference in adults. OSAS and RBD are predominantly seen in males, and RLS is more prevalent in women. Sleep disorders due to affective disorders are more common in women. Some disorders are specific to a single gender (catamenial hypersomnia).

In prepubertal children, there are no significant differences in prevalence of common sleep disorders (including OSAS), although referral patterns may influence frequency of diagnosis. Some parasomnias including enuresis, RMD and sleep terrors are more common in males, while bruxism, somniloquy, and nightmares are equally prevalent in boys and girls.

Growth phase

Maturation of the sleep-wake cycle and consolidation of sleep state features occurs gradually over several months to years in healthy children. Abnormal psychomotor development affects sleep maturation adversely, leading to persistence of infantile sleep patterns into childhood. These children may also have coexisting medical and neurologic disorders that affect sleep. In addition, social and language development influences the interaction between caregivers and children. These factors predispose young children with a variety of developmental disorders to sleep disturbances. Prematurity, autistic spectrum disorders, severe mental retardation and static encephalopathy are associated with a high incidence of sleep disorders. In these children, consolidated sleep may not occur in the first year of life, parasomnias persist well beyond early childhood, and sleep disruption often adversely affects quality of life.

Environmental factors

Transition from wakefulness to sleep, as well as sustained nocturnal sleep, are influenced by a variety of environmental factors. The child's ability to settle down to sleep is a learned behavior that involves disengagement from the caregivers in a secure, comfortable sleep environment. Parenting styles, social and cultural expectations, as well as sleeping arrangements are among the environmental determinants of sleep patterns in children. In otherwise healthy children,

environmental influences play a significant role in several pediatric sleep disorders.

Sleep-wake transition

Sleep-onset association disorder

Sleep onset in infants is often facilitated by the parents. Initially, feeding, rocking and cuddling are common antecedents to onset of sleep. Later, these interventions are replaced with transitional objects (pacifiers, bottles, blankets). The place and setting in which the child falls asleep become environmental reinforcements for transition to sleep. Children who learn to sleep using one or more of these aids develop a sleep-onset association with the facilitatory object, place or person. They seek the same aids to settle down after nocturnal arousals. The lack of these sleep aids during the night leads to prolonged periods of arousal, during which the child attempts to restore the environment that facilitated onset of sleep. If the sleep-onset association involves parental interaction or a place other than the child's customary sleeping area, parents have to intervene before the child settles down. The frequency and duration of these interventions leads to sleep disruption for the caregivers, and is often the reason for seeking medical advice. A new set of nondisruptive sleep-onset associations need to be cultivated for resolution of the sleep-onset association disorder. This process may take several days to weeks.

Limit-setting sleep disorder

Voluntary disengagement from the environment is an initial step before going to sleep. In children, this process requires parental supervision and reinforcement. Children may find ways to postpone bedtimes by making repeated requests for minor interventions. If the caregivers do not reinforce limits consistently, this behavioral pattern delays sleep onset, leading to insufficient sleep for the preschool-aged child. Older children may lack the self-discipline to go to bed at an appropriate time, and adolescents often choose to sleep on an irregular schedule. In all cases, there is no difficulty after sleep onset. Sleep-related complaints resolve after a consistent sleep schedule is enforced.

Socioeconomic factors

A child's sleep environment varies widely based on the socioeconomic status of the family. Among the lower socioeconomic classes, inadequate sleeping areas, lack of electricity, overcrowding and a noisy environment contribute to the child's sleep difficulties. Conversely, easy access to television, computers and video-games and numerous social engagements or after-school activities may predispose children in more affluent families to insufficient or disrupted sleep. Consumption of caffeinated beverages, inadequate or inappropriate food intake and poor sleep hygiene affect sleep in all children.

Stressors

Sleep disorders may be precipitated by extrinsic and intrinsic stressors. Extrinsic stressors affect sleep based on their duration and severity. The impact may be mild and self-limited in some instances (e.g. prior to travel or a test). Changes in school or residential settings produce changes that may last for several weeks to months. Other social stressors, including domestic or societal violence, geopolitical events and major environmental disasters that affect entire segments of society, may induce long-term changes in children's sleep patterns (post-traumatic stress disorder of childhood). Intrinsic stressors include fever, systemic illness, chronic pain and medical disorders.

Diagnostic evaluation

A thorough history and physical exam often provide clues to the cause of sleep disorders. A 2–4 week sleep diary provides information about sleep phase and average sleep amount in an individual child. Sleep diaries are diagnostic for sleep phase disorders, and may be complemented by actigraphy for objective analysis. Several sleep questionnaires are available to assess probable cause and impact of sleepiness, including Pediatric Sleep Questionnaire (PSQ) and Epworth Sleepiness Scale (ESS). The authors use an acronym, INBED, which outlines a clinical protocol for the evaluation and management of sleep disorders (see Pearls & Perils).

In a child with sleep disruption or excessive daytime sleepiness, additional investigations may be necessary to confirm a suspected diagnosis. Polysomnography is the "gold standard" for diagnostic evaluation of sleep disorders, and is combined with the multiple sleep latency test (MSLT) for objective assessment of daytime sleepiness. Polysomnography provides information about sleep stages and architecture, limb movements, sleep-related respiratory disorders and nocturnal seizures. Modifications of the technique also allow diagnosis of acid-reflux, effect of interventions to maintain airway patency and oxygenation, and video-review of nocturnal events.

PEARLS & PERILS

INBED Protocol

- **I** Individual sleep characteristics (FAQ); sleep "Ph"ase, "A"mount and "Q"uality
- **N** Nature ("B"iologic factors); genetics, gender, growth phase
  Nurture ("E"nvironmental factors); sleep-wake transitions, socioeconomic factors, stressors
  Neither ("D"iagnostic evaluation)
- **B** Behavioral therapy
- **E** Environmental therapy
- **D** Drug therapy

The multiple sleep latency test consists of four to five naps that are usually performed 2 hours apart and reviewed for sleep onset latency and occurrence of sleep-onset REM periods within 20 minutes of sleep onset. The sleep latency is calculated as the average time to sleep onset, with a maximum period of 20 minutes allowed if sleep does not occur. The test is not standardized in very young children, but is useful in older children and adolescents for diagnostic studies and assessing impact of therapeutic interventions. Sleep-onset REM periods may be seen in children with DSPS, REM rebound after prior REM deprivation, following withdrawal from REM suppressant medications as well as with narcolepsy.

KEY CLINICAL QUESTIONS

- Does the child wake up refreshed and well rested? (Restorative sleep usually makes a significant sleep disorder unlikely.)
- Does the child function well during the day? (Sleep disorders affect child mood, social and school functioning, and may lead to inappropriate behavior.)
- Has anybody been injured or hurt, or likely to be so? (Screen for violent nocturnal behavior, seizures, sleepwalking, obstructive sleep apnea syndrome, periodic limb movement disorder, adverse social implications.)
- Are any other family member affected by sleep complaints, or in similar way? (Familial predisposition, effect on caregivers.)

Management

The management of sleep disorders in children is dictated by the primary source of the sleep disturbance. If multiple contributory factors are identified in the genesis of a sleep disorder, one or more of the following approaches may be necessary.

Behavioral therapy

Behavioral therapy is extremely helpful as a primary intervention in several sleep disorders (e.g. sleep-onset association disorder and limit-setting sleep disorder). Behavioral techniques are useful in the treatment of parasomnias (anticipatory awakening in night terrors, reinforcement therapy for enuresis, stress reduction in anxious children). Desensitization therapy preceding the use of face masks to maintain airway patency improves compliance and tolerance of therapy. Family education and counseling is essential in management of sleep disorders that are related to inappropriate parental expectations or interventions.

Environmental therapy

A quiet, comfortable and secure sleep environment is conducive to restorative sleep. Variations in ambient temperature, humidity, noise and light act as environmental triggers that produce sleep disruption. Humidifiers and fans may be used as needed, along with removal of noise and light sources. Age-appropriate sleep settings are important in young children, to ensure safety and minimize extrinsic causes of arousals. A supine position during sleep is particularly important in young infants. Time in bed should match sleep need to minimize prolonged sleep latency, repeated arousals and sleep fragmentation.

Specific environmental interventions may be used in certain sleep disorders. Bright light therapy is used in restoring restful sleep in sleep phase disorders. Chronotherapy is a technique of voluntary, sequential delay of the sleep period, to allow resynchronization of sleep phase with time zone, and is particularly helpful in severely phase-delayed adolescents. Overnight sleep-deprivation also induces phase advance the following day and may be used as a weekend technique for DSPS in selected cases. Positional therapy is helpful in cases of acid-reflux disease or positional apnea.

Drug therapy

A recent survey of community-based pediatricians indicates that prescriptions for sedatives are most commonly used in children with pain or neurodevelopmental disorders (including mental retardation, autism and ADHD) or during travel. Antihistamines and alpha-agonists were the most common prescription medications, while melatonin and herbal remedies were utilized as nonprescription alternatives. In children with nocturnal seizures, acid-reflux disease or asthma, optimization of specific therapy is preferable.

Specific therapy is available for some sleep disorders. Excessive daytime sleepiness is usually treated with stimulant medications, including methylphenidate, dexmethylphenidate and dextro-amphetamine. Several formulations are available to enable titration for efficacy. The use of stimulants is associated with side effects on appetite and increase in headaches and tic disorders in a subset of patients, and should be closely monitored to avoid misuse. Modafinil, approved for use in narcolepsy in adults, may be useful in selected patients. Cataplexy is treated with tricyclics and selective serotonin reuptake inhibitors. Iron supplementation is useful in treating periodic limb movement disorder in pediatric patients.

Conclusion

Sleep disorders occur at all ages. An age-appropriate expectation of sleep phase and need coupled with an understanding of common age-specific sleep disorders enables the clinician to evaluate and manage a number of these conditions. The use of a simple protocol (INBED protocol, outlined above)

CONSIDER CONSULTATION WHEN...

- Indications for polysomnography:
  - Failure of conventional therapy
  - Clinical suspicion of obstructive sleep apnea syndrome or periodic limb movement disorder
  - Complaints of excessive daytime sleepiness
  - Suspicion of nocturnal seizures
  - Violent sleep-related behavior
  - Unusual or atypical parasomnias

may be helpful in formulating a clinical approach to sleep disorders, and making appropriate referrals for diagnostic studies and further evaluation.

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Appendix: A Proposed Approach to Nosology

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While the practice of medicine has experienced major technological advances in recent years, nosologic systems (e.g., *International Classification of Diseases – 10* and the *Diagnostic and Statistical Manual – IV* of the American Psychiatric Association) present at times a confusing array of diagnostic possibilities. Many diseases/disorders may even be represented in more than one place in the diagnostic system. Lack of a comprehensive framework leads to diagnostic confusion in the clinical, teaching, and often in the research setting. Clearly, organization and orderliness are needed to better discriminate between entities. *Webster's International Dictionary* defines nosology as the branch of medical science that deals with the orderly classification of diseases. My purpose is to propose such a system. This system will submit *a priori* that if a disease/disorder exists, there must also exist features which discriminate it from similar entities. It is clinically derived by expert opinion, categorical and multi-dimensional. Where the state of the art permits, discriminators have been empirically validated.

Classification issues have historic roots. Hippocrates suggested that "whoever undertakes to speak or write on medicine, should have first laid themselves some hypothesis as to their argument, such as hot or cold or moist or dry or whatever else they choose, thus reducing their subject within a narrow compass." The work of Thomas Sydenham on acute diseases first published in 1675 is seminal. Sydenham suggested that all diseases can be classified as to a certain definite species in the same manner as botanists describe their plants. He further suggested that pathologic phenomena should be described in precise detail in the same way that a portrait painter seeks to capture the likeness of a subject. He noted that particular and constant symptoms should be distinguished from accidental phenomena. John Locke, in describing Sydenham, suggested that he had a poor opinion of those who attempted to look at disease from a chemical point of view. On the other hand, he noted that Sydenham recognized the utility of chemotherapeutics, recognizing, for instance, that certain chemicals could induce vomiting, implying that treatment outcome was not a good basis for classification, but overlooking its potential value as a validator of diagnosis.

Carl Linné graduated as a doctor of medicine in 1735. While he is best known for his biological classification system (e.g. phyla, genera, species), his attempt to use this approach for medicine was never widely accepted, principally because of a confusion between the definitions of symptom and disease. Laennec in 1826 was among the first to link symptoms to pathologic anatomy when he described the pathology of disseminated tuberculosis. In the mid-nineteenth century, the pathophysiologic basis of disease came into focus. Methods for counting cells, methods for the measurement of the color of blood, as well as methods for the examination of urine, were developed. In the later nineteenth century, an etiologic approach for the classification of disease became possible with the identification of a specific bacterium as the cause for a specific disease (Koch-Pasteur). This became the first good example of using the best and most robust discriminator, etiology. As the reader can see, there was therefore an evolutionary progression from phenomenologic descriptions to those which were based on etiology. Each reflected the state of knowledge at that time.

Many disorders in psychiatry and neurology still can be described only phenomenologically. While seemingly the least robust, phenomenologic validity is attainable. Skinner suggested that a phenomenologically based system should have certain features so as to make descriptions of specific entities valid. These include *reliability*; that is, agreement across examiners using the same diagnostic methodology; *coverage*, referring to the applicability of the classification domain of the patients for which it was intended; *descriptive validity,* implying homogeneity in characterizing behavioral symptoms, personality characteristics, social history data, and other kinds of information which are used to make a diagnosis; and *predictive validity*, where a classification system can determine the potential effectiveness of treatment or the natural history of a psychiatric disorder. While Skinner's conceptual framework was meant to be applied to psychiatric disorders described phenomenologically, it can obviously be generalized. It can also provide a mechanism for a classification system.

Classification in science is important to medicine. A successful and therefore useful classification should be simple

and easy to use. Secondly, it should be organized hierarchically and have the flexibility to reflect the state of the art as it evolves. Lastly, the goal ideally should be to define the disease/disorder etiologically through the rigorous application of the scientific method. Classification domains in medicine are usually defined according to the following schema:

1 phenomenologically, by listing commonly agreed observations and distinguishing between entities based on these observations (a good example of this would be the clinical classification of the epilepsies);
2 anatomically, by the site of origin of the disorder;
3 pathologically, by the gross or microscopic pathologic anatomy, revealed by either traditional pathologic study or imaging;
4 pathophysiologically, by demonstrating altered chemical or electrophysiologic parameters;
5 etiologically, by cause.

Under these general domains, subdomains can be identified, e.g. histopathology versus radiologic pathology. Much of the confusion that arises in diagnosis occurs when the clinician crosses classification domains – for example, the inclusion of an anatomically oriented "temporal lobe seizure" in a phenomenologically based classification system that includes complex partial seizures. It is, therefore, extremely important from both a clinical and a research standpoint that the classification domain to be used should be pre-determined, and that contrasting discriminators be comparable (e.g. bacterial meningitides should not be enmeshed with viral meningitides). For a disease/disorder to exist, it must have some feature or features which discriminate between it and similar entities. Discriminating features may have inclusionary as well as exclusionary features. The ideal is to have a single discriminator. This then makes the contrast between a particular entity and similar entities more robust. When there is more than a single discriminator involved, this in essence becomes a criterion-based system. While this is obviously less robust, a criterion-based system may simply reflect the state of the art.

Just as there are discriminant features, disease/disorder entities often have consistent as well as variable features. In the current Mosby/Yearbook *Neurology/Psychiatry Access Series*, the series editor has defined consistent features as those that occur 75% of the time and variable features as those that occur less than 75% of the time. These need not be consistent with the discriminator domain, i.e. cerebral spinal fluid glucose is consistently low in bacterial tuberculous meningitis. Tables I–III reflect what is believed to be the best way of distinguishing between these and similar entities, again reflecting the state of the art. In this textbook series, contributor experts were asked to identify discriminant, consistent, and variable features. William Nyhan used this model for distinguishing inborn errors of metabolism from one another using pathophysiologic discriminators. Current knowledge permitted the use of only one discriminator (Table I). When the defective gene is identified for each of these disorders, each can then be discriminated from the other based on genotype. This will enhance etiologic discrimination and will more powerfully distinguish similar entities from one another.

Joseph Sirven and Michael Sperling use the same system to classify the epilepsies, but the result is much different (Table II). In this case, discriminators are phenomenologically based, again reflecting the state of the art. A phenomenologically based system is probably the most appropriate to use at this state of the art rather than using one that is etiologically derived. Unfortunately, the universal use of this system will probably impede its evolution into a system which is etiologically based, although usage alone should not preclude developing an etiologically based system. Practicality also plays an important operative function in domain selection. To demonstrate that this system can be applied to other medical diseases/disorders, the reader is referred to Table III. Here valvular stenotic heart disease is classified using this nosologic system.

It should always be acknowledged that classification of science is dynamic, not etched in stone, but clearly in order that clear discourse be possible. Medicine needs a clear nosologic framework today, irrespective of how it may have changed.

In summary, to put this system into operation, experts should agree on the following questions.

1 Which features discriminate one group of similar diseases/disorders from one another (e.g. enzyme deficiency)?
2 Into what classification domain does this fall (e.g. genetic disorder – defective gene, pathophysiologic domain)?
3 Can a single discriminator suffice, or are multiple discriminators required, reflective of the state of the art (e.g. in a genetic disorder, a single discriminator is sufficiently robust)?
4 If multiple discriminators are needed (i.e. a criterion-based system), are inclusionary as well as exclusionary criteria to be used?
5 What consistent and variable features should be used to enhance understanding and more clearly define the entity.
6 What should be the relative frequency to distinguish between consistent and variable features?

In conclusion, I propose that as knowledge permits, medicine should define a discriminator-based system for the classification of diseases and disorders. The use of additional consistent and variable features will further enhance distinctions between diagnostic entities.

TABLE I

Lesch–Nyhan syndrome

Discriminating feature	Consistent features	Variable features
Complete deficiency of hypoxanthine-guanine phosphoribosyltransferase	1 Hyperuricemia 2 Urisosuria 3 Mental retardation 4 Spastic cerebral palsy 5 Chroeoathetosis 6 Self-mutilation	1 Convulsions 2 Hematuria 3 Urinary tract stones 4 Urinary tract infections 5 Tophi 6 Urate nephropathy 7 Vomiting

Purine nucleoside phosphorylase deficiency

Discriminating features	Consistent features	Variable features
1 Deficiency of PNP	1 Immunodeficiencies 2 T-cell depletion 3 Infections 4 Hypouricemia 5 Nucleoside accumulation	Neurologic abnormalities

Phenylketonuria

Discriminating features	Consistent features	Variable features
1 Deficient hepatic phenylalanine 2 Elevated plasma phenylalanine 3 Depressed plasma tyrosine	1 Mental retardation 2 Diminished pigment 3 Phenylpyruvic aciduria 4 Phenyllactic aciduria 5 Phenylacetylglutamic aciduria	1 Vomiting 2 Eczematoid rash 3 Odd odor 4 Restriction fragment length polymorphism

Abnormalities in the metabolism of biopterin

Discriminating features	Consistent features	Variable features
1 Defective activity of dihydropteridine reductase 2 Evidence of deficient synthesis of tetrahydrobiopterin	1 Hyperphenylalaninemia 2 Degenerative neurologic disease 3 Convulsions 4 Spasticity	1 Rigidity 2 Tremors 3 Dystonic movements

Maple syrup urine disease

Discriminating features	Consistent features	Variable features
Complete deficiency of branched-chain ketoacid decarboxylase	1 Elevated concentrations of leucine, isoleucine and valine 2 Positive dinitrophenylhydrazine test of urine 3 Branched-chain ketoaciduria	1 Maple syrup odor to urine 2 Mental retardation 3 Spasticity 4 Opisthotonos 5 Coma 6 Convulsions 7 Hypodense cerebral myelin

Disorders of propionate metabolism

Propionicacidemia

Discriminating features	Consistent features	Variable features
Deficiency of propionyl-CoA carboxylase	1 Methylcitraturia 2 Hydroxypropionaturia 3 Propionicacidemia	1 Hyperammonemia 2 Anemia 3 Hyperglycinemia, hyperglycinuria

(Continued)

TABLE I *(Continued)*

Disorders of propionate metabolism

Propionicacidemia

Discriminating features	Consistent features	Variable features
	4 Recurrent episodes of ketosis and acidosis, leading to coma and potentially fatal illness 5 Osteoporosis 6 Vomiting 7 Hypotonia 8 Anorexia 9 Moniliasis	4 Pathologic fractures 5 Mental retardation 6 Immunodeficiency 7 Abnormal MRI of the basal ganglia

Methylmalonicacidemia

Discriminating features	Consistent features	Variable features
Deficiency of methylmalonyl CoA mutase	As in propionicacidemia, plus failure to thrive	As in propionicacidemia

Multiple carboxylase deficiency

Discriminating features	Consistent features	Variable features
1 Deficiency of holocarboxylase synthetase 2 Deficiency of biotinidase	As in propionicacidemia, plus 1 Alopecia 2 Dermatosis 3 Lacticacidemia, lacticaciduria 4 Deficient leukocyte carboxylases 5 Convulsions in biotinidase deficiency 6 Sensorineural deafness and visual defects in biotinidase deficiency 7 Ataxia in biotinidase deficiency	As in propionicacidemia

Isovalericacidemia

Discriminating features	Consistent features	Variable features
1 Isovalerylglycinuria 2 Deficiency of isovaleryl-CoA dehydrogenase	1 Episodes of acute illness 2 Ketoacidosis 3 Neutropenia, thrombocytopenia	1 Acrid "sweaty foot" odor 2 Mental retardation 3 Hyperammonemia 4 Anemia 5 Ataxia 6 Convulsions

Glutaricaciduria

Discriminating features	Consistent features	Variable features
Glutaricaciduria	1 Spasticity 2 Convulsions 3 Cerebral degeneration 4 Involuntary movements	Metabolic acidosis

3-Hydroxy-3-methylglutaricaciduria

Discriminating features	Consistent features	Variable features
1 3-Hydroxy-3-methylglutaricaciduria 2 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	1 3-Methylglutaconicaciduria 2 3-Methylglutaricaciduria 3 Hypoketotic hypoglycemia 4 Acute overwhelming illness 5 Metabolic acidosis 6 Lethargy or coma	1 Lacticaciduria 2 Lacticacidemia 3 Hyperammonemia 4 Hypotonia 5 Hepatomegaly 6 Vomiting

(Continued)

TABLE I (*Continued*)

3-Hydroxy-3-methylglutaricaciduria

Discriminating features	Consistent features	Variable features
		7 Elevated liver function tests 8 Convulsions 9 Cerebral atrophy

γ-Hydroxybutyricaciduria

Discriminating features	Consistent features	Variable features
Succinic semialdehyde dehydrogenase deficiency	1 γ-Hydroxybutyricaciduria 2 Convulsions 3 Ataxia 4 Mental retardation	1 Hyperactivity 2 Somnolence

Nonketotic hyperglycinemia

Discriminating features	Consistent features	Variable features
1 Elevated CSF and plasma glycine ratio	1 Hyperglycinemia 2 Hyperglycinuria 3 Neonatal coma and apnea 4 Myoclonic seizures (infantile spasms) 5 EEG burst suppression pattern 6 Cerebral atrophy	1 Hypertonia 2 Hypotonia 3 Increased deep tendon reflexes 4 Hiccuping

Homocystinuria

Discriminating features	Consistent features	Variable features
1 Homocystinuria 2 Cystathionine synthase deficiency	Mixed disulfide of cysteine and homocysteine in urine	1.Hypermethioninemia 2 Ectopia lentis 3 Mental retardation 4 Thromboembolic phenomena 5 Failure to thrive 6 Genu valgum 7 Osteoporosis

Urea cycle disorders

Discriminating features	Consistent features	Variable features
1 OTC deficiency 2 CPS deficiency 3 Argininosuccinic synthase deficiency 4 Argininosuccinase deficiency	1 Oroticaiduria in OTC deficiency 2 Hyperammonemia in OTC deficiency 3 Hyperglutaminemia in OTC deficiency 4 Coma in OTC deficiency CPS deficiency as in OTC, except for orotic aciduria Citrullinemia as in OTC deficiency, plus 5 Citrullinemia 6 Citrullinemia As in OTC deficiency, plus 7 Increased concentrations of argininosuccinate in urine and CSF	1 Hyperalaninemia 2 Hyperaspartic acidemia 3 Convulsions 4 Mental retardation 5 Trichorrhexis nodosa (in argininocuccinic aciduria)

Argininemia

Discriminating features	Consistent features	Variable features
1 Arginase deficiency 2 Argininemia	1 Spastic diplegia 2 Developmental delay 3 Hypertonia 4 Opisthotonus 5 Involuntary movements	1 Hyperammonemia 2 Hepatomegaly 3 Abnormal liver function tests 4 Convulsions 5 EEG abnormalities

TABLE II

The epilepsies

Simple partial seizures

Discriminating features	Consistent features	Variable features
1 No impairment of consciousness 2 Stereotyped 3 Focal spikes in interictal EEG	1 Brief duration 2 Paroxysmal 3 No impairment of consciousness 4 No post-ictal period	1 May manifest as abnormal sensations (smells, flashing lights, paresthesias), focal motor activity, or psychic phenomena (déjà vu, fear) 2 Associated with a focal structural lesion 3 May occur independent of or before a complex partial seizure

Complex partial seizures

Discriminating features	Consistent features	Variable features
1 Consciousness is altered 2 Stereotyped 3 Focal spikes in interictal EEG	1 Approximately 60- to 180-second duration 2 Paroxysmal 3 Post-ictal confusion	1 Presence of aura 2 Automatisms 3 Autonomic features 4 May secondarily generalize to a tonic–clonic seizure 5 Associated with focal structural lesion 6 May elevate prolactin level

Generalized tonic–clonic seizures

Discriminating features	Consistent features	Variable features
Initial tonic phase followed by clonic activity involving all extremities	1 Loss of consciousness 2 Typically 60 seconds duration 3 Post-ictal period associated with confusion and drowsiness 4 Elevation of prolactin	1 Tongue biting or injury 2 Urinary incontinence 3 Nonspecific prodrome 4 Post-ictal paralysis

Absence seizures

Discriminating features	Consistent features	Variable features
1 Very brief duration (5 to 15 seconds) 2 Family history of typical absence seizures 3 Response to ethosuximide and valproate	1 EEG correlate to typical absence of 3 cycles per second of generalized spike-and-wave; in atypical absence of 1.5 to 2.5 generalized spike-and-wave 2 No aura 3 Impaired consciousness 4 No post-ictal state	1 Automatisms 2 Change in body tone 3 Precipitation by hyperventilation

Myoclonic seizures

Discriminating features	Consistent features	Variable features
1 Shock-like muscle contractions 2 No impairment of consciousness	1 Brief duration 2 No aura 3 No post-ictal state 4 Generalized spike wave in the interictal EEG	1 Specific muscle groups involved (isolated or whole body; unilateral or bilateral) 2 Association with a progressive neurologic syndrome 3 Occur spontaneously or may be provoked by sensory stimulation

(Continued(

TABLE II (*Continued*)

Mesial temporal lobe epilepsy

Discriminating features	Consistent features	Variable features
1 Unitemporal or bitemporal spikes in the interictal EEG 2 Hippocampal sclerosis	1 Simple partial and/or complex partial seizures 2 Impaired memory	1 MRI demonstrating hippocampal atrophy or a focal temporal structural lesion 2 History of febrile convulsions at an early age 3 Psychic or emotional auras

Juvenile myoclonic epilepsy

Discriminating features	Consistent features	Variable features
1 Multiple seizure types including myoclonic seizures, absence seizures, and generalized tonic–clonic seizures 2 Presence of myoclonus	1 Onset at puberty 2 Seizures often occur shortly after awakening 3 4 to 6 Hz generalized polyspike and slow wave on EEG 4 Good response to ethosuximide or valproic acid	1 Concurrent absence seizures 2 Seizures precipitated by sleep deprivation 3 Normal neurologic examination

Lennox–Gastaut syndrome

Discriminating features	Consistent features	Variable features
Triad of (1) mental retardation, (2) generalized slow spike-and-wave on EEG, (3) multiple seizure types – atonic, atypical absence, myoclonic, partial, and tonic–clonic seizures	1 Atonic seizures 2 Onset before age 8 3 Seizures are refractory to treatment 4 Poor prognosis	1 Association with symptomatic early brain insults 2 Cryptogenic onset in 30% of cases 3 Behavioral disturbances

Psychogenic seizures

Discriminating features	Consistent features	Variable features
1 Gradual onset 2 Variability in duration of episodes 3 No increase in serum prolactin 4 Induced by suggestion	1 Normal EEG during seizures and in the interictal state 2 Never occur during sleep	1 Manifestations of episodes (altered responsiveness, motor activity, vocalizations) 2 Asynchronous extremity movements 3 Minnesota Multiphasic Personality Inventory suggestive of conversion

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TABLE III

Valvular stenotic heart disease

Pulmonary stenosis

Discriminating features	Consistent features	Variable features
1 Echocardiographic appearance	1 Systolic murmur	1 EKG changes 2 Ejection clicks

Types

1 Sub-pulmonary
2 Supravalvular

Aortic stenosis

Discriminating features	Consistent features	Variable features
1 Echocardiographic appearance	1 Systolic murmur	1 EKG changes 2 Chest pain 3 Ejection clicks

Types

1 Supravalvular
2 Sub-aortic (membranous vs. idiopathic hypertropic sub-aortic stenosis)

Mitral stenosis

Discriminating features	Consistent features	Variable features
1 Echochardiographic appearance	1 Diastolic murmur	1 Opening sound 2 Pulmonary edema 3 Wheezing (cardiac)

Types

1 Suprastenosis ring
2 Coarctation

Tricuspid stenosis

Discriminating features	Consistent features	Variable features
1 Echocardiographic appearance	1 Diastolic murmur	1 Hepatomegaly 2 Clicks

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Chapter 16

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Developmental language disorders

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